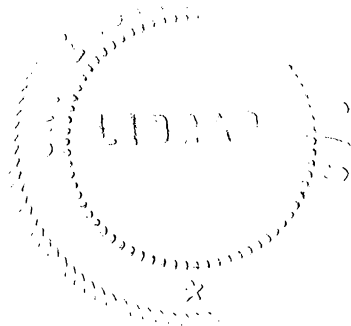


THE SYNTHESIS OF INTERMEDIATES
FOR CONVERSION TO CORTISONE ANALOGUES



by

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INTRODUCTION

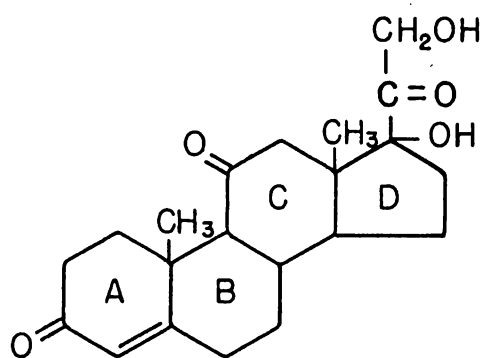
This thesis will describe in three parts the results of an investigation concerned with attempts to synthesize three different compounds, each of which would be expected to have biological activity similar to that of the hormone cortisone (I). The three divisions are based on the structures II, III, and IV:

- A. 3,4-bis-(4-Oxo-2,3-cyclohexenyl)-2,5-hexanedione (II).
- B. 3-(4-Oxo-2,3-cyclohexenyl)-4-(3-hydroxy-3-acetoxy-acetyl)-2-hexanone (III).
- C. 3-(4-Oxo-2,3-cyclohexenyl)-4-ethyl-8-hydroxy-8-acetoxyacetyl-5,6,7,8,9,10-hexahydro-2-tetralone (IV).*

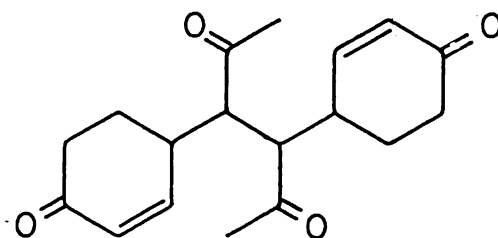
The resemblance between structures III and IV and the structure of cortisone (I) is particularly evident. Hirschfelder molecular models also clearly show the similarity.

The fact that in certain cases synthetic substances have proven to be equal, and even superior, in physiological effect to natural products which they resemble structurally is too well known to require much emphasis here. In the field of hormones, perhaps the most

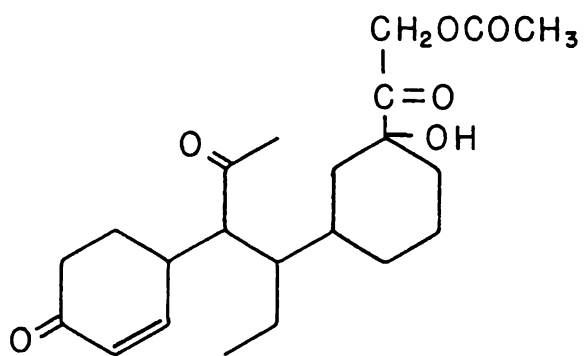
* It should be made clear that while the successful synthesis of the three compounds would be very desirable, anyone who has engaged in similar researches would agree that either one of these goals would be reached only with difficulty. Therefore, the purpose of this thesis is one of exploration in attempting to open up avenues which might lead to successful synthetic substitutes for the valuable agent, cortisone.



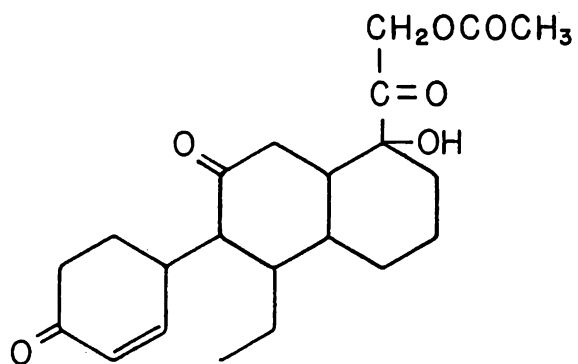
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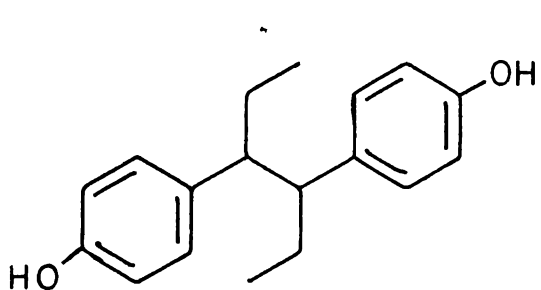
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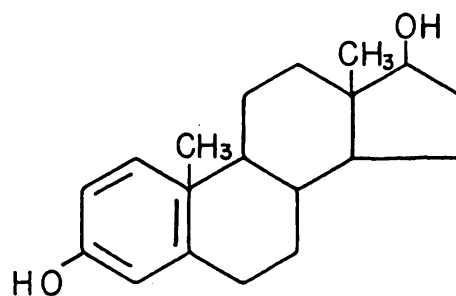
III



IV



V



VI

familiar example is the artificial estrogen, hexestrol (V), which is essentially as effective as estradiol (VI). Of more interest perhaps, in the present work is the fact that 10-nortestosterone (VIII) (p.5) showed activity comparable to that of testosterone (VIII) (1) and that 19-norprogesterone (IXa) exhibited progestational activity in rabbits comparable to that of progesterone (IXb) (2).

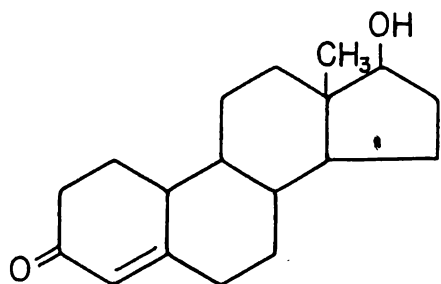
There is little doubt that the hormonal activity of either a naturally occurring hormone or a synthetic substitute is due to a proper combination of a number of factors, such as the hydrophilic-lipophilic distribution, the metabolic changes, the chemical structure, and especially, the stereochemical configuration. The importance of the proper stereochemical configuration is shown by the fact that meso-hexestrol produces the estrus response in virgin rabbits at a dosage of 0.2 γ , whereas dl-hexestrol produces the same response only at a level of 500 γ (3). However, at the present time, because of inadequate knowledge of the effect of such factors on biological activity, a study of changes in structure seems to afford the best field for investigation (4).

A study of the relationship between structure and activity of cortisone-like substances is more difficult than in the field of the sex hormones because of the lack of a satisfactory test method, especially for activity against rheumatoid arthritis. Nevertheless, there are such methods as the Selye test and the adrenal atrophy test, which should suggest whether or not synthetic analogues may be worthy of further study in higher animals or man.

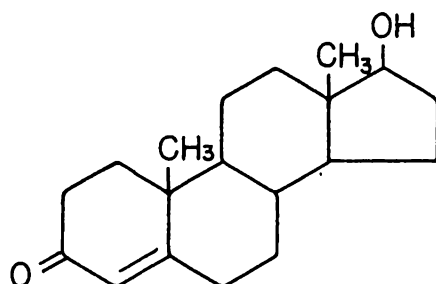
HISTORICAL

Cortisone, or Kendall's compound E, is only one of the twenty-eight crystalline compounds which have been isolated from the adrenal cortex, but the discovery of its dramatic effect in relieving the symptoms of rheumatoid arthritis (5) has made it by far the most important. It is unlikely that cortisone is the primary product of the adrenal gland, nor indeed that the other compounds isolated are, but rather that they are all transformation products of a single hormone - at most two - which is the primary substance of the gland (6).

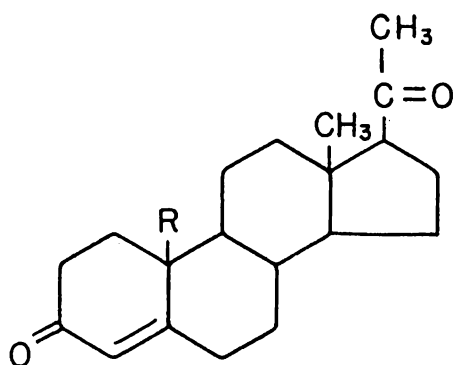
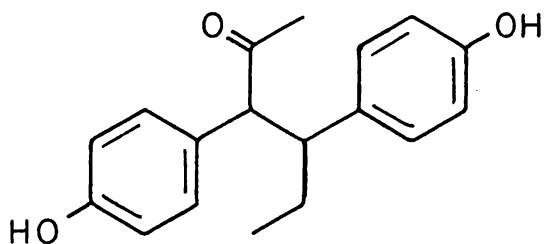
The discovery of the effect of cortisone on rheumatoid arthritis prompted an intense interest in its synthesis and in the synthesis of related compounds. A partial synthesis from desoxycholic acid was achieved in 1946 (7), and several total syntheses were reported in 1951 (8). However, neither of these syntheses is easily adaptable to large-scale production except at great expense, and the hope of discovering a synthetic substitute which could be easily prepared has attracted many workers. The reported results have been confined mostly to aromatic compounds which possess the characteristic ketol side-chain of cortisone attached to fairly large nuclei, such as biphenyl, bibenzyl, diethylbibenzyl, and diethylstilbene (9,10,11,12). However, these compounds possessed little or no activity. Several workers (13,14,15) have reported the preparation of compounds which possess an oxygen in a position corresponding to the 11-keto group in



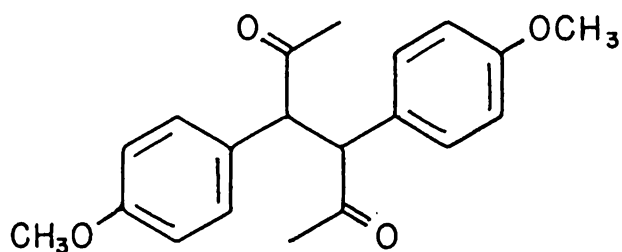
VII



VIII

IX (a) R = H
(b) R = CH₃

X



XI

cortisone. In the one case where physiological data were reported (15) while the compound (X, p. 5) did possess powerful estrogenic activity, it was not considered promising as a cortisone substitute.

PART A

DISCUSSION OF RESULTS

The ultimate goal here was to be II, p. 2, a compound similar to that prepared by Burckhalter and Sam (15). A necessary intermediate is 3,4-dianisyl-2,5-hexanedione (XI, p. 5) Although ten different approaches were made in attempts to prepare this compound, none of the desired product was obtained. In two cases, evidence was obtained that XI was probably the primary product of the reaction, but it was possible to isolate it only as its dehydration product, the furan (XVII, p.10). The ten different attempts are summarized in Table I, p.9 .

A thorough discussion of the preparation of homo-anisonitrile was given by J. Sam (26,15). Further work has revealed that the troublesome isolation of the intermediate homoanisylchloride is not necessary. A simple washing with sodium bicarbonate solution of the benzene solution in which the chloride is prepared to remove completely the last traces of hydrochloric acid was found to stabilize the chloride indefinitely. A sample of the crude chloride treated in this way has been kept for six months with no polymerization nor evolution of hydrogen chloride. The benzene solution of the crude chloride was added to a solution of sodium cyanide with very efficient stirring and the reaction was complete in five hours. The efficiency of the stirring determined the length of time necessary, best results being obtained when the

stirring was rapid enough to cause emulsification. Yields of 82.5% from the alcohol were consistently obtained.

Reaction 1.

The intermediate dianisylsuccinonitrile (XII) was prepared by a modification of the procedure used by Lapworth for the preparation of alpha-phenyl-beta-cyano-dihydrocinnamic acid (16). The melting point of IXX is reported (17) as 230°, but the present work has indicated that this is the melting point of the mixture of the meso form and the dl pair. Each form was separated and identified, although under the conditions used here for the preparation, the meso is obtained almost exclusively. This product (XII) by reaction with methylmagnesium iodide, should lead in one step to the desired ketone XI, but none of XI was isolated from any experiment, although the reaction conditions were varied in regard to proportions of reactants, temperature, and time of heating. Only the purple polymer, which could not be characterized, was obtained.

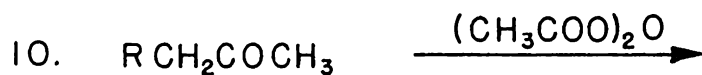
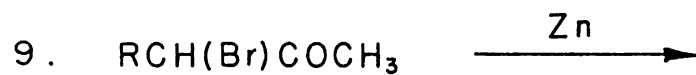
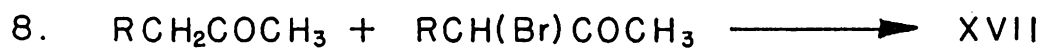
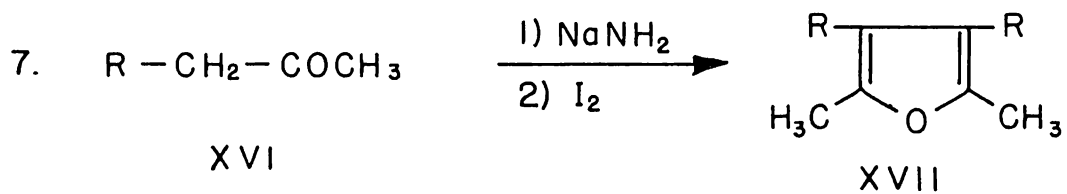
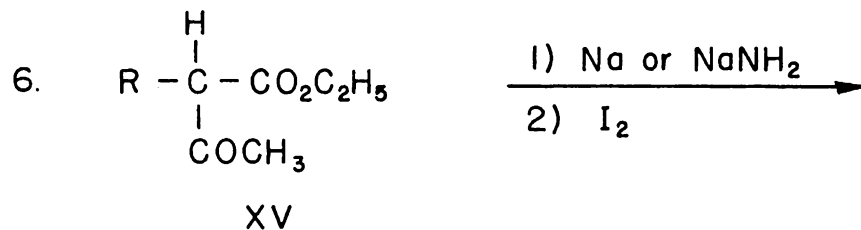
An attempt was made to prepare the disodium salt of dianisylsuccinonitrile (XII) by allowing it to react with sodamide in ether. However, the strong base removed the elements of hydrocyanic acid, and regenerated alpha-cyano-4,4'-dimethoxystilbene. This behavior of alpha-cyanodihydrostilbenes in the presence of strong base has been observed previously (18), and another instance is discussed under Reaction 5 below.

Table I

(R = *p* CH₃O C₆H₄-)

1.
$$\begin{array}{c} \text{H} \\ | \\ \text{R} - \text{C} - \text{CN} \\ | \\ \text{R} - \text{C} - \text{CN} \\ | \\ \text{H} \end{array} \xrightarrow{\text{CH}_3\text{MgI}}$$
 XII
2.
$$\begin{array}{c} \text{H} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{H} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{H} \\ | \\ \text{H} \end{array} \xrightarrow{\text{LiCH}_3}$$
 XIII
3.
$$\begin{array}{c} \text{H} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{H} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{H} \\ | \\ \text{H} \end{array} \xrightarrow{\begin{array}{l} 1) \text{PCl}_5, \text{POCl}_3 \\ 2) \text{C}_2\text{H}_5\text{O MgCH}(\text{CO}_2\text{C}_2\text{H}_5)_2 \\ 3) \text{H}^+ \end{array}}$$
4.
$$\begin{array}{c} \text{H} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{Na} \\ | \\ \text{R} - \text{C} - \text{CO}_2\text{Na} \\ | \\ \text{H} \end{array} \xrightarrow{\begin{array}{l} 1) \text{POCl}_3 \\ 2) \text{C}_2\text{H}_5\text{OMgCH}(\text{CO}_2\text{C}_2\text{H}_5)_2 \\ 3) \text{H}^+ \end{array}}$$
5.
$$\begin{array}{c} \text{CN} \\ | \\ \text{R} - \text{C} - \text{COCH}_3 \\ | \\ \text{R} - \text{C} - \text{COCH}_3 \\ | \\ \text{CN} \end{array} \xrightarrow{\text{H}^+ \text{ or } \text{OH}^-}$$
 XIV

Table I, Cont.



Reaction 2.

Dianisylsuccinonitrile can be hydrolyzed according to the procedure of Hunter and Korman (19) to the acid XIII, which is identical with that prepared by a different route (20). The meso isomer of the nitrile was used for hydrolysis, which appeared to give a mixture of acids but from which only one form was isolated.

The reaction of free acids with methylolithium has been used with considerable success for the preparation of methyl ketones (21,22). For example, it succeeded admirably in the present work in the preparation of a small amount of anisyl acetone from anisylacetic acid, the yield being quantitative. However, it failed completely with XIII, the acid having been recovered unchanged.

Reactions 3 and 4.

Each of these reactions depends on the successful preparation of the acid chloride. Three methods were tried: 1. using thionyl chloride in benzene; 2. using phosphorus pentachloride in phosphorus oxychloride; 3. using the sodium salt of the acid and phosphorus oxychloride in benzene. No attempt was made to isolate the acid chloride, but it was used immediately in subsequent reactions. On working up the reaction mixture in the usual manner, no identifiable ketonic material was obtained.

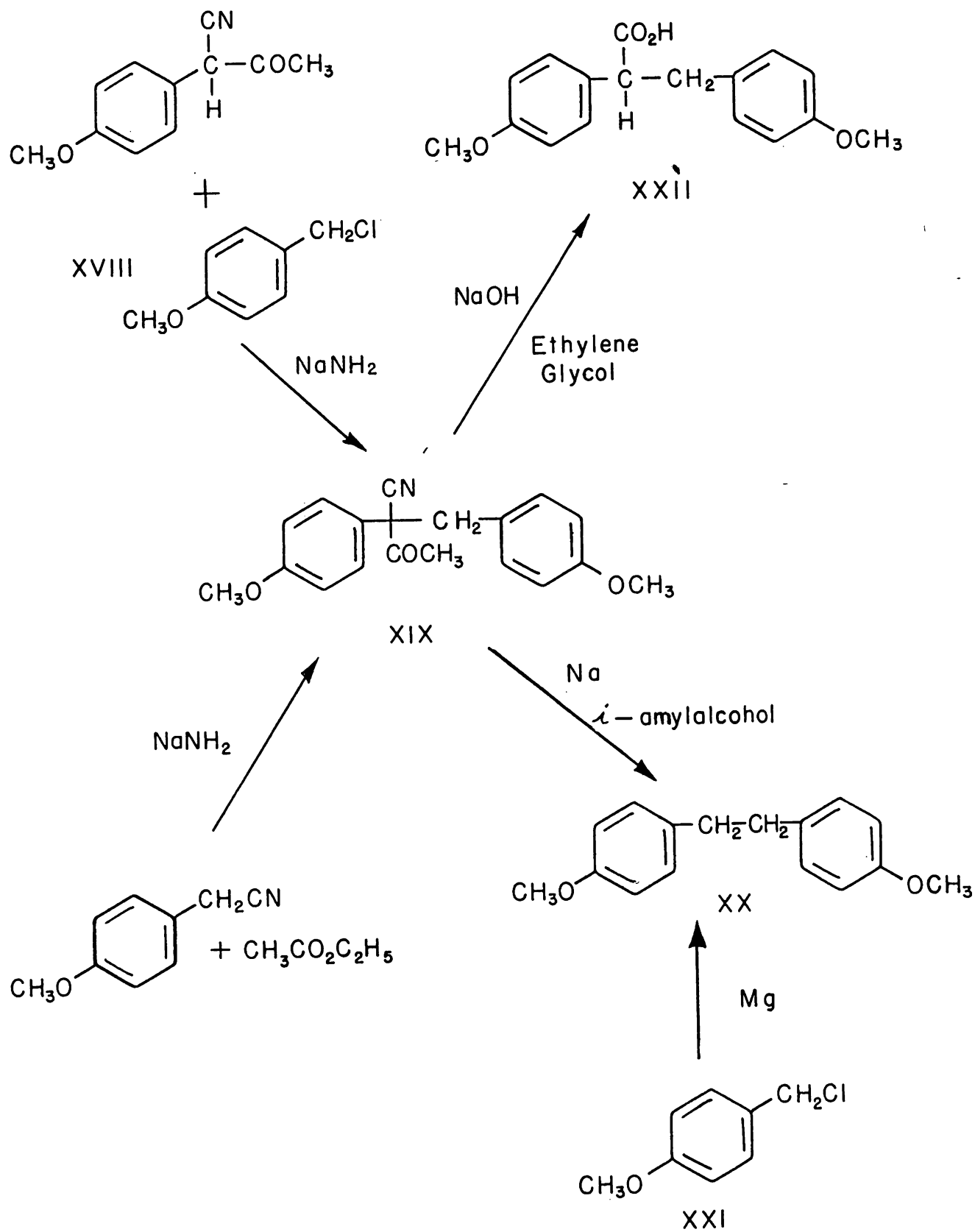
Reaction 5.

The starting material (XIV) for this reaction was prepared by the action of iodine on the sodium salt of 1-cyano-1-anisylacetone (XVIII, p. 13) (22). The reaction proceeded smoothly to give XIV in yields of 80%. Treatment of XIV with sodium hydroxide in ethylene glycol-water solution resulted in the loss of both acetyl groups and the formation of dianisylsuccinic acid (XIII). Acid hydrolysis produced either no change when the acid was dilute or intractable tars when the acid was more concentrated.

1-Cyano-1-anisylacetone (XVIII), needed for the preparation of XIV, was prepared by condensation of homoanisonitrile with ethyl acetate in the presence of a basic catalyst. When this catalyst was sodium ethoxide (23) no difficulty was encountered and excellent yields of XVIII were obtained. However when sodamide was used as the catalyst two products were obtained, one of which was XVIII and the other a material whose structure was proved to be XIX, derived presumably from XVIII and unchanged homoanisonitrile.

Treatment of XIX with sodium and isoamyl alcohol removed both the cyano and the acetyl groups, and produced 1,2-dianisylethane (XX), identified by mixed melting point with an authentic sample prepared from homoanisylchloride (XXI) and magnesium (24).

Refluxing XIX in sodium hydroxide-ethylene glycol solution also caused the loss of the acetyl group as well as hydrolysis of the nitrile group to the acid, the product being 2,3-dianisylpropionic



acid (XXII).

Refluxing XIX in aqueous alcoholic potassium hydroxide solution gave a neutral compound which contains no nitrogen, nor does it react with ketone reagents. Its structure is unknown.

An unequivocal synthesis of XIX from homoanisylchloride (XXI) and 1-cyano-1-anisylacetone (XVIII) proves conclusively that its structure is the one proposed.

Reaction 6.

This reaction was proposed because of the successful use of unsubstituted acetoacetic ester in the same type of reaction (22) and because of the ease of preparation of XIV, p. 9. However in this case only the unchanged anisylacetoacetic ester (XV) was recovered.

Reaction 7.

The hydrogen in the benzyl position of anisyl acetone should be fairly acidic, and might be expected to form the sodium salt when treated with sodamide. This proved to be the case and reaction with iodine proceeded in the expected manner to join the two molecules. Undoubtedly the desired XI, p. 5, formed; however the product could be purified only by distillation, and it did not then react with ketone reagents. During the distillation, just before the main product distilled, there was evolved a low-boiling material which condensed in large part in the cold trap and appeared to be water. When the evolution of this material had ceased, the main product distilled smoothly. This product is apparently the furan, XVII, p. 10,

for the reasons cited above . In addition, the calculated micro-analytical figures agree with those found.

Reaction 8.

Preformed 1-bromo-1-anisylacetone was then allowed to react with the sodium salt of anisylacetone. Again the expected reaction undoubtedly took place, but it appeared to be followed by loss of water during distillation and by cyclization apparently to the same furan, XVII.

Reaction 9.

No identifiable product could be obtained from this reaction.

Reaction 10.

3,4-Diphenyl-2,5-hexanedione may be prepared by treating phenylacetone with acetyl peroxide (25). However when anisylacetone was so treated only a very small amount of a high-melting product was obtained, and it was not characterized.

Since the only product obtained in appreciable yield from all these reactions was apparently the furan (XVII), the approach to the synthesis of 3,4-dianisyl-2,5-hexanedione was abandoned, and attention was concentrated on the synthesis of compounds III and IV, p. 2, which appeared to be considerably more promising.

PART A

EXPERIMENTAL 1, 2

Homoanisonitrile

Hydrogen chloride from a commercial cylinder was passed through a solution (contained in a two-liter separatory funnel) of 330 g. of anisic alcohol (Givaudan-Delawanna, without further purification) in one liter of benzene for one and one-half hours. The concentrated hydrochloric acid which separated was removed, and the benzene solution was washed with water and then with saturated sodium bicarbonate solution until the washings were no longer acidic. The benzene solution, without further treatment, was then added slowly to a boiling solution of 453 g. of sodium cyanide in 830 ml. of water. Stirring by means of a Hershberg stirrer was rapid enough to cause emulsification. The mixture was refluxed for five hours, cooled, and the layers separated. The aqueous layer was washed with ether and the ether combined with the benzene layer. The solvents were removed by distillation, and when the distillate was no longer cloudy the solution was filtered from the precipitated salt and subjected to vacuum distillation. The homoanisylcyanide distilled

1. Microanalyses were carried out by Mr. C. M. Beazley, Skokie, Illinois.
2. All melting points were taken on a Fisher-Johns apparatus.

at 92-95° (0.2mm.); it amounted to 289 g., a yield from the alcohol of 82.5%. It was satisfactory for use in condensations with substituted benzaldehydes without further purification.

Dianisylsuccinonitrile (XII, p. 9) (17)

This compound was prepared by a modification of the procedure used by Lapworth (16) for the preparation of alpha-phenyl-beta-cyanodihydrocinnamic acid.

To a boiling solution of 26.7 g. (0.10 mole) of 4,4'-dimethoxy-alpha-cyanostilbene (43,15) in 600 ml. of 95% ethanol was added a solution of 36.46 g. (0.18 mole) of potassium cyanide in 90 ml. of water. The solution was stirred under reflux for two hours, during which time a fine white solid precipitated. After two hours, the solid dianisylsuccinonitrile (XII) was collected by filtration, (13 g., 45%). The filtrate was acidified with a solution of 20 g. of glacial acetic acid in 60 ml. of water. The combined filtrates from several runs were evaporated to dryness under reduced pressure leaving a dark-colored mass, which upon solution in boiling acetic acid and cooling deposited more of the succinonitrile. In this manner a total of 91 g. (85%) of dianisylsuccinonitrile (XII) was obtained from 133.5 g. of 4,4'-dimethoxy-alpha-cyanostilbene.

The melting point of the crude colorless dianisylsuccinonitrile varied from 220 to 230°, but recrystallization from glacial acetic acid raised the melting point to 245-246°. Repeated fractional crystallization from ethanol of a sample of the material melting at 230° gave finally a small amount of a compound melting at 196-197°,

which has the same empirical formula as the higher melting compound. By analogy with the work of Chalanay and Knoevenagel (27) on diphenylsuccinonitrile, the meso configuration was assigned to the higher melting compound.

Anal. Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.89; H, 5.52.

Found: (meso) C, 73.80; H, 5.73.

(dl) C, 74.00; H, 5.35.

4,4'-Dimethoxy-alpha-cyanostilbene from dianisylsuccinonitrile.

To a suspension of 23.4 g. (0.6 mole) of sodamide in 200 ml. of dry ether was added 44.2 g. (0.15 mole) of meso-dianisylsuccinonitrile. The suspension was refluxed for four hours, and then poured onto 100 g. of ice, after which the mixture was acidified with concentrated hydrochloric acid. The solid was removed by filtration; it amounted to 24 g. A further 12 g. was obtained by evaporation of the ether layer. Recrystallization of the combined solids from ethanol or ethyl acetate gave 9 g. of recovered starting material insoluble in either solvent and 27 g. (60%) of 4,4'-dimethoxy-alpha-cyanostilbene, m.p. 107-108°. Reported 107-108° (26). Mixed melting point with an authentic sample showed no depression.

1-Cyano-1-anisylacetone (XVIII, p. 13).

a. Using sodium ethoxide as catalyst.

The procedure of Organic Syntheses (28) for the preparation of alpha-phenylacetoacetonitrile was followed. From 74 g. (0.5 mole) of homoanisylcyanide there was obtained 44 g. of

recovered homoanisylcyanide and 73 g. (77.5%) of crude 1-cyano-1-anisylacetone isolated by ether extraction. It may be purified by recrystallization from methanol or by distillation as described under b.

b. Using sodamide as catalyst.

To a stirred suspension of 46.8 g. (1.2 mole) of sodamide in 100 ml. of boiling anhydrous ether contained in a one-liter three-necked flask equipped with a condenser protected by a drying tube filled with absorbent cotton, a stirrer, and a dropping funnel was added a solution of 88.8 g. (0.6 mole) of homoanisylcyanide in 100 ml. of anhydrous ether. The suspension was boiled under reflux for one hour and then a solution of 105.6 g. (1.2 mole) of ethyl acetate (purified by distillation from phosphoric anhydride) in 100 ml. of anhydrous ether was added. The suspension was boiled under reflux with stirring for an additional two hours. It was cooled to room temperature, poured onto 200 g. of ice and acidified with concentrated hydrochloric acid. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined ether layers were washed with water and dried over calcium chloride. The solvent was removed by distillation and the residue was subjected to distillation at a pressure of 2 mm. Three fractions were obtained - a forerun boiling at 122°, which was recovered homoanisylcyanide (10 g.); a middle fraction boiling at 164-165° (57 g., 51%), which was 1-cyano-1-anisylacetone (XVIII, p. 13); and a third fraction (15 g.) boiling above 174°, which was identified as 1-cyano-1-anisyl-1-homoanisylacetone (XIX).

The middle fraction, b. p. 164-165° (2 mm.), solidified in the receiver and on recrystallization from methanol, melted at 86-87°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 70.00; H, 5.87.

Found: C, 70.03; H, 5.83.

The 2,4-dinitrophenylhydrazone of XVIII was prepared, m. p. 173-174°, after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{15}O_5N_5$: C, 55.14; H, 4.07.

Found: C, 54.88; H, 4.09.

The third fraction, boiling above 174° (2mm.) also solidified, m. p. 116-117°, after recrystallization from methanol. This is 1-cyano-1-anisyl-1-homoanisylacetone (XIX).

Anal. Calcd. for $C_{19}H_{19}O_3N$: C, 73.80; H, 6.19.

Found: C, 73.84; H, 6.10.

1-Cyano-1-anisyl-1-homoanisylacetone (XIX).

To a boiling suspension of 2.26 g. (0.058 mole) of sodamide in anhydrous ether was added 11 g. (0.058 mole) of 1-cyano-1-anisylacetone (XVIII). When no more ammonia was evolved a solution of 9.1 g. (0.058 mole) of homoanisylchloride (XXI) was added and the mixture refluxed for one hour. Water was then added to dissolve the precipitated sodium chloride and the layers were separated. The ether layer was dried and evaporated to leave 11 g. of solid, m. p. 104-108°. Recrystallization from ethanol raised the melting point to 116-117° and there was no depression when mixed with 1-cyano-1-anisyl-1-homoanisylacetone described above.

1,2-Dianisylethane (XX).

To a solution of 3.0 g. (0.014 mole) of 1-cyano-1-anisyl-1-homoanisylacetone (XVIII) in 60 ml. of boiling iso-amyl alcohol was added 2.65 g. (0.015 mole) of metallic sodium in small pieces. The mixture was refluxed for one hour after all the sodium had been added and then poured into water and filtered. There remained on the funnel one gram of white solid, m. p. 125-126°. Recrystallization from ethanol raised the melting point to 127-128°. (Reported m. p. 125° (24)). There was no depression when mixed with a sample of 1,2-dianisylethane prepared from homoanisylchloride by the action of magnesium in ether solution (24).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.00; H, 7.50.

Found: C, 79.08; H, 7.56.

2,3-Dianisylpropionic acid (XXII).

A mixture of 5.0 g. (0.024 mole) of 1-cyano-1-anisyl-1-homoanisylacetone, 3.5 g. of sodium hydroxide in 4 ml. of water, and 40 ml. of ethylene glycol was refluxed for thirty-six hours. The solution was diluted with twice its volume of water and acidified. The acid which separated was removed by filtration (3.0 g.), m.p. 126.5-127°, after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.40; H, 6.33.

Found: C, 71.34; H, 6.40.

When a solution 5.0 g. of 1-cyano-1-anisyl-1-homoanisylacetone and 3.5 g. of potassium hydroxide in 4.0 ml. of water and 100 ml. of

ethanol was refluxed for three days and then cooled, a solid precipitated which was removed by filtration (3.0 g.). Two recrystallizations from ethanol and one from ethyl acetate gave a colorless solid which melted at 188-189°. It did not react with 2,4-dinitrophenylhydrazine, nor did it contain nitrogen. Ammonia was not evolved during the refluxing period.

Anal. Found: C, 71.40; H, 6.82.

Acidification of the basic filtrate and extraction with ether resulted in the recovery of 2.0 g. of unchanged 1-cyano-1-anisyl-1-homoanisylacetone.

3,4-Dicyano-3,4-dianisyl-2,5-hexanedione (XIV, p. 9.).

To a suspension of 4.3 g. (0.11 mole) of sodamide in 100 ml. of dry benzene contained in a one-liter three-necked flask equipped with a stirrer, a condenser and a dropping funnel, was added a solution of 10 g. (0.05 mole) of 1-cyano-1-anisylacetone in 100 ml. of dry benzene. The suspension was refluxed until the evolution of ammonia had ceased (about seven hours). The suspension was allowed to cool to room temperature and a solution of 9.5 g. of iodine in ether was added dropwise until the color of iodine persisted. The precipitated sodium iodide was removed by filtration and the filtrate was washed successively with water, half-saturated sodium bisulfite solution, and water. After drying and evaporating solvent there remained 9.0 g. of dark-colored solid. Recrystallization from methanol gave 8.0 g. (80%) of crystalline 3,4-dicyano-3,4-dianisyl-2,5-hexanedione (XIV), m. p. 193-193.5°.

Anal. Calcd. for $C_{22}H_{20}O_4N_2$: C, 70.02; H, 5.35.

Found: C, 70.27; H, 5.59.

Anisylacetone.

The method of Organic Syntheses (28) for the preparation of methylbenzyl ketone gave very poor yields with 1-cyano-1-anisylacetone, perhaps because of sulfonation of the nucleus. Therefore the method of Walker and Hauser was followed (29).

From 101.4 g. of anisylacetic acid - prepared by basic hydrolysis of homoanisylcyanide (30) - the acid chloride was made by the method of Wilds (31). This was added to a solution of diethyl ethoxymagnesiummalonate, prepared from 16.05 g. of magnesium, and the reaction was continued as described by Walker and Hauser (29). The yield was 65 g. (71.5% from the acid) of anisylacetone boiling at 157° (25 mm.) (Reported 142° (14mm.) (32).

The refractive index after redistillation was n_D^{20} 1.5246.

Reported: n_D^{20} 1.5253. (32).

The semicarbazone of anisylacetone was prepared, m. p. 170-170.5°. Reported: 169° (33); 175° (32).

2,5-Dimethyl-3,4-dianisylfuran (XVII, p. 10).

a. From anisylacetone alone.

To a boiling suspension of 4.3 g. (0.11 mole) of sodamide in 50 ml. of anhydrous ether contained in a 500 ml. three-necked flask equipped with a stirrer, a dropping funnel, and a condenser protected with a drying tube filled with absorbent cotton, was

added a solution of 16 g. (0.105 mole) of anisylacetone in 100 ml. of anhydrous ether. After four hours, ammonia was no longer evolved and a solution of 12.7 g. of iodine in 250 ml. of anhydrous ether was added dropwise to the warm solution. The sodium iodide (15 g., 0.10 mole) was removed by filtration and the solvent evaporated from the filtrate to leave 17 g. of dark viscous oil. A few milliliters of ethanol was added to the oil. After it had stood overnight the solution deposited 0.4 g. of crystalline solid, m. p. 197-201°. It is thought that this may be 3,4-dianisyl-2,5-hexanedione (XI, p. 5) but its structure was not proved.

The filtrate was dissolved in ether, washed first with water, then with half-saturated sodium bisulfite solution and finally with water. After drying and evaporating the solvent, the residue was subjected to distillation under reduced pressure during which some decomposition (evolution of water?) took place. There was obtained 2 g. of unchanged anisyl acetone, b. p. 96° (0.5 mm.) and 4.5 g. (30%) of 2,5-dimethyl-3,4-dianisyl-furan, b. p. 240-243° (1.5 mm.). Upon recrystallization from methanol this melted at 135-135.5°.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.92; H, 6.55.

Found: C, 77.75; H, 6.50.

b. From anisylacetone and 1-bromo-1-anisylacetone.

To a suspension in 100 ml. of anhydrous ether of the sodium salt of anisylacetone (prepared from 15.2 g. 0.1 mole, of anisylacetone and 4.3 g. of sodamide) was added an ether solution

of 1-bromo-1-anisylacetone (prepared from 15.2 g., 0.1 mole, of anisylacetone (34, 35, 36) at such a rate that gentle refluxing was maintained. The suspension was refluxed for one-half hour and water was then added to dissolve the precipitated sodium bromide. The layers were separated, and the ether layer was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide and water, and then dried over calcium chloride. The solvent was evaporated to leave 28 g. of dark viscous oil. Distillation of this oil gave 9 g. of unreacted anisylacetone and 7.5 g. (48.7%) of 2,5-dimethyl-3,4-dianisylfuran, identical with the material prepared in a.

Anisylacetoacetic ester (XV, p. 10.

A solution of 1-cyano-1-anisylacetone (85.6 g., 0.4 mole) in 1500 ml. of absolute ethanol was saturated with hydrogen chloride at 0° and allowed to stand overnight at room temperature. The alcohol was removed under reduced pressure and the residue dissolved in 500 ml. of 95% ethanol. After heating for one hour on the steam bath, the alcohol was removed by evaporation in a current of air. The residue was dissolved in ether and washed with water and 10% sodium bicarbonate solution. After drying over calcium chloride the solvent was evaporated and the residue distilled. There was obtained 29 g. (47.5%) of anisylacetone, b. p. 88-95° (0.5 mm.), and 33 g. (36.4%) of anisylacetoacetic ester, b. p. 120-121° (0.5 mm.), m. p. after recrystallization from Skellysolve A, 66.5-67°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.83.

Found: C, 65.93; H, 6.72.

Hydrolysis of XV with dilute alcoholic-aqueous hydrochloric acid gave a ketone whose semicarbazone melted at 175-176°. A mixed melting point with anisylacetone semicarbazone showed no depression.

When a benzene solution of XV was allowed to react with metallic sodium and then treated with iodine, as described under the preparation of 3,4-dicyano-3,4-dianisyl-2,5-hexanedione (XIV, p. 22), no reaction took place and the ester was recovered unchanged.

PART B

DISCUSSION OF RESULTS

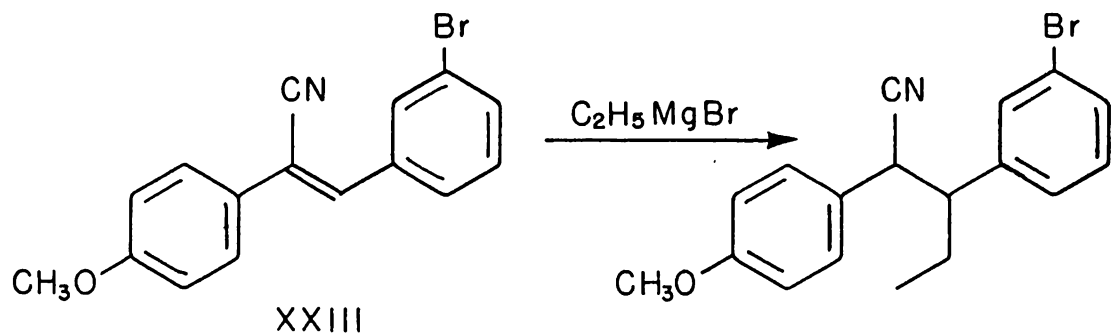
The ultimate goal of this phase of research was to be II, p. 2. The scheme followed for the synthesis of this compound is indicated in the flow-sheet on pp. 29 and 30. The reactions were carried out as indicated as far as XXXI, but synthetic difficulties resulting in low yields of key intermediates have prevented a successful culmination of this approach. Preliminary experiments have been carried out which have led to a compound thought to be XXXIV, but insufficient material was obtained for complete characterization.

1. Synthesis of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valero-nitrile (XXIV, p. 29).

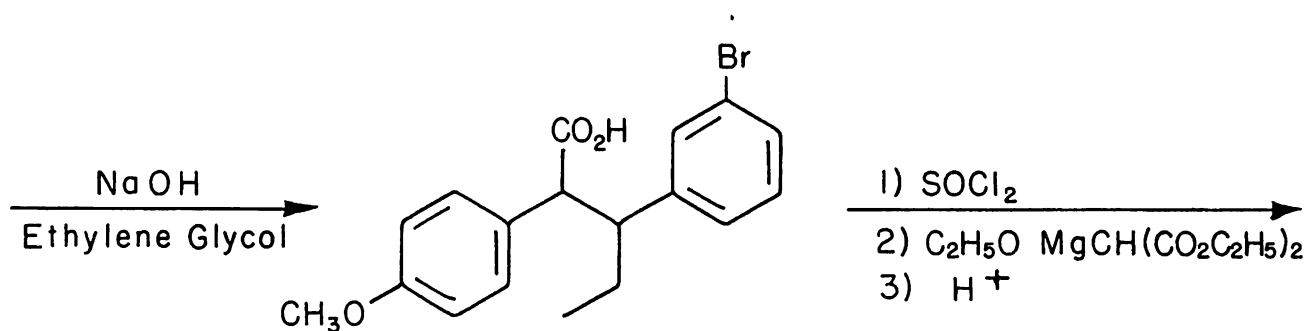
This compound was prepared by the general method of Kohler (40) and was obtained in two modifications corresponding to the two dl pairs to be expected due to the asymmetry about carbons 2 and 3. Generally, equal amounts of each isomer were obtained.

2. Synthesis of 3-(4-methoxyphenyl)-4-(3-bromophenyl)-2-hexanone (XXVI).

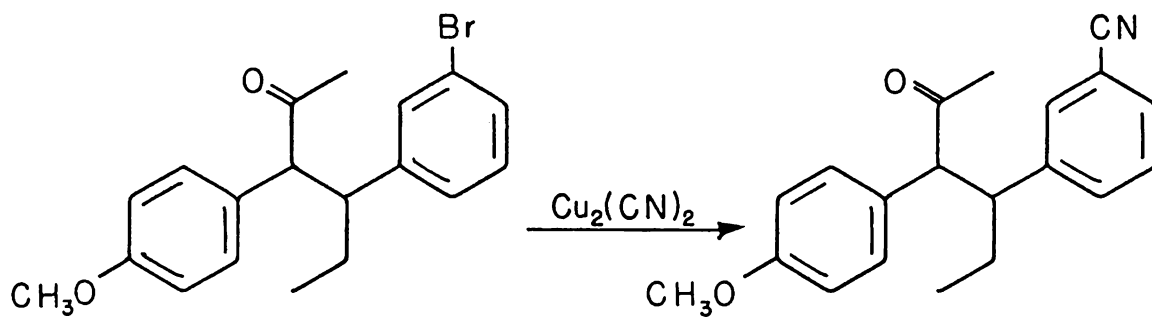
The method of preparing methyl ketones from nitriles, by reaction of the nitrile with methylmagnesium iodide (40), while quite successful in the case of the higher-melting isomer of alpha, beta-bis-(p-methoxyphenyl)-valeronitrile (15), failed completely in the present instance with either isomer of XXIV. Failure was caused perhaps by the more highly hindered character of the nitrile group. This highly hindered character is also reflected in the fact that basic hydrolysis of XXIV to the acid (XXV) was much slower than was the case with alpha-beta-bis-(p-methoxyphenyl)-valeronitrile. As much as three days was necessary for complete hydrolysis of XXIV. From either isomer of the nitrile (XXIV) a mixture of two isomers (XXV a and b) of the acid was obtained. These were separated by fractional crystallization. However, repeated recrystallization of XXVb from Skellysolve B or benzene converted it to XXVa.



a, m.p. 111 - 113°
b, liq.

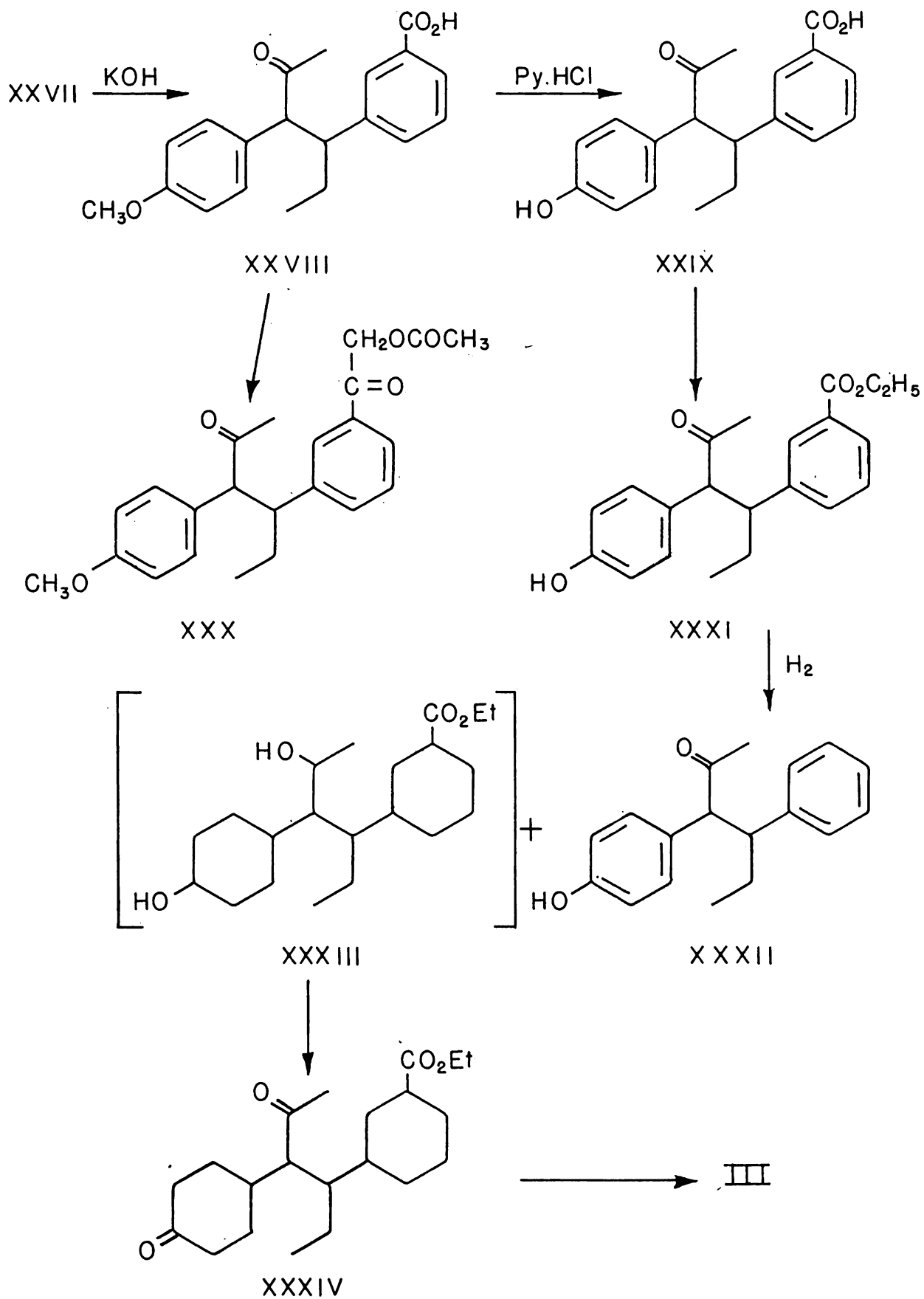


a, m.p. 149-151°
b, m.p. 123-124°



a, m.p. 105-106°
b, liq.

XXVII



The reaction between methyllithium and the free acid, which in some cases (21) results in the formation of the methyl ketone, failed with both XXV a and b. Therefore each isomer of the acid was converted, via the acid chloride and diethyl ethoxymagnesium malonate (29), to a mixture of isomers of the ketone (XXVI), one of which is a solid (XXVIa) and the other a high-boiling liquid (XXVIb).

3. Synthesis of 3-(4-methoxyphenyl)-4-(3-cyanophenyl)-2-hexanone (XXVII).

The conversion of the bromide (XXVI) to the cyanide (XXVII) was effected in good yield by the use of cuprous cyanide in quinoline (9, 15, 37, 38). Only one isomer of the cyanide was obtained from either isomer of the bromide. It is a high-boiling liquid and was purified by distillation.

When it was discovered that only one isomer of the cyanide (XXVII) was obtained, the possibility of using the crude mixtures of isomers in previous reactions was investigated. It was ascertained that all the reactions could be carried out on crude materials, without decreasing the overall yield nor increasing insuperably the difficulty of purification of the product, XXIX.

4. Synthesis of 3-(4-hydroxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXIX, p. 30).

This compound may be prepared from XXVII in two ways: one involves two steps - hydrolysis of the cyano group with

aqueous-alcoholic potassium hydroxide, followed by demethylation of the resulting acid by heating with pyridine hydrochloride; the second in one step by heating XXVII with pyridine hydrochloride containing a trace of water, when demethylation and hydrolysis take place simultaneously. However, the yield in the one step preparation is considerably less than in the two step preparation.

The carboxyl group in XXIX reacts normally - thus, for example, the ester may be formed readily by refluxing with ethanol and sulfuric or hydrochloric acid - but the phenolic hydroxyl is unusual in that it was impossible to form the acetate derivative, even by refluxing for several hours in pyridine solution with acetic anhydride.

5. Synthesis of 3-(4-methoxyphenyl)-4-(3-acetoxyacetylphenyl)-2-hexanone (XXX).

This compound bears the ketol grouping characteristic of cortisone, and also contains the keto group in a position which may be considered to correspond to the 11-keto group in cortisone (I, p. 2). This similarity is further indicated by the lack of reactivity of the keto group to carbonyl reagents in XXVI, XXVII, XXVIII and XXIX. The 11-keto group in cortisone (I) is also unreactive to ketone reagents (19). XXX was prepared from the acid (XXVII) via the acid chloride and the diazoketone. The ketol acetate was prepared directly from the diazoketone by reaction with acetic acid, in 57% overall yield from the acid (39).

6. Synthesis of 3-(4-oxocyclohexyl)-4-(3-carbethoxy-cyclohexyl)-2-hexanone (XXXIV).

This compound was to be prepared by high-pressure hydrogenation of XXXI, followed by oxidation of the resulting alcohol (XXXIII). XXXIII was not purified because the hydrogenation introduced two asymmetric centers, which were then removed by subsequent oxidation. Thus, from a single substance (XXXI) only one compound (XXXIV) was formed.

A few preliminary experiments have been made on this series of reactions and there appears to be considerable difficulty; whether it is in the hydrogenation or the oxidation is not known with certainty. A pure sample of XXXIV has not yet been isolated. However, it is known with certainty that if the hydrogenation is carried out at 190° or above, decarboxylation of XXXI takes place without reduction and XXXII may be isolated from the reaction mixture. This compound (XXXII) was prepared previously by Satriana and co-workers (13).

The preparation of adequate amounts of pure XXXIV would reasonably point toward its successful conversion to III. It would involve replacement of the carbethoxy group by the ketolacetate group as in the preparation of XXX, from XXVIII. Then, the quaternary hydroxyl at ring D might be introduced by formation of the enol acetate, treatment of the enol acetate with a per acid, then hydrolysis of the epoxide so formed (45). The double bond of

ring A might be introduced by bromination followed by dehydrobromination (45).

PART B

EXPERIMENTAL 1, 2

alpha-(4-methoxyphenyl)-3-bromocinnamotrile (XXIII, p. 29)

The procedure employed by Kohler (40) for the preparation of diphenylacrylonitrile was followed. Five milliliters of a 50% solution of potassium hydroxide in water (this proved to be just as effective and easier to prepare than the sodium ethoxide solution used by Kohler) was added to a well-stirred solution of 44 g. (0.3 mole) of homoanisylcyanide and 55.5 g. (0.3 mole) of m-bromobenzaldehyde (41) in 100 ml. of ethanol. About one-half hour after the potassium hydroxide solution was added the solid alpha-(4-methoxyphenyl)-3-bromocinnamotrile began to separate out. The mixture was allowed to stand for three hours and then filtered. The yellow solid was washed first with water and then with a small amount of cold alcohol. Recrystallization from ethanol yielded 70 g. (74%) of alpha-(4-methoxyphenyl)-3-bromocinnamotrile (XXIII), m. p. 93-94° (26).

1. Microanalyses by Mr. C. M. Beazley, Skokie, Ill.
2. All melting points were taken on a Fisher-Johns apparatus.

2-(4-Methoxyphenyl)-3-(3-bromophenyl)-valeronitrile (XXIV)

The procedure employed by Kohler for the preparation of diphenylvaleronitrile was followed here (40). In a 500-ml. three-necked flask, equipped with a stirrer, a dropping funnel and a reflux condenser and protected by a drying tube filled with absorbent cotton, were placed 4.8 g. of magnesium and 100 ml. of anhydrous ether. A solution of 24 g. of ethyl bromide in 100 ml. of anhydrous ether was added slowly with stirring. After all of the ethyl bromide had been added the mixture was refluxed for an additional fifteen minutes. Thirty-one and four tenths grams (0.1 mole) of alpha-(4-methoxyphenyl)-3-bromocinnamionitrile was then added in small portions from a 250 ml. Erlenmeyer flask connected to the reaction flask by means of a short piece of rubber tubing of large diameter. The dark-brown solution was refluxed for an additional three hours. The clear light-brown solution was poured with stirring into a mixture of ice and 200 ml. of concentrated hydrochloric acid. The layers were separated and the aqueous layer was extracted with ether. The extract was combined with the ether layer and the ether was removed by distillation. The remaining solid was recrystallized from ethanol. There was obtained 20 g. of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeronitrile (XXIVa), m. p. 111-113°. Reported, m. p. 111-113° (26).

The alcohol was removed from the filtrate and the residue distilled to yield 10 g. of the second isomer (XXIVb), b. p. 215° (2 mm.). Reported 215° (2 mm.) (26).

When a total of 159.1 g. of alpha-(4-methoxyphenyl)-3-bromocinnamionitrile was treated as above, there was obtained 68 g.

of the solid isomer (XXIVa) and 67 g. of the liquid isomer (XXIVb), a total of 135 g. (77%).

2-(4-Methoxyphenyl)-3-(3-bromophenyl)-valeric acid (XXV).

The procedure of Hunter and Korman was followed (19). A mixture of 34.42 g. (0.10 mole) of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeronitrile (XXIVa), 25.8 g. of sodium hydroxide, 516 ml. of ethylene glycol, and 43 ml. of water was refluxed until no more ammonia was evolved (about seventy-two hours). The solution was then diluted with one liter of water and filtered. The filtrate was acidified by pouring in a thin stream into a mixture of concentrated hydrochloric acid and ice, and the precipitated acid was removed by filtration and recrystallized from ethanol-water, after treatment with animal charcoal to remove colored impurities. There was obtained 8 g. (22%) of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeric acid (XXVa), m. p. 140-150°. Further recrystallization from ethanol-water raised the melting point to 149-151°.

Anal. Calcd. for $C_{18}H_{19}BrO_3$: C, 59.51; H, 5.27.

Found: C, 59.83; H, 5.39.

Evaporation to dryness of the filtrate from the recrystallization left an oil which solidified upon trituration with Skellysolve A to a white solid, m. p. 124-125°. (23.0 g., 63.5%). Recrystallization from methanol-water gave a crystalline solid, m. p. 123-124° (XXVb).

Anal. Calcd. C, 59.51; H, 5.27.

Found: C, 59.82; H, 5.73.

When this material (XXVb) was further recrystallized from benzene or Skellysolve B, the crystals took several days to deposit and the melting point rose to 144-145°. Evidently the lower-melting isomer (XXVb) is easily changed to the higher-melting form (XXVa).

From the liquid isomer of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeronitrile (XXIVb), the same two acids were obtained in about the same proportions.

3-(4-Methoxyphenyl)-4-(3-bromophenyl)-2-hexanone (XXVI).

The method of Walker and Hauser (29) for the preparation of methyl ketones was used with the modification that the absolute ethanol was added all at once. To 1.92 g. of magnesium in a 500-ml. three-necked flask, equipped with a stirrer, a dropping funnel, and a condenser, and protected by a drying tube filled with absorbent cotton, was added all at once a mixture of 12.2 ml. of absolute ethanol, and 0.5 ml. of carbon tetrachloride. The reaction was allowed to proceed for about ten minutes and then a solution of 17.3 g. (16.4 ml., 0.11 mole) of diethyl malonate in 100 ml. of anhydrous ether was added at such a rate as to maintain gentle refluxing. When all had been added, the solution was clear. To this solution was added an ether solution of the acid chloride (prepared from 23 g. (0.075 mole) of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeric acid (XXVa) by allowing it to react with 15 ml. of thionyl chloride in 100 ml. of benzene. Reaction was

catalyzed by a drop of pyridine). The solution was allowed to reflux for one-half hour after all the acid chloride had been added; it was then acidified with cooling by means of dilute sulfuric acid. The layers were separated and the solvent removed from the organic layer by distillation. The residue of crude substituted diethyl malonate was hydrolyzed and decarboxylated by boiling with 23 ml. of glacial acetic acid, 3.0 ml. of concentrated sulfuric acid, and 15.5 ml. of water until no more carbon dioxide was evolved (eight hours). The solution was cooled and made alkaline, with continued cooling in an ice-bath, by means of 40% sodium hydroxide solution. The layers were separated, the aqueous layer was washed once with ether, and the washings were combined with the organic layer. The solution was then dried over calcium chloride and the solvent was evaporated to leave 21.5 g. of crude ketone. Recrystallization from ethanol gave 10 g. (45.5%) of product, m. p. 95-98°. A sample was purified for analysis by a second recrystallization from ethanol, m. p. 105-106° (XXVIa).

Anal. Calcd. for $C_{19}H_{21}BrO_2$: C, 63.16; H, 5.86.

Found: C, 63.08; H, 5.92.

Evaporation of solvent from the mother liquor and distillation of the residue gave 9 g. (37.6%) of XXVIb, b. p. 175° (0.5 mm.), n_D^{20} 1.5709.

Anal. Calcd. C, 63.16; H, 5.86.

Found: C, 63.39; H, 5.97.

When the lower-melting isomer of the acid (XXVb) was subjected to the same series of reactions, both isomers of the ketone

(XXVI a and b) were formed as above.

3-(4-Methoxyphenyl)-4-(3-cyanophenyl)-2-hexanone (XXVII).

The procedure of Hager and Burgison (9), employed by them for the preparation of 4,4'-dicyano-alpha, alpha'-diethylstilbene, was followed here. A mixture of 10 g. (0.028 mole) of 3-(4-methoxyphenyl)-4-(3-bromophenyl)-2-hexanone (XXVIa), 8.0 g. of cuprous cyanide, and 50 ml. of quinoline was refluxed for six hours. The hot liquid was then poured slowly into 600 ml. of concentrated hydrochloric acid with stirring. Three hundred milliliters of chloroform were added and the mixture was allowed to stand overnight. The layers were separated and the acid layer was extracted further with four 100 ml. portions of chloroform. The combined chloroform extracts were washed with water and the chloroform was removed by distillation. The residue was subjected to distillation at reduced pressure. There was obtained 7.0 g. (82.5%) of 3-(4-methoxyphenyl)-4-(3-cyano-phenyl)-2-hexanone (XXVII), b. p. 167° (0.02 mm.), n_D^{20} 1.5590. From XXVIb, the same liquid was produced in equal yield.

Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.14; H, 6.88.

Found: C, 77.93; H, 7.00.

3-(4-Methoxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXXVIII, p. 30)

A solution of 6.0 g. (0.019 mole) of 3-(4-methoxyphenyl)-4-(3-cyanophenyl)-2-hexanone (XXVII, p. 29), 6.0 g. of potassium hydroxide, 6.0 ml. of water, and 30 ml. of ethanol was refluxed

until no more ammonia was evolved (four to five hours). The alcohol has removed under reduced pressure and the residue taken up in water and washed with ether to remove unreacted nitrile. Acidification of the basic solution by pouring it in a thin stream into a mixture of ice and concentrated hydrochloric acid precipitated the acid (XXVIII) which was removed by filtration and amounted to 6.3 g. A sample was prepared for analysis by recrystallization from ethanol, m. p. 185-185.5°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.79.

Found: C, 73.31; H, 6.76.

3-(4-Hydroxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXIX).

A mixture of 6.3 g. (0.019 mole) of 3-(4-methoxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXVIII) and 50 g. of pyridine hydrochloride was refluxed for three hours and then poured into 500 ml. of water. The precipitated 3-(4-hydroxyphenyl)-4-(3-carboxyphenyl)-hexanone-2 (XXIX) was removed by filtration (6.0 g., 99.5%). The melting point of the crude material was 230-235°. Recrystallization from ethanol or acetone raised the melting point to 242-243°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45.

Found: C, 72.94; H, 6.67.

3-(4-Hydroxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXIX), without purification of intermediates.

From 179 g. of XXIII, p. 29, 119.2 g. of ethyl bromide, and

14.26 g. of magnesium was prepared in the manner described above 190 g. of a mixture of XXIV a and b. This mixture was isolated in the following manner: after the reaction mixture had been poured into acid it was allowed to stand overnight. The liquid was decanted from the oily mixture which had settled to the bottom of the container and extracted with ether. The ether extracts were added to the oily mixture and enough ether was added to dissolve all the organic material. The ether solution was washed with water and the ether was removed by distillation. The ether-free residue was refluxed with 154.8 g. of sodium hydroxide, 258 ml. of water, and 3000 ml. of ethylene glycol. After seventy-two hours the solution was diluted with three liters of water and allowed to stand until the oily material which separated had settled to the bottom of the container. The solution was filtered and acidified with dilute hydrochloric acid. The oily acid which precipitated was removed by extraction with benzene. The benzene solution was washed with water and the benzene removed by distillation. When the distillate was no longer cloudy the solution was filtered to remove the inorganic salts which had precipitated. The distillation was continued under reduced pressure to leave 170 g. of crude acid (XXV a and b).

The acid was redissolved in anhydrous benzene and converted to the acid chloride with 44 ml. of thionyl chloride and a drop of pyridine. The acid chloride, after evaporation of the excess thionyl chloride and the benzene, was dissolved in anhydrous ether and

added to a solution of diethyl ethoxymagnesiummalonate prepared from 12.0 g. of magnesium, 56.6 ml. of absolute ethanol, and 101 ml. of diethyl malonate. The crude ester was isolated in the usual manner and converted to the ketone by refluxing with 18.7 ml. of concentrated sulfuric acid, 98 ml. of water and enough glacial acetic acid to produce a homogeneous solution. On this large scale the reaction was complete after 12 hours. On working up the mixture as described above there was obtained 152 g. of crude ketone (XXVI a and b, p. 29).

This was converted to the cyanide (XXVII) by refluxing with 218 g. of cuprous cyanide and 1400 ml. of quinoline. (The quinoline used was Eastman Kodak Technical, purified by distillation once before use). After reaction the solution was poured into eight liters of concentrated hydrochloric acid and the product was extracted with chloroform. The crude XXVII obtained by evaporation of the chloroform after treatment with charcoal was hydrolyzed by refluxing with 129 g. of potassium hydroxide, 129 ml. of water, and 700 ml. of ethanol. The acid (XXVIII, p. 30) was isolated, after evaporation of the alcohol and dilution with water, by acidification with concentrated hydrochloric acid and extraction with chloroform in which it is more soluble than in ether. Evaporation of the chloroform left 105 g. of XXVIII, which was refluxed with 315 g. of pyridine hydrochloride. After the solution had been poured into water, 100 g. of acid (XXIX) was isolated by filtration. The melting point of the crude material was 120-130°. One recrystallization from water and two from ethanol gave 60 g. (28.2% overall), m. p. 240-242°.

3-(4-Hydroxyphenyl)-4-(3-carbethoxyphenyl)-2-hexanone (XXXI).

A solution of 14 g. (0.045 mole) of 3-(4-hydroxyphenyl)-4-(3-carboxyphenyl)-2-hexanone (XXIX) in 200 ml. of absolute ethanol and 10 ml. of concentrated sulfuric acid was refluxed for eight hours. About 150 ml. of ethanol were then removed by distillation and the residue was diluted with water and extracted with ether. The ether solution was washed successively with water, saturated sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to leave 14 g. of crude ester (XXXI). Recrystallization from ethanol gave 10 g. (65%), m. p. 155-156°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.10.

Found: C, 73.69; H, 7.30.

3-(4-Methoxyphenyl)-4-(3-acetoxyacetylphenyl)-2-hexanone (XXX).

A solution in benzene of 3-(4-methoxyphenyl)-4-(3-chlorocarbonylphenyl)-2-hexanone (prepared from 5 g. (0.015 mole) of the acid (XXVIII) by reaction with thionyl chloride in benzene catalyzed by one drop of pyridine) was added to a cold solution of diazomethane in ether (prepared from 10 g. of nitrosomethylurea (42) and allowed to stand overnight at room temperature. The solvents were evaporated at the water pump without heating to leave 6.5 g. of viscous oil. To this oil was added 7.7 ml. of glacial acetic acid and the solution was warmed on the steam bath until the vigorous evolution of nitrogen had slackened somewhat, whereupon it was allowed to reflux for one-half hour. The acetic acid was removed under reduced pressure,

while heating on the steam bath, and the residue taken up in ether and washed with water and 10% sodium hydroxide solution. The ether extract was dried and evaporated to leave 5.5 g. of viscous oil. Distillation gave 3.0 g. (57%) of 3-(4-methoxyphenyl)-4-(3-acetoxyacetylphenyl)-2-hexanone, b. p. 162-165° (0.01 mm.), m. p. after recrystallization from ethanol, 98-100°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85.

Found: C, 72.35; H, 7.05.

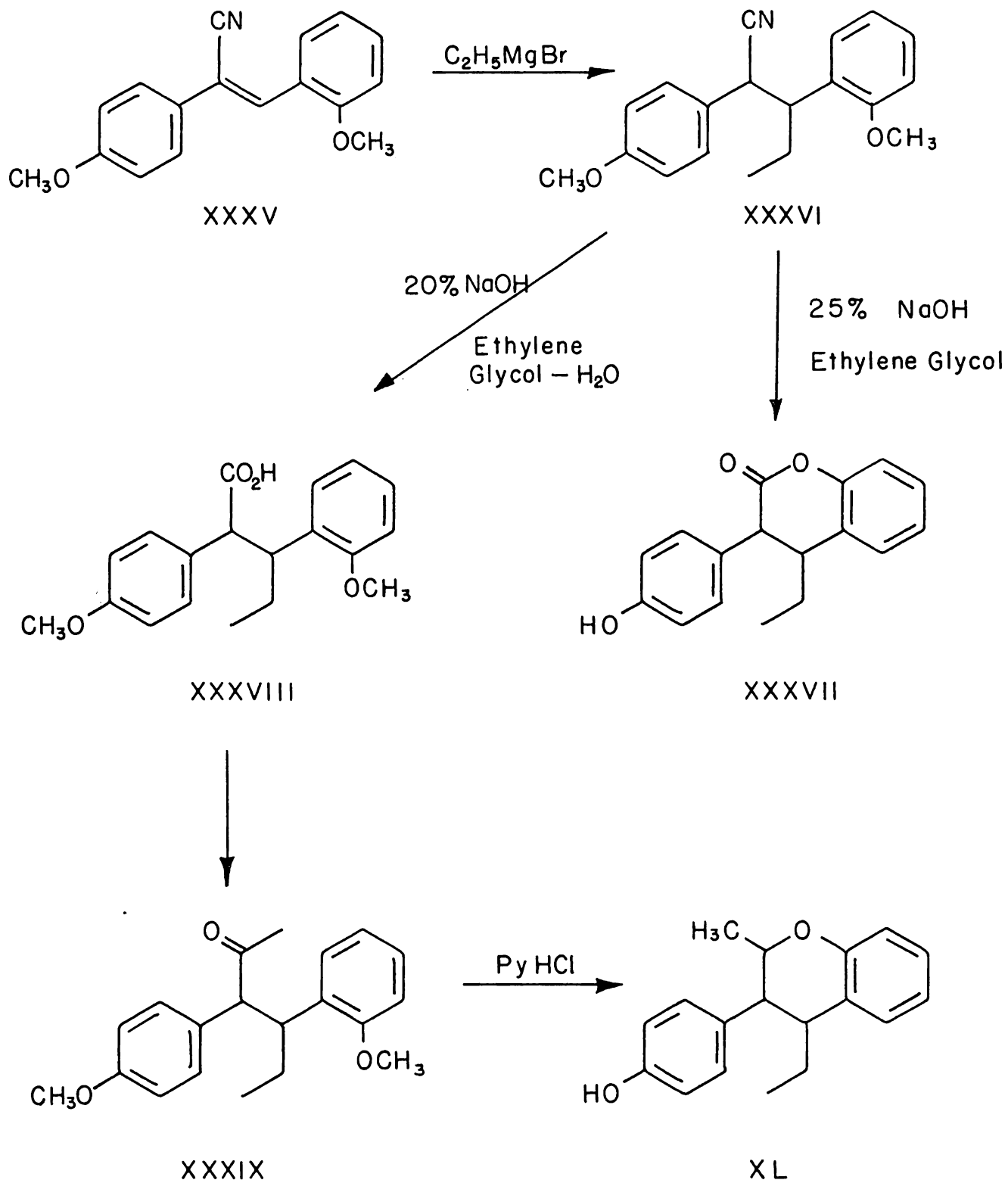
PART C

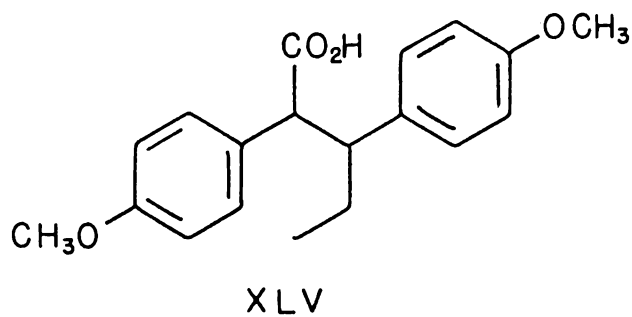
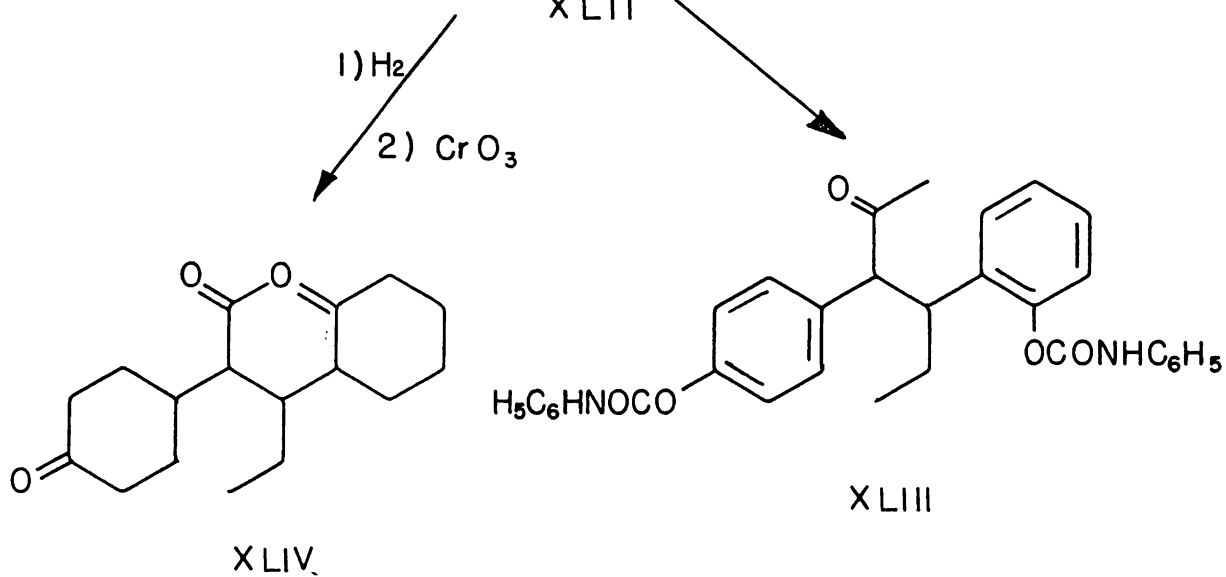
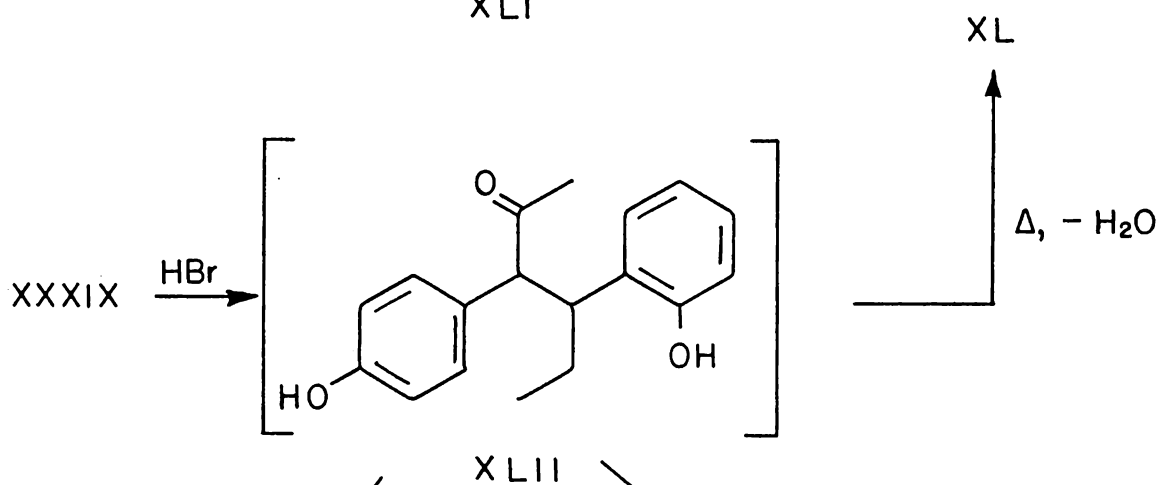
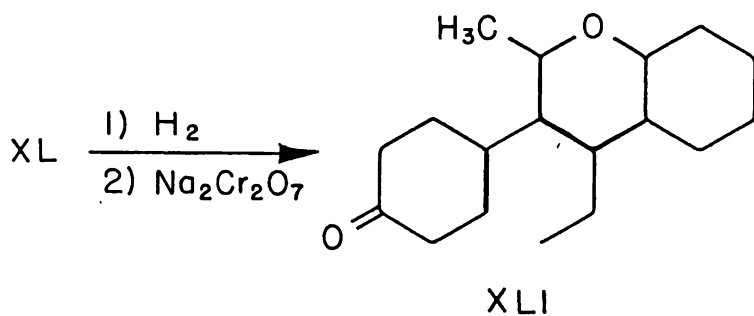
DISCUSSION OF RESULTS

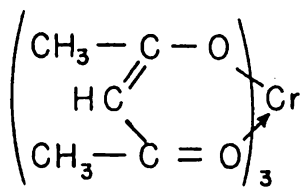
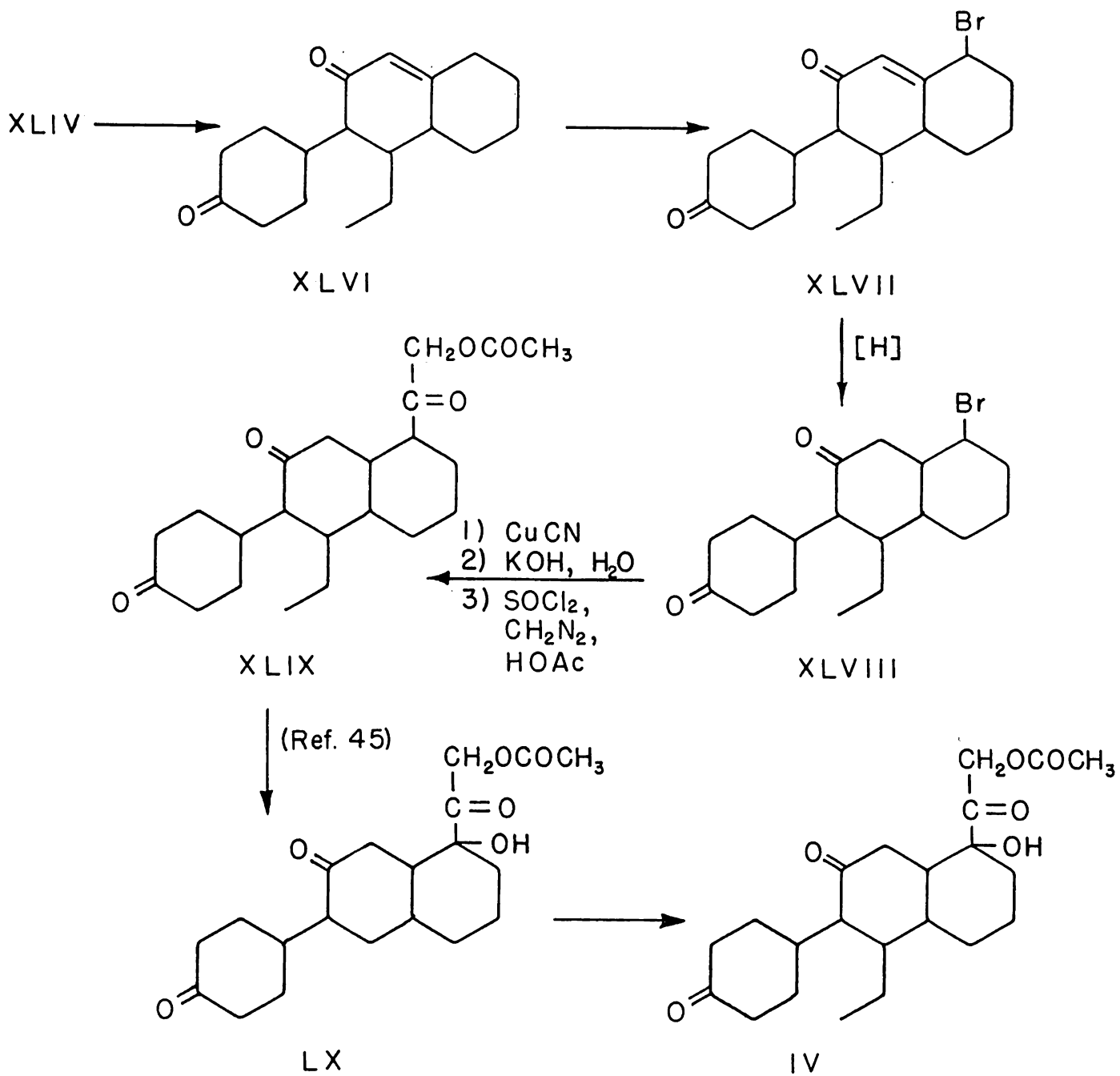
The goal in this part was IV, p. 2, a compound which resembles cortisone (I), even more closely than does III. The proposed synthesis is outlined on pp. 47, 48, 49 and has been carried out as far as XLII.

1. Synthesis of 2-(4-methoxyphenyl)-3-(2-methoxyphenyl)-valeric acid (XXXVIII, p. 47).

This compound was prepared by basic hydrolysis of the nitrile (XXXVI) in the same manner as was used for the preparation of XXV, p. 29, and of alpha, beta-bis-(p-methoxyphenyl)-valeric acid (15). However, alpha, beta-bis-(p-methoxyphenyl)-valeronitrile was hydrolyzed by refluxing in 4% sodium hydroxide solution for eighteen hours (15). In the present instance, the 4% solution had no effect on the nitrile (XXXVI) and it was necessary to increase the concentration of sodium hydroxide to 25% to effect hydrolysis. This difference in behavior is probably due to the steric effect of the methoxyl substituent in the second benzene ring. In alpha, beta-bis-(p-methoxyphenyl)-valeronitrile this substituent is in the para-position, while in XXXVI it is in the ortho-position. When a substituent is in the meta-position, as it is in XXIV, p. 29, the hydrolysis conditions are intermediate between those for the







LXI

compounds mentioned above; i.e., a 4% solution is used with greatly increased reaction time.

If the concentration of sodium hydroxide used for the hydrolysis of XXXVI is still further increased, then demethylation and hydrolysis occur simultaneously and the product is probably the lactone (XXXVII) since the product obtained under these conditions is soluble in sodium hydroxide solution but insoluble in sodium bicarbonate solution. It gives a positive hydroxamic acid test for the presence of an ester linkage, and a bicarbonate-soluble material was produced by boiling it with potassium hydroxide solution.

2. Synthesis of 3-(4-methoxyphenyl)-4-(2-methoxyphenyl)-2-hexanone (XXXIX).

Another indication of the steric effect of the substituents in the second ring is furnished by the observation that the methyl ketone could not be formed from the nitrile (XXVI) by reaction with methylmagnesium iodide. It was necessary to proceed through the acid, as described above under the preparation of XXVI, in Part A.

3. Synthesis of 3-(4-hydroxyphenyl)-4-(2-hydroxyphenyl)-2-hexanone (XLII, p. 48).

Demethylation of XXXIX presented some difficulties. Pyridine hydrochloride gave by demethylation followed by ring closure of the enol form, the substituted benzopyran (XL). Aluminum chloride or bromide in benzene gave only very low yields of phenolic material. Refluxing hydrobromic acid in glacial acetic

acid gave phenolic material in moderately good yield, but it proved impossible to purify the material by recrystallization although it appears to be a low-melting solid. Distillation causes loss of water and probably ring closure to the benzopyran (XL). Before it was realized that XL was the pyran instead of XLII, XL was reduced and then oxidized to XLI. The phenol (XLII) was identified by the preparation of the bis-phenylurethan derivative (XLIII). Since distillation was impossible, XLII was purified for the next step by shaking with Raney nickel in alcohol solution.

4. Attempted synthesis of 3-(4-oxocyclohexyl)-4-(2-oxocyclohexyl)-2-hexanone (XLIV).

Reduction of the phenol (XLII) by shaking with hydrogen at high-pressure, followed by oxidation with chromic anhydride of the resulting alcohol would be expected to produce XLIV. When the reactions were carried out, an anomalous product was obtained.

It was soluble in organic solvents (ether, acetone, chloroform, benzene, alcohol) and insoluble in water. It did not melt below 300° and left a residue on ignition. Solution in ether, chloroform or benzene and washing with acid or alkali appeared to cause no change. It is suggested that this material is the chromium complex of the ketone (XLIV) analogous to the compound chromic acetylacetonate (LXI) (46)., but this hypothesis has not been proved.

PART C

EXPERIMENTAL

2-(4-Methoxyphenyl)-3-(2-methoxyphenyl)-valeronitrile (XXXVI, p. 47).alpha-(4-Methoxyphenyl)-2-methoxycinnamionitrile (43)

was allowed to react with ethyl magnesium bromide and the product isolated as described for the preparation of 2-(4-methoxyphenyl)-3-(3-bromophenyl)-valeronitrile (XXIV, p. 29). The product was purified by distillation and only one isomer was obtained. From 161 g. of alpha-(4-methoxyphenyl)-2-methoxycinnamionitrile (XXXVI) was obtained 134 g. (75%) of 2-(4-methoxyphenyl)-3-(2-methoxyphenyl)-valeronitrile (XXXVI), b. p. 158° (0.01 mm.), n_D^{20} 1.5562.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.25; H, 7.16.

Found: C, 77.60; H, 7.47.

2-(4-Methoxyphenyl)-3-(2-methoxyphenyl)-valeric acid (XXXVIII).

To a solution of 25 g. of sodium hydroxide in 25 ml. of water and 75 ml. of ethylene glycol contained in a 300-ml. flask equipped with a stirrer and a condenser arranged for distillation was added 25 g. (0.085 mole) of 2-(4-methoxyphenyl)-3-(2-methoxyphenyl)-valeronitrile (XXXVI). The mixture was heated, collecting the water which distilled, until ammonia began to be evolved. The condenser was then arranged for reflux and the mixture boiled for three hours. The solution was cooled slightly and poured into 800 ml. of water. It was filtered

and then extracted with ether to remove any unreacted nitrile. Acidification with carbon dioxide and extraction with ether removed any phenolic material. Finally, acidification with hydrochloric acid and extraction with ether removed the carboxylic acid. The ether solution was dried over sodium sulfate and evaporated to leave 24.5 g. (92.5%) of 2-(4-methoxyphenyl)-3-(2-methoxyphenyl)-valeric acid (XXXVIII) as an oil. It was purified for analysis by distillation, b. p. 202° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05.

Found: C, 72.66; H, 7.50.

If no water is used in the hydrolysis solution the product obtained is insoluble in sodium bicarbonate solution, is soluble in sodium hydroxide, gives a positive hydroxamic acid test for the presence of an ester linkage, and yields a bicarbonate soluble material on refluxing with 10% potassium hydroxide solution. It appears to be a low-melting solid but was not further characterized. It is suggested that this material is the lactone, XXXVII.

3-(4-Methoxyphenyl)-4-(2-methoxyphenyl)-2-hexanone (XXXIX).

This ketone was prepared from the acid in the same manner as described for the preparation of 3-(4-methoxyphenyl)-4-(3-bromophenyl)-2-hexanone (XXVI, p. 29) in Part B. From 34.0 g. (0.108 mole) of 2-(4-methoxyphenyl)-3-(2-methoxyphenyl)-valeric acid (XXXVIII) there was obtained a crude yield of 30.5 g. (89%) of the ketone (XXXIX). Distillation gave 28 g., b. p. 144-145° (0.04 mm.), n_D^{20} 1.5560.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74.

Found: C, 77.04; H, 7.54.

2-Methyl-3-(4-hydroxyphenyl)-4-ethyl-1,4-benzopyran (XL).

A mixture of 28 g. (0.09 mole) of 3-(4-methoxyphenyl)-4-(2-methoxyphenyl)-2-hexanone and 84 g. of pyridine hydrochloride was refluxed for three hours and then poured into water. Extraction with ether, drying and evaporation of the ether left 26 g. (100%) of XL. It was purified by distillation, b. p. 169-170° (0.3 mm.).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 80.40; H, 6.84.

Found: C, 80.48; H, 7.08.

2-Methyl-3-(4-oxocyclohexyl)-4-ethyl-2,3,5,6,7,8,9,10-octahydro-benzopyran (XLI).

A mixture of 14 g. (0.052 mole) of 2-methyl-3-(4-hydroxyphenyl)-4-ethyl-1,4-benzopyran, 2 g. of Raney nickel, and 100 ml. of absolute ethanol was shaken with hydrogen at 2500 p.s.i. and 180° for twenty-four hours. The bomb was cooled and the catalyst removed by filtration. The alcohol was evaporated and the residue taken up in ether and the ether extract washed with 10 % sodium hydroxide solution. The ether extract was then dried, the ether was evaporated and the residue was oxidized with sodium dichromate according to the procedure of Johnson, Gutsche and Banerjee (44), to give 10 g. of red oil. Distillation gave 5 g. (31%) of 2-methyl-3-(4-oxocyclohexyl)-4-ethyl-2,3,5,6,7,8,9,10-octahydrobenzopyran, b. p. 142-145° (0.02 mm.).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86.

Found: C, 77.81; H, 11.12.

3-(4-Hydroxyphenyl)-4-(2-hydroxyphenyl)-2-hexanone (XLII).

A solution of 40 g. (0.128 mole) of 3-(4-methoxyphenyl)-4-(2-methoxyphenyl)-2-hexanone (XXXIX) in 200 ml. of 42% hydrobromic acid and 500 ml. of glacial acetic acid was refluxed for twenty hours and then poured into three liters of water. The phenol (XLIII) was collected by filtration, 28 g. after drying in air, m. p. crude 85-90°. It proved impossible to crystallize this material and distillation caused loss of water and cyclization to XL.

A bis-(phenylurethan) (XLIII) of XLII was prepared in the usual manner and recrystallized from benzene-Skellysolve B, m. p. 150-151°.

Anal. Calcd. for $C_{32}H_{30}O_5N_2$: C, 73.54; H, 5.78.

Found: C, 73.15; H, 5.63.

Attempted preparation of 3-(4-oxocyclohexyl)-4-(2-oxocyclohexyl)-2-hexanone (XLIV).

3-(4-Hydroxyphenyl)-4-(2-hydroxyphenyl)-2-hexanone (XLII) (28 g., 0.10 mole) was dissolved in 100 ml. of absolute ethanol and shaken for twenty-four hours with 2 g. of W-7 Raney nickel (47). The catalyst was removed by filtration and the filtrate was shaken with hydrogen at 2500 p.s.i. and 200°C and 2 g. of W-7 Raney nickel

for forty hours. The bomb was cooled and opened and the catalyst removed by filtration. The filtrate was evaporated to dryness. The residue was taken up in ether and washed with 10% sodium hydroxide solution to remove unreduced phenol (10 g.). The ether was dried and evaporated to leave 13 g. of neutral material. This material was oxidized with chromic anhydride (48) to give 13 g. of dark-brown solid. This is soluble in acetone, anhydrous ether, anhydrous benzene, alcohol, chloroform, and ethyl acetate, and insoluble in water. It does not melt below 300°, and it leaves a residue on ignition. Purification by chromatography was attempted and failed. The identity of this material is unknown but it is suggested that it may be a complex of XLIV with chromium.

SUMMARY

1. The attempted synthesis of 3,4-dianisyl-2,5-hexanedione (XI, p.5) is described. Distillation of what was probably XI led to the production of 2,5-dimethyl-3,4-dianisylfuran (XVII, p.10).
2. A novel reaction, catalyzed by sodamide, between homoanisyl cyanide and ethyl acetate is described.
3. The synthesis of 3-(4-hydroxyphenyl)-4-(3-carbethoxyphenyl)-2-hexanone (XXXI, p. 30) and of 3-(4-hydroxyphenyl)-4-(2-hydroxyphenyl)-2-hexanone (XLII, p. 48), key intermediates in the attempted preparation of III and IV, p. 2., is described.
4. An interesting steric effect on the rate and ease of hydrolysis of certain nitriles is discussed.

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