Anal. Calcd. for $C_{30}H_{31}O_{10}N_3$: CH_3O, 5.22; acetyl, 7.25. Found: CH_3O, 5.02; acetyl, 7.22.

Methyl β-D-Glucoside-2,3,4,6-tetracarbanilate.—A small amount of methyl β-D-glucoside-2,3,6-tricarbanilate was carbanilated in dry pyridine with phenyl isocyanate giving, from hot acetone, white crystals melting at 221–222°. This product did not depress the melting point of the methyl β-D-glucoside-2,3,4,6-tetracarbanilate made by direct carbanilation of methyl β-D-glucoside.[3]

Summary

1. Crystalline methyl β-D-glucoside-2,3,6-tricarbanilate has been prepared from methyl β-D-glucoside-2,3-dicarbanilate in a five-step synthesis.

2. The intermediates in this synthesis, all crystalline, have been described and identified.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. II. Some Analogs of Progesterone and Desoxycorticosterone

BY A. L. WILDS AND CLIFFORD H. SHUNK[1,2]

In seeking synthetic compounds which might show the hormonal activity of testosterone, progesterone or desoxycorticosterone, it has seemed attractive to us to prepare analogs of the hormones lacking Ring C. In the present paper is described the synthesis of such analogs of progesterone and desoxycorticosterone. In these initial approaches, begun in 1941 and interrupted during the war, we have aimed the synthesis for reasons of simplification toward structures of the type of XIV and XV lacking the angular methyl groups and with a six-membered ring D, with the intention of extending the work to closer analogs should the physiological tests be encouraging.

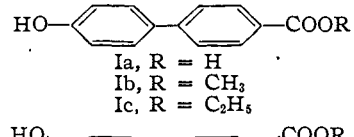
For the synthesis of these α,β-unsaturated cyclic ketones we have employed the very useful Robinson–Mannich base method[3] with the perhydrogenated biphenyl keto acid IVa. Recently we have described an improved modification of this method using the 2-hydroxymethylene derivative of 4-cyclohexylcyclohexanone to synthesize 6-cyclohexyl-Δ^{1-9}-octalone-2 (XIV, R = H).[4]

The intermediate keto acid IVa was prepared from 4-(4′-hydroxyphenyl)-benzoic acid (Ia), which is readily available from 4-methoxybiphenyl.[5,6] Hydrogenation of the methyl ester of the hydroxy acid in the presence of W-6 Raney nickel catalyst gave a mixture of isomeric perhydro hydroxy esters IIb from which only one of the four stereoisomers could be isolated in pure form. Oxidation of the mixture of hydroxy acids, however, gave the two possible keto acids IVa, from which were obtained Isomer A, m. p. 174–175° (22% over-all yield from Ib) and Isomer B, m. p. 96–96.5° (36% over-all yield).

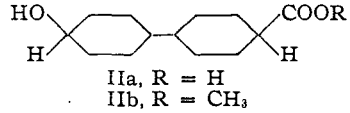
It was also possible to limit the hydrogenation of the ester Ic so as to obtain material (IIIc) with only one ring reduced. After oxidation of the non-phenolic fraction, the keto acid VIIIa was obtained in 45–48% yield, along with some of the fully reduced acid IVa. None of the phenolic acid was isolated with the carboxyl-substituted ring reduced, which is the product of sodium and alcohol reduction of Ia.[6]

The conversion of the keto esters IVb (Isomer A) and VIIIb to the tricyclic unsaturated keto acids VIIa and XIa followed the procedure applied by us to 4-cyclohexylcyclohexanone in preparing the simpler ketone XIV (R = H).[4] In the condensation of the keto esters with methyl formate, very satisfactory yields (91–86% of the hydroxymethylene derivatives Va and IXa resulted when an excess of the reagents was used.[7] It is worthy of note that the esters Vb and IXb, the primary reaction products, were saponified in excellent yields under very mild conditions in working up the reaction mixtures.

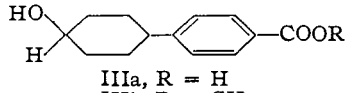
Either the hydroxymethylene acids or esters were suitable for the Mannich base condensation, in the former cases an additional equivalent of sodium methoxide being used to prepare the salts. In this reaction the crystalline products were largely VIa (or VIc) and Xa (or Xc), in which the formyl group was eliminated. Cy-



Ia, R = H
Ib, R = CH_3
Ic, R = C_2H_5



IIa, R = H
IIb, R = CH_3



IIIa, R = H
IIIb, R = CH_3
IIIc, R = C_2H_5

(1) National Research Council Predoctoral Fellow, 1946-1948.

(2) Present address, Merck and Co., Inc., Rahway, New Jersey.

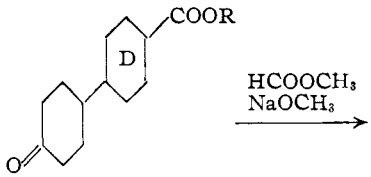
(3) See du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and later papers.

(4) Shunk and Wilds, THIS JOURNAL, **71**, 3946 (1949).

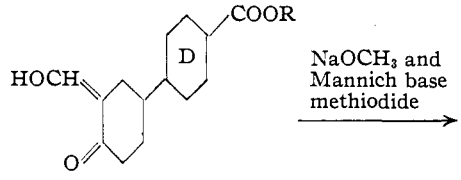
(5) Fieser and Bradsher, *ibid.*, **58**, 1738 (1936).

(6) Johnson, Gutsche and Offenhauer, *ibid.*, **68**, 1648 (1946).

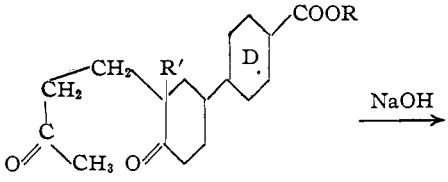
(7) There was no indication of the formation of bis-hydroxymethylene derivatives; the ultraviolet absorption spectrum showed a single maximum at 281 mμ with no indication of a maximum at around 300–310 mμ as would be expected for a bis-hydroxymethylene derivative.



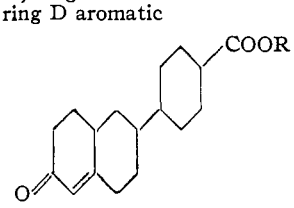
IVa, R = H
IVb, R = CH_3
VIIIa, R = H; ring D aromatic
VIIIb, R = CH_3; ring D aromatic



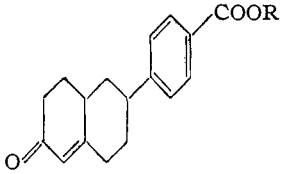
Va, R = H
Vb, R = CH_3
IXa, R = H; ring D aromatic
IXb, R = CH_3; ring D aromatic



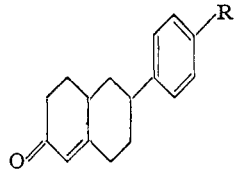
VIa, R = R^1 = H
VIb, R = H; R^1 = —CHO
VIc, R = CH_3; R^1 = H
Xa, R = R^1 = H; ring D aromatic
Xb, R = H; R^1 = —CHO; ring D aromatic
Xc, R = CH_3; R^1 = H; ring D aromatic



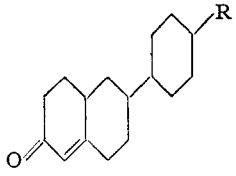
VIIa, R = H
VIIb, R = CH_3



XIa, R = H
XIb, R = CH_3



XII, R = —$COCH_3$
XIII, R = —$COCH_2OCOCH_3$



XIV, R = —$COCH_3$
XV, R = —$COCH_2OCOCH_3$

clization was effected in good yield under mild treatment with alkali to give the unsaturated keto acids VIIa (Isomer A) and XIa in 65% and 60% over-all yields, respectively, from the keto esters IVb and VIIIb.[8]

When isomer B of IVb was treated with methyl formate and sodium methoxide some (19%) of the crystalline hydroxymethylene derivative Va of Isomer A could be isolated, indicating that partial inversion of the carbomethoxyl group occurred. When the remaining oil was carried through the subsequent steps, a pure cyclic keto acid VIIa corresponding to Isomer B was not obtained, although a crystalline 2,4-dinitrophenylhydrazone of the methyl ester VIIb could be isolated.

For converting the keto acids VIIa and XIa to the desired acetyl or acetoxyacetyl derivatives the most convenient method involved using the acid chloride of these α,β-unsaturated keto acids. Previous results in attempting to prepare such acid chlorides in other series had been unsatisfactory due to the sensitivity of the α,β-unsaturated ketone grouping to the reagents normally used, such as thionyl chloride, and probably to an instability of such acid chlorides themselves toward heat. A very mild method was developed in the present investigation, involving short reaction of the finely divided sodium salt of the acid with oxalyl chloride below 15°. In a model run sodium benzoate was converted to the acid chloride in 82% yield (estimated by conversion to benzanilide) in five minutes at 0–15°. This mild method of preparing acid chlorides had been utilized by us to prepare desoxycorticosterone acetate from 3-keto-Δ^4-etiocholenic acid.[9] It would seem to be highly promising for application to other sensitive acids.

By reaction of the acid chloride of VIIa with sodiomalonic ester followed by acid hydrolysis (or by reaction with dimethylcadmium) the desired acetyl derivative XIV was prepared in the Isomer A series. With diazomethane followed by reaction of the diazoketone with acetic acid the acetoxyacetyl derivative XV (Isomer A) resulted.[10] In each case the yield was rather low. As yet comparable derivatives have not been prepared from Isomer B, although it is possible that these isomers are present in the non-crystalline portions of XIV and XV through isomerization. With similar procedures the partially aromatic derivative XIa was converted into the corresponding acetyl and acetoxyacetyl derivatives XII and XIII.

These analogs of progesterone and desoxy-

(8) It is interesting to note that the ester group of XIb was saponified only to a small extent (*ca.* 6%) with dilute methanolic potassium hydroxide in the cyclization step, while the hydroxymethylene ester IXb, was saponified to a considerable extent under similar conditions with dilute *aqueous* alkali. This increased effectiveness of aqueous alkali with alkali-(or water)-soluble compounds seems to be in accord with previous work and theoretical considerations.

(9) Wilds and Shunk, THIS JOURNAL, **70**, 2427 (1948).

(10) The possibility that diazomethane might add to the double bond of the α,β-unsaturated ketone grouping of the acid chloride of VIIa was eliminated in model experiments with XIV (R = H) and from the ultraviolet absorption spectrum, which was unchanged.

corticosterone acetate are being tested for physiological activity under the direction of Drs. R. K. Meyer and Elva G. Shipley of the Department of Zoology. In preliminary assays the acetyl derivatives XII and XIV showed negative progestational activity in guinea pigs at a total dose of 5 mg. and 1 mg., respectively. Estrogenic activity was not found at a dose of 240γ (rats). Further tests on these as well as XIII and XV are in progress. It should be pointed out that these isomers may not correspond to the proper configuration for highest activity. Tentatively we consider the carboxyl group in the Isomer A series to be *trans*[11]; if this is the case the corresponding isomers of XIV and XV would have side chain configurations analogous to 17-α in the steroid series, rather than 17-β as for progesterone and desoxycorticosterone. This possibility, and the discovery of androgenic activity in the corresponding analog of androstenedione,[12] makes it highly desirable to prepare the corresponding derivatives related to isomer B of IVa.

Experimental[13]

Preparation of 4-(4'-Carboxycyclohexyl)-cyclohexanone (IVa) and 4-(4'-Carboxyphenyl)-cyclohexanone (VIIIa) 4-(4'-Hydroxyphenyl)-benzoic Acid (Ia).—4-Methoxybiphenyl, obtained in 95–97% yield from 4-hydroxybiphenyl and methyl sulfate, was converted to 4-(4'-methoxyphenyl)-acetophenone (m. p. 155–156°) in 56% yield by the procedure of Johnson, Gutsche and Offenhauer.[6] Oxidation of the ketone (174 g.) with sodium hypobromite[6] followed by demethylation of the resulting crude methoxy acid (176 g.; purest sample, m. p. 251–253°) with 460 ml. of 48% hydrobromic acid and 2200 ml. of acetic acid, refluxing fourteen hours while protected from air by means of a mercury trap, gave 4-(4'-hydroxyphenyl)-benzoic acid (Ia) in 95% yield (based on the methoxy ketone), m. p. 285–290°. Sublimation of a sample at 180° (0.1 mm.) and recrystallization from acetic acid raised the m. p. to 292–294° (uncor.; reported, 293–294°).[5]

The **methyl ester** (Ib) was obtained in 92–95% yield, m. p. 226–227°, by refluxing for two hours with methanol saturated at 50° with hydrogen chloride gas. Recrystallization from acetone, using Norit, gave small colorless cubes, m. p. 227–228° (reported, 224–225°).[5]

The **ethyl ester** (Ic) was prepared similarly in 87% yield, heating for twenty-four hours; material recrystallized from acetone–carbon tetrachloride melted at 142–143°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8. Found: C, 74.4; H, 5.7.

4-(4'-Carboxycyclohexyl)-cyclohexanol (IIa).—A suspension of 40 g. of methyl 4-(4'-hydroxyphenyl)-benzoate (Ib) in 85 ml. of absolute methanol was hydrogenated using 10 g. of W-6 Raney nickel catalyst[14] at 85° and an initial hydrogen pressure of 4500 p. s. i. (twelve hours required). After filtering from the catalyst (employing a total of 500 ml. of methanol) 50 ml. of 45% potassium hydroxide was added and the solution refluxed for two hours, then diluted with 2 l. of water and extracted with three portions of chloroform. Evaporation of this extract gave 8.5 g. of semi-solid neutral material. The alkaline solution was acidified, extracted with three portions of chloroform, dried over sodium sulfate and the solvent removed to leave 28.0 g. (70%) of a mixture of acids. Recrystallization of a portion from acetone gave one of the stereoisomers of IIa as small colorless prisms, m. p. 194–195°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.0; H, 9.8. Found: C, 68.9; H, 9.9.

An attempt to separate the mixture of acids by fractional acidification after dissolving in sodium carbonate solution[15] failed, leading to mixtures melting in the range 115–205°.

In one run the reduced ester mixture was not hydrolyzed but instead partially crystallized from ether–petroleum ether. Recrystallization of the solid (m. p. 90–95°, obtained in 18% yield) from carbon tetrachloride gave one of the isomeric **methyl esters IIb**, m. p. 98–100°. Alkaline hydrolysis of this ester gave the same solid acid as obtained above (m. p. and mixed m. p. 194–195°).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 70.0; H, 10.1. Found: C, 69.6; H, 10.0.

4-(4'-Carboxycyclohexyl)-cyclohexanone (Isomer A) (IVa).—The crude mixture of 4-(4'-carboxycyclohexyl)-cyclohexanols (28 g.) was dissolved in 500 ml. of acetic acid, cooled to 16° and stirred while 23 g. (180% excess of chromium trioxide dissolved in 20 ml. of water and 50 ml. of acetic acid was slowly added over one hour. The mixture was kept at 16–20° for another hour after addition was complete, then treated with 25 ml. of methanol and poured into 2 l. of water containing 50 ml. of hydrochloric acid. The mixture was extracted several times with chloroform (avoiding too vigorous shaking at first which resulted in emulsions) and the extract washed with dilute hydrochloric acid, water and dried over sodium sulfate. After removing the solvent the residue was crystallized from acetone giving in two crops 8.7 g. (31%) crude Isomer A of the keto acid melting at 168–175°. From the filtrate by crystallization from ether–petroleum ether (40–60°) was obtained 14.1 g. (50%) of a mixture, m. p. 84–90° (to a cloudy melt), which was largely Isomer B. Recrystallization of the higher melting material give pure **Isomer A of 4-(4'-carboxycyclohexyl)-cyclohexanone (IVa)**, m. p. 174–175°.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0. Found: C, 69.3; H, 9.0.

The **methyl ester of Isomer A (IVb)**, obtained in 99% yield with ethereal diazomethane, crystallized as colorless prisms from petroleum ether (40–60°), m. p. 39–40°.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 70.9; H, 9.4.

The **2,4-dinitrophenylhydrazone of the methyl ester of Isomer A**, prepared in 57% yield in methanol containing a small amount of hydrochloric acid, crystallized from methyl acetate as orange prisms, m. p. 197–198°.

Anal. Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.4; H, 6.3. Found: C, 57.5; H, 6.3.

4-(4'-Carboxycyclohexyl)-cyclohexanone (Isomer B) (IIa).—Partial but incomplete purification of the lower melting isomer from the material of m. p. 84–90° resulted from fractional acidification of its solution in sodium carbonate[15] or adsorption of the methyl ester on alumina and fractionally eluting; in each case the lower melting isomer was concentrated in the first fractions. The best method of purification was to remove as much of Isomer A as possible by fractional crystallization and then to seed a solution (18.8 g., m. p. 80–95°) in 90 ml. of warm benzene with a sample of pure isomer B (see below), allowing to cool very slowly. In this way the acid separated as large clear prisms which lost solvent on drying at room temperature, changing to 12.3 g. of white powder, m. p. 90–93°. If any of Isomer A crystallized at this point it was in the form of small rosettes of prisms which could be separated by hand. Further recrystallization from benzene and then ether–petroleum ether gave pure Isomer B as colorless prisms, m. p. 96–96.5°.

(11) We hope to establish the point by conversion of the keto acids IVa to the corresponding 4-cyclohexylcyclohexanecarboxylic acids.

(12) Wilds, Shunk and Hoffman, THIS JOURNAL, **71**, 3266 (1949).

(13) All melting points are corrected unless indicated otherwise. Those marked micro m. p. were determined with a calibrated microscope hot stage, all others in a Hershberg apparatus.

(14) Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

(15) Linstead and Doering, *ibid.*, **64**, 2001 (1942).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0. Found: C, 69.3; H, 9.0.

When the solid isomer of 4-(4′-carboxycyclohexyl)-cyclohexanol, m. p. 194–195°, was oxidized with chromium trioxide, Isomer B of the keto acid was obtained in 85% yield, m. p. and mixed m. p. 96–96.5°.

The methyl ester of Isomer B was an oil which could not be crystallized. It yielded the **2,4-dinitrophenylhydrazone of the methyl ester** of Isomer B in 55% yield as orange needles from methanol melting at 107–109°, resolidifying and remelting at 131–132°.

Anal. Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.4; H, 6.3. Found: C, 57.7; H, 6.3.

4-(4′-Carboxyphenyl)-cyclohexanol (IIIa).—A suspension of 5 g. of ethyl 4-(4′-hydroxyphenyl)-benzoate (Ic, purified by refluxing in ethanol with Raney nickel)[16] in 14 ml. of absolute ethanol and 1 ml. of triethylamine was hydrogenated using 2 g. of W-6 Raney nickel catalyst[14] at an initial hydrogen pressure of 2400 p. s. i. The theoretical amount of hydrogen for one ring was absorbed in thirty minutes at 110°. After removing the catalyst and the solvent, the residue was dissolved in ether and extracted with three portions of cold 5% potassium hydroxide (see below).

From the ether was obtained 3.80 g. of an oil which partially solidified. Recrystallization of a small portion from ether–petroleum ether (40–60°) gave one isomer of the **ethyl ester** of 4-(4′-carboxyphenyl)-cyclohexanol (IIIc) as fine, colorless needles, m. p. 134–135°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.6; H, 8.1. Found: C, 72.9; H; 8.2.

The remainder of the neutral product was hydrolyzed by refluxing for two hours with 60 ml. of methanol and 10 ml. of 45% potassium hydroxide. After diluting and extracting with chloroform 0.17 g. of neutral material was found. The alkaline layer was acidified and extracted with warm chloroform to give 3.20 g. of a mixture of acids, m. p. 195–217°. Recrystallization of a portion from acetone afforded one isomer of 4-(4′-carboxyphenyl)-cyclohexanol (IIIa) as stout prisms, m. p. 236–237°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.6; H, 7.2.

Conversion of this acid to the ethyl ester (alcoholic hydrogen chloride) gave the same isomer as above, m. p. and mixed m. p. 134–135°.

The **methyl ester** (IIIb), prepared by adding ethereal diazomethane to a chloroform solution of the acid, crystallized from carbon tetrachloride as colorless needles, m. p. 137–138°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.7. Found: C, 71.5; H, 7.8.

From the potassium hydroxide washings of the crude hydrogenation mixture was obtained 1.00 g. of oily acidic material which was converted to the methyl ester with methanol and sulfuric acid. From this could be isolated some unreduced methyl 4-(4′-hydroxyphenyl)-benzoate, m. p. 224–226° and a small amount of the methyl ester of 4-(4′-carboxyphenyl)-cyclohexanol, m. p. 137–138°. None of the compound with only the ring containing the carbomethoxy group reduced could be isolated.

4-(4′-Carboxyphenyl)-cyclohexanone (VIIIa).—The crude acid (m. p. 195–217° from above) was oxidized in 80 ml. of acetic acid with 2.00 g. of chromium trioxide in 2 ml. of water and 10 ml. of acetic acid keeping the temperature at 15–18° as described above for the fully hydrogenated compound (IVa). A portion of the solid keto acid from the chloroform extracts was recrystallized from acetone as stout prisms, m. p. 228–230°. The compound showed an absorption maximum at 236 mμ (E = 15,600).[17]

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.6; H, 6.5. Found: C, 71.6; H, 6.5.

(16) Mozingo, *Organic Syntheses*, **21**, 15 (1941).

(17) Ultraviolet absorption spectra determined in 95% alcohol using a Beckman quartz spectrophotometer; E = molecular extinction coefficient.

The remaining crude acid was dissolved in chloroform and treated with excess ethereal diazomethane. The **methyl ester of 4-(4′-carboxyphenyl)-cyclohexanone** (VIIIb) crystallized from ether as colorless platelets, m. p. 93–94.5°.[18]

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.5; H, 6.7.

The **2,4-dinitrophenylhydrazone of the methyl keto ester**, obtained in 92% yield, crystallized from methyl acetate as orange prisms, m. p. 223–224°.

Anal. Calcd. for $C_{20}H_{20}O_6N_4$: C, 58.2; H, 4.9. Found: C, 58.3; H, 5.0.

By the above method, using triethylamine in the hydrogenation step, the methyl keto ester (VIIIb) was obtained in 45–48% over-all yield from ethyl 4-(4′-hydroxyphenyl)-benzoate. In one run using the methyl ester and ordinary Raney nickel catalyst at 180° without triethylamine the yield was 33%. In order to separate the last of the desired keto ester from the product also present having both rings hydrogenated, chromatographic adsorption on alumina was necessary. Fractional elution of the methyl ester from 8.3 g. of crude acids (m. p. 173–183°) with ether–petroleum ether (1:1) removed most of the fully reduced material from which was obtained after saponification, 3.4 g. m. p. 170–175° and 1.2 g., m. p. 164–173°, of 4-(4′-carboxycyclohexyl)-cyclohexanone. The latter eluates with pure ether yielded after crystallization from the same solvent 1.2 g. of the methyl ester of 4-(4′-carboxyphenyl)-cyclohexanone, m. p. 88–94°.

Preparation of 6-(4′-Carboxycyclohexyl)-Δ^{1-9}-octalone-2 (VIIa)

2-Hydroxymethylene-4-(4′-Carboxycyclohexyl)-cyclohexanone (Isomer A) (Va).—Alcohol-free sodium methoxide was prepared from 5.0 g. of sodium, drying at 150° under reduced pressure, then adding 20 ml. of dry, thiophene-free benzene and distilling. To a suspension of the pulverized solid in 100 ml. of benzene in a nitrogen atmosphere was added 110 g. of dry methyl formate, the mixture stirred for one hour at room temperature, then cooled in an ice-bath and a solution of 14.8 g. of 4-(4′-carbomethoxycyclohexyl)-cyclohexanone (Isomer A, m. p. 35–38°) in 100 ml. of benzene added rapidly. The mixture was stirred at room temperature for twenty hours, cooled and ice-cold 2% sodium hydroxide and ether added. The organic layer was extracted with two fresh portions of the cold alkali (total volume 500 ml.) and the combined alkaline layers, after reëxtracting with ether, were allowed to stand initially at 10° and finally at 18° for four hours. Then the solution was cooled, acidified with hydrochloric acid and extracted thoroughly with chloroform, washing the latter with water and drying over sodium sulfate. The residue, after removing the organic solvent under reduced pressure, was crystallized from acetone, giving in two crops 13.4 g. of the hydroxymethylene derivative of the keto acid, m. p. 165–167°. Repeating the saponification of material in the filtrate using 2% sodium hydroxide as before at 18° gave an additional 0.9 g. of product, m. p. 161–164°, for a total yield of 91%. Recrystallization of the compound from acetone afforded small colorless prisms, m. p. 167–168°, which gave a purple color with alcoholic ferric chloride and showed a single absorption maximum (in 95% alcohol) at 281 mμ (E = 7,350).[17]

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.9; H, 8.1.

The **aniline derivative**, prepared in 80% yield from 10 mg. of the hydroxymethylene derivative and 8 mg. of aniline in 0.4 ml. of methanol (two hours at room temperature), crystallized from methanol as bright yellow leaflets, m. p. 236–237°.

Anal. Calcd. for $C_{20}H_{25}O_3N$: C, 73.4; H, 7.7. Found: C, 73.5; H, 7.5.

(18) Oxidation of the crystalline methyl ester of 4-(4′-carboxyphenyl)-cyclohexanol (m. p. 137–138°) gave this same keto ester (m. p. 92–94°) in 86% yield.

When the amount of alkali used in the extraction step was insufficient to saponify the methyl formate also present in the alkaline extracts, the **methyl ester of 2-hydroxymethylene-4-(4'-carboxycyclohexyl)-cyclohexanone** (Vb) was obtained as an oil after acidification. Evaporative distillation at 150° (0.1 mm.) gave material which crystallized as colorless prisms from ether–petroleum ether, m. p. 71–72°. In one run 25% of the ester was obtained in addition to 45% of the acid.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.7; H, 8.3. Found: C, 67.7; H, 8.2.

Saponification of the ester in 2% sodium hydroxide, through which nitrogen was bubbling, for forty minutes at room temperature gave the same acid as above in 86% yield, m. p. and mixed m. p. 166–168°.

The **pyrazole derivative** was prepared in low yield by heating the ester with hydrazine dihydrochloride in methanol containing some pyridine. After evaporative distillation at 170° (0.1 mm.) and recrystallization from dilute methanol, **5-(4'-carbomethoxycyclohexyl)-4,5,6,7-tetrahydrobenzo[d]pyrazole** was obtained as colorless prisms, m. p. 138–140°.

Anal. Calcd. for $C_{15}H_{22}O_2N_2$: C, 68.7; H, 8.5. Found: C, 68.9; H, 8.5.

2-(γ-Ketobutyl)-4-(4'-carboxycyclohexyl)-cyclohexanone (Isomer A) (VIa).—To a solution of 0.68 g. (0.030 equivalent) of sodium in 30 ml. of methanol was added 3.72 g. (0.0148 mole) of hydroxymethylene acid (Va) under nitrogen, and the mixture was cooled and treated with the methiodide prepared from 6.09 g. (0.043 mole) of 1-diethylaminobutanone-3 dissolved in 10 ml. of methanol. After standing at room temperature for eighteen hours the cooled mixture was added to ice-cold dilute hydrochloric acid and extracted thoroughly with chloroform. After washing with water the extract was evaporated under reduced pressure and the residual oil (negative ferric chloride test) crystallized from ether giving: (a) 3.45 g., m. p. 121–125° (cloudy, clear at 131°); (b) 0.25 g., m. p. 110–130°; from carbon tetrachloride (c) 0.04 g., m. p. 154–157° (gas); and (d) 0.10 g., m. p. 130–144°. This material corresponded to a yield of 81–88%, depending upon the proportion of products in which the formyl group was retained or eliminated. Recrystallization of a portion of (a) from acetone–ether and then from acetone gave the compound VIa lacking the formyl group, m. p. 154.5–155.5°.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.4; H, 8.9. Found: C, 69.4; H, 8.7.

Recrystallization of (c) from acetone gave **2-formyl-2-(γ-ketobutyl)-4-(4'-carboxycyclohexyl)-cyclohexanone (Isomer A) (VIb)**, m. p. 165–166° (gas evol.), still retaining the formyl group.

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.1; H, 8.1. Found: C, 67.1; H, 8.0.

2-(γ-Ketobutyl)-4-(4'-carbomethoxycyclohexyl)-cyclohexanone (Isomer A) (VIc).—A similar reaction of 347 mg. of the methyl ester of the hydroxymethylene keto acid Vb and the sodium methoxide from 30 mg. of sodium in 2 ml. of methanol and 2 ml. of benzene with the methiodide from 360 mg. of 1-diethylaminobutanone-3 in 2 ml. of methanol gave 400 mg. of oil from which 77 mg. of solid, m. p. 60–63°, could be crystallized from cold methanol. Further recrystallization gave the diketo ester VIc lacking the formyl group, m. p. 65–67°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.1; H, 9.2. Found: C, 70.1; H, 9.0.

The oil in the filtrate was evaporatively distilled at *ca.* 0.1 mm. giving 300 mg. of oily distillate which corresponded in analysis mainly to material lacking the formyl group.

Anal. Calcd. for $C_{19}H_{28}O_5$ (with formyl): C, 67.8; H, 8.4; for $C_{18}H_{28}O_4$ (without formyl): C, 70.1; H, 9.2. Found: C, 69.6; H, 8.9.

6-(4'-Carboxycyclohexyl)-Δ^{1-9}-octalone-2 (Isomer A) (VIIa).—A solution of 6.12 g. of a mixture of 2-(γ-ketobutyl)-4-(4'-carboxycyclohexyl)-cyclohexanone and its 2-formyl derivative (m. p. 134–144°) in 500 ml. of 2% sodium hydroxide was kept at 20° under nitrogen for fifty minutes.[19] Then the solution was cooled, acidified and extracted with chloroform, washing the extracts with water and evaporating. Trituration of the residue with acetone yielded 3.53 g. of the cyclic ketone, m. p. 181–187°; evaporation of the filtrate and trituration with ether gave 1.05 g. of a mixture, m. p. 150–160°, and crystallization of a third crop from acetone afforded an additional 0.60 g. of ketone, m. p. 175–181° (mixed m. p. 177–184°). Recrystallization of the second crop (m. p. 150–160°) from acetone gave a mixture which was separated mechanically into 0.22 g. of the crude cyclic ketone as clumps of prisms, m. p. 172–176° (mixed m. p. 178–184°) and 0.09 g. of a fine powder, m. p. 188–191°, which gave a melting point depression (173–178°) when mixed with the ketone of m. p. 181–187°. From the filtrate was obtained another 0.40 g. of the ketone, m. p. 173–182°, bringing the total to 4.75 g.; this corresponds to a yield of 83–90%, depending upon the composition of the starting product.

Recrystallization of the first crop from acetone did not change the m. p. of 181–187°. When, however, the material was inserted into a bath preheated to 182°, it melted completely, then partially solidified to remelt at 187°, indicating it to exist in two different crystallographic forms. The ketone showed an absorption maximum at 239 mμ with $E = 15{,}700$.[17]

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.9; H, 8.8. Found: C, 74.1; H, 8.6.

Three recrystallizations from acetone of the fine powder, m. p. 188–191°, mentioned above, raised its melting point to 205–206°. The analysis indicated this material to be either the intermediate 9-hydroxy-6-(4'-carboxycyclohexyl)-decalone-2 or a stereoisomer of the uncyclized 2-(γ-ketobutyl)-4-(4'-carboxycyclohexyl)-cyclohexanone.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.4; H, 8.9. Found: C, 69.5; H, 8.8.

Treatment of 13 mg. of this compound with 2% sodium hydroxide at 20° for fifty minutes as during the cyclization converted it to the same cyclic unsaturated ketone obtained above; total yield, 9 mg. (74%), most melting at 180–185° (mixed m. p. undepressed).

The **methyl ester of 6-(4'-carboxycyclohexyl)-Δ^{1-9}-octalone-2 (Isomer A) (VIIb)**, prepared in 90% yield by treating a chloroform solution of the acid with ethereal diazomethane, crystallized from ether–petroleum ether as small, colorless prisms, m. p. 74–75°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.4; H, 9.0. Found: C, 74.7; H, 9.0.

The **2,4-dinitrophenylhydrazone of the keto methyl ester (Isomer A)**, prepared in methanol containing a drop of hydrochloric acid, crystallized from benzene as red platelets, m. p. 222–225°.

Anal. Calcd. for $C_{24}H_{30}O_6N_4$: C, 61.3; H, 6.4. Found: C, 61.4; H, 6.1.

6-(4'-Carbomethoxycyclohexyl)-Δ^{1-9}-octalone-2 (Isomer B) (VIIb).—Isomer B of 4-(4'-carboxycyclohexyl)-cyclohexanone (10.5 g., m. p. 96–97°) was converted with ethereal diazomethane to the methyl ester, obtained as an oil upon evaporation of the solvent. The oily ester was converted to the hydroxymethylene derivative as described above for Isomer A, and the alkaline extract allowed to stand at 10–18° for four hours before acidifying. The product crystallized partially when triturated with ether, yielding 2.26 g. (19%), m. p. 158–162°, of the hydroxymethylene derivative of Isomer A (mixed m. p. 158–162°), indicating that partial isomerization had occurred during the formylation reaction. Further treatment of the

(19) This was determined as the optimum time for cyclization in a smaller run by withdrawing aliquots periodically and examining the product for intensity of absorption at 239 mμ, with the following results: 7.5 minutes, 54%; 15 min., 67%; 30 min., 79%; 45 min., 85%; 60 min., 83%; 90 min., 73%; 180 min., 65%; 240 min., 54%.

remaining oily product with 2% sodium hydroxide at 18° for four hours afforded no additional crystalline material. The oil (9.17 g.) was alkylated with the methiodide of 1-diethylaminobutanone-3 as for Isomer A, and the product also a viscous acidic oil, was cyclized with 2% sodium hydroxide at 20° for fifty minutes. The resulting reddish oily acid could not be crystallized; from the ultraviolet absorption (E_{239} = 7,050) it was estimated to contain about 45% of cyclic unsaturated ketone.

A portion was converted to the methyl ester with diazomethane, and adsorbed from petroleum ether–benzene (1:1) solution on a column of alumina. In the fraction eluted with petroleum ether–benzene (1:3) absorption as high as E_{239} = 13,800 was obtained for the oily material. Reaction of 144 mg. with 2,4-dinitrophenylhydrazine in methanol containing a small amount of hydrochloric acid gave 149 mg. of red solid, m. p. 115–150°, which was dissolved in 400 ml. of petroleum ether and passed through a column of talc and Filter-Cel (1:1), eluting with an additional 500 ml. of solvent. From the eluates on concentration was obtained 95 mg. of fine needles, m. p. 153–163° (sintering at 145°); two recrystallizations from benzene raised the melting point of the **2,4-dinitrophenylhydrazone of the keto methyl ester** (Isomer B) to 166–167°.

Anal. Calcd. for $C_{24}H_{30}O_6N_4$: C, 61.3; H, 6.4. Found: C, 61.3; H, 6.4.

Preparation of 6-(4′-Carboxyphenyl)-Δ^{1-9}-octalone-2 (XIa)

2-Hydroxymethylene-4-(4′-carboxyphenyl)-cyclohexanone (IXa).—4-(4′-Carbomethoxyphenyl)-cyclohexanone (VIIIb; 10.8 g.) was converted to the hydroxymethylene derivative using sodium methoxide from 3.84 g. of sodium and 75 g. of methyl formate in 200 ml. of benzene for twenty-four hours, following the same procedure as described above for the carboxycyclohexyl derivative IVb. The sodium hydroxide extract was allowed to stand at 10–17° for seven hours and the product isolated as before. A total of 9.84 g. (86%) of the hydroxymethylene derivative, m. p. 191–194°, was obtained by crystallization from acetone. Further recrystallization gave material melting at 194–196°, giving a purple color with alcoholic ferric chloride and showing absorption maxima at 237 mμ (E = 16,100) and 279 mμ (8,510) and a minimum at 258 mμ (5,840).[17]

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.0; H, 5.5.

The **aniline derivative** formed quickly in methanol at room temperature; small, yellow prisms from methanol, m. p. 254–256°.

Anal. Calcd. for $C_{20}H_{19}O_3N$: C, 74.7; H, 6.0. Found: C, 75.2; H, 6.0.

In a run similar to that above except that the cold 2% sodium hydroxide extract was acidified immediately, the **methyl ester** (IXb) of the hydroxymethylene derivative was obtained in 68% yield, m. p. 76–84°. Recrystallization from ether yielded clusters of colorless needles, m. p. 84–86°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.5; H, 6.3.

Saponification of the above ester in 5% sodium hydroxide at room temperature for one hour gave the same acid as described above, m. p. 188–192° (98% yield, mixed m. p. 191–195°).

In a run in which ethyl formate was used, ester exchange took place giving the **ethyl ester** of the hydroxymethylene derivative (IXa) in 76% yield, m. p. 60–68°. Recrystallization from ether–petroleum ether gave colorless prisms, m. p. 66–67°. The compound was not very stable, changing to an oil after several days at room temperature.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 70.3; H, 6.5.

2-(γ-Ketobutyl)-4-(4′-carboxyphenyl)-cyclohexanone (Xa).—2-Hydroxymethylene-4-(4′-carboxyphenyl)-cyclohexanone (IXa, 3.66 g.) was alkylated in a total of 70 ml. of methanol containing 0.68 g. of sodium and using the methiodide from 6.0 g. of 1-diethylaminobutanone-3 as described above for the carboxycyclohexyl compound. After thirty-six hours at room temperature the product was isolated and crystallized from benzene, giving 2.48 g., m. p. 155–159°, and 1.39 g., m. p. 125–150°; this represents a yield of 82–90%, depending upon the amount of product retaining the formyl group. Recrystallization of a portion of the first crop from acetone afforded the compound from which the formyl group had been eliminated, as colorless crystals, m. p. 162–164°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0. Found: C, 70.6; H, 7.0.

The extent of deformylation was variable, for from another run in which there was no apparent difference in procedure, the product (51% yield) was mainly **2-formyl-2-(γ-ketobutyl)-4-(4′-carboxyphenyl)-cyclohexanone (Xb)**, m. p. 125–140°. Recrystallization from benzene gave the pure compound as colorless prisms, m. p. 141–142° with evolution of gas.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3; H, 6.4. Found: C, 68.4; H, 6.2.

When the methyl ester (IXb) of the hydroxymethylene derivative was employed, using only one equivalent of sodium methoxide, the **methyl ester of 2-(γ-ketobutyl)-4-(4′-carboxyphenyl)-cyclohexanone (Xc)** was obtained in 51% yield, m. p. 72–74°. Recrystallization from methanol yielded stout colorless prisms, m. p. 74–75°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 72.0; H, 7.2.

6-(4′-Carboxyphenyl)-Δ^{1-9}-octalone-2 (XIa).—Cyclization of 7.20 g. of a mixture of the γ-ketobutyl acids (with and without the formyl group) as obtained directly from the alkylation reaction (m. p. 138–152°) was carried out in 500 ml. of 2% sodium hydroxide under nitrogen at 20° for fifty minutes. Recrystallization of the product from acetone gave 4.21 g., m. p. 197–200° (cloudy, clear at 204°) and 1.19 g., m. p. 188–200°, for a total yield of 80–88%, depending on the composition of the starting material; the over-all yield from the hydroxymethylene derivative IXa was 72%. Recrystallization from acetone gave small prisms melting at 199–201° to a cloudy melt which cleared at 206°. The compound showed a single absorption maximum at 240 mμ with E = 33,400.[20]

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.3; H, 6.6.

Cyclization of the pure 2-formyl-2-(γ-ketobutyl) derivative (Xb) gave the same cyclic ketone in 85% yield.

The **methyl ester** (XIb) prepared in 74% yield with diazomethane, was evaporatively distilled at 160° (0.1 mm.) and recrystallized from benzene–petroleum ether as stout prisms, m. p. 118–119°. Occasionally a sample melted at 103–104°, solidified and remelted at 118–119°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1. Found: C, 75.9; H, 6.8.

The same methyl ester was obtained by cyclizing 178 mg. of 2-(γ-ketobutyl)-4-(4′-carbomethoxyphenyl)-cyclohexanone (Xc) in 10 ml. of methanol containing 0.4 g. of potassium hydroxide and 0.4 ml. of water, allowing to stand at room temperature under nitrogen for one hour. After dilution and extraction, 10 mg. (6%) of the cyclic acid, m. p. 194–198°, was obtained from the alkaline extract. From the neutral fraction after evaporative distillation at 170° (0.1 mm.) and crystallization from ether was obtained 83 mg. (50%) of the methyl ester, m. p. 102–104°; seeding the melt with a crystal of the higher form raised the m. p. to 117–118°.

The **2,4-dinitrophenylhydrazone** of the methyl ester of the cyclic ketone, prepared in methanol solution, crystallized as fine red needles from methyl acetate, m. p. 237–238°.

(20) This high extinction coefficient is due to the presence of the aromatic carboxyl group (*cf.* VIIIa) as well as the α,β-unsaturated ketone.

Anal. Calcd. for $C_{24}H_{24}O_6N_4$: C, 62.1; H, 5.2. Found: C, 62.6; H, 5.3.

Preparation of the Analogs of Progesterone and Desoxycorticosterone

Preparation of an Acid Chloride in the Presence of an α,β-Unsaturated Ketone.—In order to test the oxalyl chloride–sodium salt procedure for preparing an acid chloride and to ascertain conditions under which the α,β-unsaturated ketone grouping would not be affected, model experiments were carried out with 6-cyclohexyl-Δ^{1-9}-octalone-2 (XIV, R = H).[4] When refluxed in benzene solution with 1.5 equivalents of oxalyl chloride and a drop of pyridine for two hours, none of the ketone could be recovered as the semicarbazone. Similar results were obtained at room temperature for two hours, but at 0° for two hours, 70% of the ketone could be recovered as the semicarbazone.

On the basis of these results, a mixture of 320 mg. of 6-cyclohexyl-Δ^{1-9}-octalone-2 dissolved in 2 ml. of dry benzene, 200 mg. of dry, powdered sodium benzoate and a drop of pyridine were cooled in an ice-bath and treated with 210 mg. of freshly distilled oxalyl chloride, giving an immediate evolution of gas which stopped after one minute. The flask was removed from the ice-bath, and after five minutes the solvent was removed under reduced pressure at 15° or below, followed by addition and removal of three portions of benzene. A solution of the resulting oil in 5 ml. of cold benzene was treated with 0.3 g. of aniline. After five minutes the mixture was diluted and extracted and a total of 224 mg. (82%) of benzanilide isolated by trituration of the product with petroleum ether, m. p. 162–163°. Evaporation of the petroleum ether filtrate and conversion to the semicarbazone gave 350 mg. of this derivative of the starting ketone, corresponding to 88% recovery.

Anilide of 6-(4′-Carboxyphenyl)-Δ^{1-9}-octalone-2.—The finely powdered acid XIa was dissolved in a 5% excess of 0.2 *N* sodium hydroxide and the resulting solution frozen in Dry-Ice and evaporated to dryness under reduced pressure. The resulting fluffy powder was then dried at 105° (0.1 mm.) for four hours.

To 1 ml. of dry benzene was added 58 mg. of the sodium salt and a drop of pyridine, and after cooling in ice, 60 mg. of oxalyl chloride was added and the mixture removed from the ice-bath. The evolution of gas stopped after five minutes and the solvent was removed under reduced pressure below 15°, adding two more portions of dry benzene and removing. The residue was stirred with 2 ml. of dry benzene and filtered through a sintered glass funnel into a benzene solution of 200 mg. of aniline. After five minutes the mixture was diluted and extracted, washing with acid and alkali, and the anilide obtained from the neutral portion by crystallization from acetone giving 26 mg. (38%), m. p. 204–214°. Further recrystallization raised the m. p. of the tan product to 218–219°.

Anal. Calcd. for $C_{23}H_{23}O_2N$: C, 80.0; H, 6.7. Found: C, 79.8; H, 6.9.

6-(4′-Acetylphenyl)-Δ^{1-9}-octalone-2 (XII).—The sodium salt prepared from 1.00 g. of the acid XIa was converted to the acid chloride as described above, using 20 ml. of dry benzene, four drops of pyridine, 3 ml. of oxalyl chloride, and allowing fifteen seconds before removal from the ice-bath (gas evolution complete) and then another three minutes, finally evaporating under reduced pressure below 15° as above. A solution of the residue in benzene was filtered and added to sodiomalonic ester (prepared from 0.47 g. of sodium powder and 4.7 g. of diethyl malonate in 20 ml. of ether, stirring and refluxing for three hours). The mixture was stirred at room temperature for two hours, then hydrolyzed, acidified with acetic acid and extracted with ether. The residual oil after removal of the ether was refluxed for 1.75 hours with 10 ml. of acetic acid, 10 ml. of hydrochloric acid and 4 ml. of water. After diluting and extracting thoroughly with a mixture of benzene and ether, washing with dilute sodium carbonate, dilute acid and water, the extract was dried (sodium sulfate) and the oil crystallized from ether–benzene giving 502 mg., micro[13] m. p. 92–98° and 52 mg., m. p. 89–97°. Recrystallization from benzene–petroleum ether afforded 405 mg., micro m. p. 110–112° and 82 mg., m. p. 106–110°, for a 49% yield. A lower melting modification was sometimes obtained melting at 98–100°, solidifying and remelting at 111–112°. The compound had an absorption maximum at 250 mμ with E = 29,400.[21]

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.5; H, 7.5. Found: C, 80.7; H, 7.5.

The **bis-(2,4-dinitrophenylhydrazone) of XII** prepared in alcohol containing a drop of hydrochloric acid, heating for two hours, was obtained in 100% yield, and crystallized from chloroform–ethanol as an orange-red solid, micro m. p. 258–259°.

Anal. Calcd. for $C_{30}H_{28}O_8N_8$: C, 57.3; H, 4.5. Found: C, 57.2; H, 4.2.

6-(4′-Acetoxyacetylphenyl)-Δ^{1-9}-octalone-2 (XIII).[22]—A benzene solution of the acid chloride, prepared as described above from the sodium salt of 1.00 g. of the acid XIa, was diluted with an equal volume of dry ether, cooled to −10° and added to a dry ethereal solution (at −30°) of diazomethane prepared from 6 g. of nitrosomethylurea.[23] After one-half hour at −15° and one-half hour at 0° the solvent was removed at reduced pressure leaving a yellow oil which was added to 20 ml. of purified boiling acetic acid.[24] After three minutes the solution was cooled, evaporated under reduced pressure and the resulting oil was dissolved in 20 ml. of benzene, and passed through a column of 10 g. of acid-washed alumina, eluting with 150 ml. of benzene. Evaporation of the eluates and crystallization from methanol gave 256 mg. of product, micro m. p. 103–106° and 273 mg., m. p. 92–100°. Recrystallization of the first crop from methanol afforded 122 mg. of material with the micro m. p. 111.5–112.5°, and having an absorption maximum at 251 mμ (E = 29,600).[21]

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8. Found: C, 73.6; H, 6.7.

Evaporative distillation of the second crop and the filtrate from the first crop at 150° (0.001 mm.) yielded an additional 37 mg., micro m. p. 107–110° and 70 mg., m. p. 101–107°, corresponding to a total yield of 19%.

When 70 mg. of the sodium salt of XIa was converted to the diazoketone as described above and a solution of the yellow oil in benzene–ether treated with 1 ml. of 48% hydrobromic acid, 27 mg. (32%), micro m. p. 112–132°, of crude **6-(4′-α-bromoacetylphenyl)-Δ^{1-9}-octalone-2** (XII, R = $COCH_2Br$) could be crystallized from methanol. After further recrystallization from methanol the micro melting point of the small rosettes of needles was 138–139°.

Anal. Calcd. for $C_{18}H_{19}O_2Br$: C, 62.3; H, 5.5. Found: C, 62.8; H, 5.7.

6-(4′-Acetylcyclohexyl)-Δ^{1-9}-octalone-2 (Isomer A) (XIV). (a) Sodiomalonic Ester Method.—Isomer A of 6-(4′-carboxycyclohexyl)-Δ^{1-9}-octalone-2 (VIIa) was converted to the sodium salt as described above for the corresponding phenyl derivative XIa, giving a glassy solid which was finally dried at 105° (0.1 mm.) for four hours, cooled and powdered. A mixture of 300 mg. of the salt,

(21) The shift in maximum from 240 mμ for XIa to 250 mμ for XII and XIII parallels that observed in going from a benzoic acid to an acetophenone derivative; here this maximum is added to that due to the unsaturated ketone system giving a smooth curve with a single high maximum.

(22) A preliminary experiment in which 6-cyclohexyl-Δ^{1-9}-octalone-2 was treated with diazomethane in ether at 0° for one hour, showed that the ketone could be recovered unchanged in 97% yield as the semicarbazone, m. p. 219–220°. The absorption maximum for the crude oily ketone was unchanged, 239 mμ (E = 16,700).

(23) The ethereal diazomethane solution was distilled, dried for two hours at 0° over potassium hydroxide pellets and finally for one hour at 0° over sodium wire; *cf.* Fieser and Turner, THIS JOURNAL, **69**, 2341 (1947).

(24) The acetic acid was refluxed for six hours with 5% by weight of potassium permanganate, distilled and refractionated, using the last fraction, b. p. 117°.

2 ml. of dry benzene and two drops of pyridine was ground to a fine suspension with a glass rod, cooled in an ice-bath and treated with 1 ml. of redistilled oxalyl chloride. After the immediate evolution of gas slowed, the mixture was allowed to come to 15° and after five minutes the excess oxalyl chloride and benzene removed as described above, keeping the temperature below 15°. The acid chloride in 2 ml. of benzene was filtered and added to sodiomalonic ester (from 3 g. of malonic ester, 0.23 g. of sodium powder and 15 ml. of ether), stirring overnight at room temperature. Hydrolysis of the product with 2.5 ml. of acetic acid, 2.5 ml. of hydrochloric acid and 1 ml. of water at reflux for two hours, working up the mixture as described above, gave 240 mg. of a reddish oil. This was adsorbed on 5 g. of alumina from benzene–petroleum ether (1:1) and fractionally eluted. From the later eluates with the same mixture, followed by benzene and benzene–ether (1:1) was obtained solid material which was recrystallized from ether–petroleum ether giving 53 mg. (18%) of the diketone XIV (Isomer A), micro m. p. 92–97°. Further recrystallization from the same solvent gave stout prisms, micro m. p. 96–98°, with an absorption maximum at 239 mμ (E = 16,400).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6. Found: C, 79.0; H, 9.6.

The **bis-2,4-dinitrophenylhydrazone of XIV (Isomer A)**, prepared in alcohol containing hydrochloric acid, was obtained originally as a red solid, micro m. p. 125–129°. Recrystallization from chloroform–alcohol raised the micro m. p. to 220–221°. It is not known whether this large change was due to impurities or to polymorphic forms.

Anal. Calcd. for $C_{30}H_{34}O_8N_8$: C, 56.8; H, 5.4. Found: C, 56.8; H, 5.3.

(b) **Dimethylcadmium Method.**[25]—A solution of dimethylcadmium was prepared from 30 ml. of 0.24 N methylmagnesium bromide and 0.75 g. of cadmium chloride, refluxing and stirring under nitrogen until the Gilman test for the Grignard reagent was negative. The ether was distilled and replaced by 10 ml. of benzene and a benzene solution of the acid chloride prepared from 1.00 g. of the acid VIIa (Isomer A) was added. After refluxing and stirring one hour the mixture was cooled, hydrolyzed and the organic portion isolated as a reddish oil. This was adsorbed from benzene on a column of 20 g. of alumina and fractionally eluted with the same solvent; from the middle fractions crystalline material was obtained and recrystallized from ether–petroleum ether, affording 132 mg. (13%) of the same diketone XIV (Isomer A) as in (a), micro m. p. 95–97°, mixed m. p. 96–98°.

6-(4′-Acetoxyacetylcyclohexyl)-$\Delta^{1,9}$-octalone-2 (Isomer A) (XV).—The acid chloride from 1.00 g. of the acid VIIa (Isomer A) was treated with diazomethane as described for the phenyl derivative XIa, and the oily diazoketone added to boiling acetic acid, heating for three minutes. After removing the solvent under reduced pressure the residue was triturated with methanol giving 500 mg. of brown solid, micro m. p. 100–105°, which was evaporatively distilled at 115–140° (0.001 mm.) and recrystallized from methanol to give 225 mg., m. p. 115–120° and 110 mg., m. p. 100–115°, corresponding to 28% yield. Two recrystallizations from methanol raised the micro m. p. to 123–124.5°; the absorption spectrum showed a maximum at 239 mμ (E = 16,900).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.3; H, 8.5. Found: C, 72.6; H, 8.6.

Summary

Procedures have been developed for the synthesis of some analogs of progesterone and desoxycorticosterone lacking ring C, and with a six-membered ring D. The method involves the Robinson–Mannich base procedure for synthesizing α,β-unsaturated cyclic ketones, modified for application to hydroxymethylene ketones. The progesterone analogs were physiologically inactive; further tests are underway.

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(25) Cason, *Chem. Rev.*, **40**, 15 (1947).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Stobbe Condensation with Ethyl γ-Anisoylbutyrate. A New Route to Some Estrone Intermediates

BY WILLIAM S. JOHNSON, A. RUSSELL JONES[1] AND WILLIAM P. SCHNEIDER[2]

In work directed toward the total synthesis of estrone various investigators—notably Robinson[3] and Bachmann[4] and their respective collaborators—have developed methods for the synthesis of ketooctahydrophenanthrene derivatives like VIII in which the keto group serves as a site for attachment of the final five-membered ring D. The keto ester VIII (R^1 = CH_3, R^2 = $COOCH_3$), which was first prepared by Robinson and Walker[3b,d] (as the ethyl ester, R^2 = $COOC_2H_5$) and later made more readily available by a new method of Bachmann, Kushner and Stevenson,[4,5] has more recently gained particular prominence due to the work of Anner and Miescher[6] who obtained three of the four possible racemic modifications in crystalline form, one of which was converted into estrone by the Bachmann method for introducing ring D.[7]

The present work involves the study of a completely new approach to these important intermediates. The scheme, which is outlined in the accompanying flow sheet, avoids the necessity of relatively inaccessible meta substituted anisoles as starting materials by employing a cyclization directed into the meta position (IV → V). The method involves the first (to our knowledge) successful application of the Stobbe condensation to a keto ester.

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(3) (a) Robinson and Schlittler, *J. Chem. Soc.*, 1288 (1935); (b) Robinson and Walker, *ibid.*, 192, 747 (1936); (c) 60 (1937); (d) 183 (1938).

(4) Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

(5) See also Wilds and T. L. Johnson, *ibid.*, **70**, 1166 (1948).

(6) Anner and Miescher, *Helv. Chim. Acta*, **30**, 1422 (1947).

(7) Anner and Miescher, *Experientia*, **4**, 25 (1948); *Helv. Chim. Acta*, **31**, 2173 (1948).