[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF ALICYCLIC COMPOUNDS RELATED TO THE STEROIDS[1]

W. E. BACHMANN AND ANDRE S. DREIDING[2]

Received December 31, 1947

The route from cyclohexanone to desoxyandrosterone has been outlined in a previous paper (1). The synthesis of 9-methyl-1-decalone described there has been improved and several new intermediates have been isolated. The unsaturated Reformatsky ester (I), prepared from 2-methyl-2-carbomethoxycyclohexanone and methyl γ-bromocrotonate, was not dehydrated by boiling acetic anhydride. Thionyl chloride, however, followed by alcoholic potassium hydroxide, yielded 2-methyl-2-carboxycyclohexylidenecrotonic acid (III). Its ultraviolet absorption spectrum (curve 1) with a maximum at 270 mμ (log ϵ = 4.4) indicated that the diene system was conjugated with the carboxyl group (2). Catalytic reduction of the diene acid gave γ-2-methyl-2-carboxycyclohexanebutyric acid (IV) which proved to be the *cis* form. The distilled unsaturated Reformatsky ester (I) absorbed one mole of hydrogen in a few minutes. Alkaline hydrolysis of the product afforded crystalline γ-2-methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (V). The dimethyl ester of V was dehydrated and hydrolyzed by treatment with thionyl chloride and alcoholic potassium hydroxide. The product was catalytically hydrogenated to IV.

A 90% yield of *cis*-9-methyl-2-carbomethoxy-1-decalone was obtained from the dimethyl ester of IV by the Dieckmann method when the solvent was distilled from the mixture during the reaction. Hydrolysis and decarboxylation proceeded quantitatively to yield *cis*-9-methyl-1-decalone. The cyclic ketone was formed in 41% yield when IV was treated with boiling acetic anhydride and the product was pyrolyzed.

The formation of the dimethyl ester of IV from *cis*-2-methyl-2-carboxycyclohexaneacetic acid (m.p. 163–164°), whose configuration had been established recently,[3] proved that IV had the *cis* configuration. The acetic acid side chain was lengthened by two successive Arndt-Eistert reactions, and the resulting dimethyl ester of IV was converted to *cis*-9-methyl-1-decalone. This synthesis furnishes confirmatory evidence for the previously assigned configurations of the 9-methyl-1-decalones.

A new synthesis of γ-2-methyl-Δ^1-cyclohexenebutyric acid consisted in condensing 2-methylcyclohexanone with methyl γ-bromocrotonate and zinc, hydro-

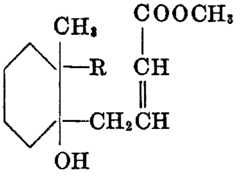
---

[1] Presented by W. E. Bachmann before the Chemical Societies in Basel, Zürich, and Geneva, Switzerland, May 8–16, 1947, under the auspices of the American-Swiss Foundation for Scientific Exchange.

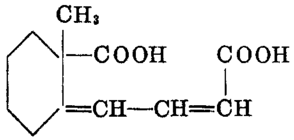
[2] From the Ph.D. dissertation of Andre S. Dreiding, 1947.

[3] Davis, Ph.D. dissertation (1942) in "Summaries of Theses," Harvard Graduate School, 1946. The diacid (m.p. 158–163°) was synthesized by adding butadiene to citraconic anhydride, hydrogenating and hydrolyzing the product, and carrying out an Arndt-Eistert reaction on the secondary acid group.

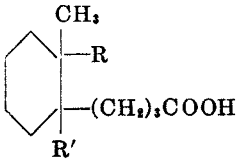
genating the unsaturated Reformatsky ester II, and dehydrating and hydrolyzing the product. The same acid was formed on pyrolysis of γ-2-methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (V) at 200°. The unsaturated acid had been prepared previously by several methods, and its acid chloride had been cyclized by stannic chloride, and the product dehydrochlorinated to 9-methyl-1-octalone (Δ^{5-10} or Δ^{4-10}) (3). We have now obtained the same ketone directly by cyclizing



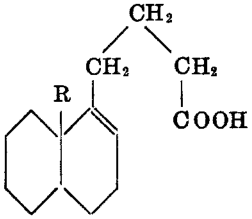
I, R = $COOCH_3$
II, R = H



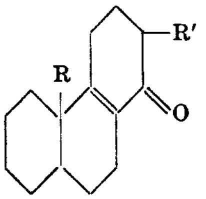
III



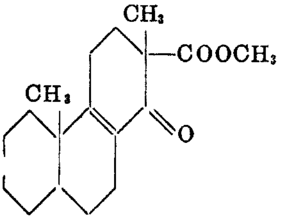
IV, R = COOH; R′ = H
V, R = COOH; R′ = OH
VI, R = H; R′ = OH



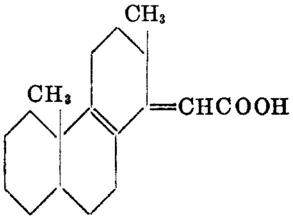
VII, R = CH_3
VIII, R = H



IX, R = CH_3; R′ = H
X, R = R′ = H
Xa, R′ = H; aromatic A ring
XI, R = CH_3; R′ = $COCOOCH_3$
XII, R = CH_3; R′ = $COOCH_3$
XIII, R = R′ = CH_3



XIV



XV

the unsaturated acid with a mixture of acetic anhydride and acetic acid containing a small amount of zinc chloride. The best results were obtained when the reaction was conducted at relatively low temperatures.[4] The reduction of the octalone to *cis*-9-methyl-1-decalone was carried out as has been described (3).

---

[4] This method of Fieser and Hershberg had been employed by several investigators for ring closure onto aromatic rings. Recently Johnson and co-workers, *J. Am. Chem. Soc.*, **67**, 1360 (1945), employed this mixture at reflux temperature for the preparation of unsaturated five-membered ring ketones. Under these conditions we obtained only 20–35% yields of three of our four six-membered ring ketones in contrast to the 75–96% yield obtained at lower temperatures.

cis-9-Methyl-1-decalone with methyl γ-bromocrotonate and zinc gave the unsaturated Reformatsky ester, which was hydrogenated and subsequently dehydrated and hydrolyzed to γ-9-methyl-Δ^1-1-*cis*-octalinbutyric acid (VII).[5] Cyclization by the zinc chloride-acetic anhydride method afforded *cis*-1-keto-4b-methyl-Δ^{4a-10a}-dodecahydrophenanthrene (IX)[5, 6] in 84% yield. In accord with the proposed structure, the ketone showed the characteristic absorption spectrum (maximum at 247 mμ; log ε = 4.0; curve 2) of α,β-unsaturated ketones (4).

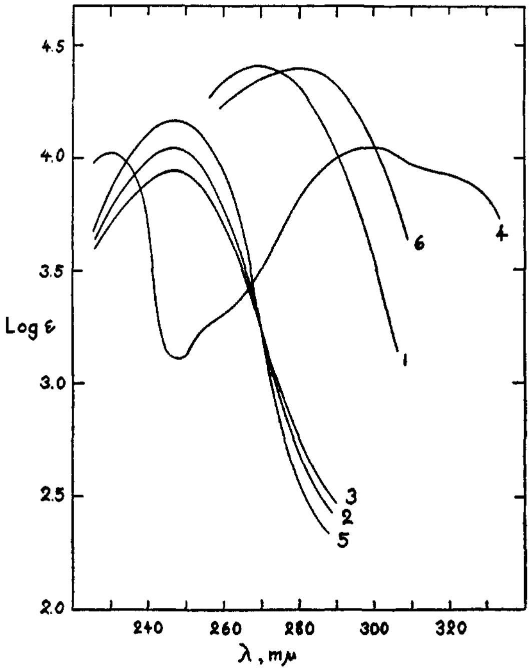


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

Curve 1: III, 2-methyl-2-carboxycyclohexylidenecrotonic acid.
Curve 2: IX, *cis*-1-keto-4b-methyl-Δ^{4a-10a}-dodecahydrophenanthrene.
Curve 3: X, 1-keto-Δ^{4a-10a}-dodecahydrophenanthrene.
Curve 4: Xa, 1-keto-1,2,3,4,9,10-hexahydrophenanthrene.
Curve 5: XIII, *cis*-1-keto-2,4b-dimethyl-Δ^{4a-10a}-dodecahydrophenanthrene.
Curve 6: XV, *cis*-2,4b-dimethyl-Δ^{4a-10a}-dodecahydro-1-phenanthrylideneacetic acid.

The same cyclization method applied to the corresponding desmethyl unsaturated acid VIII yielded the unsaturated cyclic ketone X, identical with that

---

[5] The prefix *cis* refers to the configuration between the rings (A and B rings for the polycyclic compounds).

[6] While this paper was being written, the abstract of a paper by Banerjee, *Science and Culture*, **12**, 508 (1947); *Chem. Abstr.*, **41**, 6557 (1947), appeared describing the preparation of this ketone by another method. We have also learned from Professor J. W. Cook that he and his co-workers have prepared the ketone through the use of methyl γ-bromocrotonate.

obtained by the stannic chloride method (1). The structure X received confirmation from the ultraviolet absorption spectrum (maximum at 247 mμ; log ϵ = 3.9; curve 3) (4, 5). A similar cyclization of γ-3,4-dihydro-1-naphthalenebutyric acid (1) gave 1-keto-1,2,3,4,9,10-hexahydrophenanthrene (Xa) in nearly quantitative yield (5). The unsaturated cyclic ketone showed the strong absorption maxima (curve 4) at 232 mμ (log ϵ = 4.1) and at 300 mμ (log ϵ = 4.1) characteristic of the triply conjugated system: benzene ring—double bond—keto group (4).[7]

The unsaturated ketone IX reacted smoothly with dimethyl oxalate in the presence of sodium methoxide. Pyrolysis of the crystalline glyoxalate (XI) gave the β-keto ester, *cis*-1-keto-2-carbomethoxy-4b-methyl-Δ^{4a-10a}-dodecahydrophenanthrene (XII), which on methylation gave *cis*-1-keto-2-carbomethoxy-2,4b-dimethyl-Δ^{4a-10a}-dodecahydrophenanthrene (XIV). Decarboxylation of the acid derived from (XIV) afforded *cis*-1-keto-2,4b-dimethyl-Δ^{4a-10a}-dodecahydrophenanthrene (XIII), whose absorption spectrum (maximum at 247 mμ; log ϵ = 4.1; curve 5) showed it to be an α,β-unsaturated ketone (4). The ketone was transformed into the unsaturated acid, *cis*-2,4b-dimethyl-Δ^{4a-10a}-dodecahydro-1-phenanthrylideneacetic acid (XV) through the Reformatsky reaction. The ultraviolet absorption spectrum (maximum at 280 mμ; log ϵ = 4.4; curve 6) showed it to be an $\alpha,\beta,\gamma,\delta$-diene acid (2), in agreement with the proposed structure XV. This acid, as well as XIII and XIV should prove useful for preparing the desoxyandrosterone structure.

We are indebted to the Monsanto Chemical Company for a grant which was used to provide support for Andre Dreiding during this investigation.

EXPERIMENTAL

Dimethyl ester of γ-2-methyl-2-carboxy-1-hydroxycyclohexanecrotonic acid (I). 2-Carbomethoxycyclohexanone was prepared according to the method described for the corresponding ethyl ester (6); an equal volume of absolute methanol was used to dissolve the dimethyl oxalate. The second distillation of the keto ester was carried out with a six-inch column; b.p. 95–107° (30 mm.); yield, 43%. The keto ester was methylated by the procedure described for the ethyl ester (7); yield, 90%; b.p. 69–72° (0.4 mm.); n_D^{25} 1.4570.

A mixture of 20 g. of 2-methyl-2-carbomethoxycyclohexanone, 10 g. of methyl γ-bromocrotonate, and 20 g. of cleaned zinc (20 mesh) in 50 cc. of anhydrous ether and 50 cc. of dry reagent benzene was heated nearly to the boiling point. A few small crystals of iodine were added and allowed to rest on the zinc without agitation. Within a few minutes the iodine color disappeared and a white cloud rose from the zinc at the point where the iodine had attacked it. This indicated the start of the reaction, which proceeded with slight evolution of heat as an additional 46 g. of methyl γ-bromocrotonate was added slowly over a period of about two hours. The mixture was kept refluxing for four hours more. Fresh zinc was added in 5-g. batches at hourly intervals during the first three hours. The complex was dissolved by the addition of 25 cc. of glacial acetic acid. When the solution was clear, it was decanted from the excess zinc into ice-cold water. The zinc salts were removed by extraction with ten 50-cc. portions of 1% ammonium hydroxide. The crude Reformatsky ester, obtained by concentrating the solution, was distilled through a two-inch fractionating column, b.p. 135–145° (0.05 mm.); yield, 26.66 g. (84%); n_D^{23} 1.4900.

---

[7] Wilds and co-workers, *J. Am. Chem. Soc.*, **69**, 1985 (1947), have recently examined the ultraviolet absorption spectra of a series of compounds with related structures, including this ketone. Our results are in agreement.

Anal. Calc'd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20.
Found: C, 62.87; H, 8.49.

2-Methyl-2-carboxycyclohexylidenecrotonic acid (*III*). A solution of the unsaturated Reformatsky ester (I) (1.5 g.) in 5 cc. of ether was added dropwise to a chilled mixture of 1.4 cc. of pure thionyl chloride, 0.8 cc. of pyridine, and 5 cc. of ether. After one hour at 0°, the precipitated pyridine hydrochloride was dissolved by the addition of small pieces of ice. The excess of thionyl chloride in the organic layer was decomposed by extraction with a sodium bicarbonate solution until no more carbon dioxide was evolved. The solvent was removed and the residual oil refluxed for ten hours in a solution of 2.5 g. of potassium hydroxide in 17 cc. of absolute methanol. Some methanol was removed *in vacuo*, and the residue acidified with cold dilute hydrochloric acid. The crude acid precipitated as a cream colored solid; yield, 0.98 g. (82%), m.p. 196–206°. Recrystallization from aqueous methanol yielded colorless short needles, m.p. 205.5–207° (softening at 195°).[8]

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19.
Found: C, 64.53; H, 7.06.

Refluxing the Reformatsky ester (I) in acetic anhydride for one hour did not remove water from the molecule, as evidenced by the fact that the product absorbed only one mole of hydrogen on catalytic reduction. Whether esterification of the hydroxyl group had taken place was not determined.

γ-2-Methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (*V*). A solution of 24.5 g. of the Reformatsky ester (I) was hydrogenated in methanol in the presence of 0.20 g. Adams' catalyst. Within five minutes, one mole equivalent of hydrogen was consumed. The catalyst was removed by filtration and the solvent removed in a stream of dry air. The residual colorless oil (24.8 g.) was used in part directly for the dehydration described in (a) of the next experiment.

A portion was distilled at 130–135° (0.2 mm.). A mixture of 2.5 g. of this distillate, 25 cc. of 40% potassium hydroxide, and 50 cc. of methanol was refluxed for one and one-half hours. Some of the methanol was removed in a stream of dry air, and the residual solution was acidified with cold dilute hydrochloric acid. An oil precipitated which solidified on standing in the cold for several days; weight, 1.52 g. (68%), m.p. 63–69°. Recrystallization from 20% acetic acid afforded elongated colorless prisms, m.p. 73°; yield, 1.25 g. For analysis, a sample was recrystallized from 50% ether-petroleum ether (b.p. 60–75°); m.p. 77.5°.

Anal. Calc'd for $C_{12}H_{20}O_5$: C, 58.90; H, 8.25.
Found: C, 59.06; H, 8.16.

The hydroxy acid (V), m.p. 73°, with diazomethane, yielded the dimethyl ester, which was evaporatively distilled at 130–132° (0.2 mm.), n_D^{25} 1.4519. Dehydration of the latter could not be accomplished by mild methods. Thus, treatment, for one hour, of the ester with acetic anhydride or dry hydrogen chloride gas in boiling benzene and subsequent saponification resulted only in recovery of the hydroxy acid (V).

When the hydroxy acid (V) was pyrolyzed at 220° for thirty minutes and the product subjected to evaporative distillation *in vacuo*, an oil distilled at 110–130° (0.8 mm.). This was dissolved in the minimum amount of hot 50% aqueous methanol and treated with Norit. After filtration and cooling, fine colorless plates of γ-2-methyl-Δ^1-cyclohexenebutyric acid precipitated, m.p. 39°. On recrystallization from the same solvent, it melted at 45.5–46° [reported (3c), 44°]. Neutral equivalent: 182 (requires 182). It combined rapidly with bromine in carbon tetrachloride.

cis-γ-2-Methyl-2-carboxycyclohexanebutyric acid (*IV*). (*a*) *From the saturated hydroxy ester* (*dimethyl ester of V*). To a cold solution of 10 cc. of dried pyridine in 35 cc. of anhydrous ether was added 18 cc. of thionyl chloride (Eastman Kodak, white label, is sufficiently pure). A colorless precipitate dissolved on swirling and a clear yellow solution resulted. To this was added dropwise, with swirling and cooling, a solution of 20 g. of the hydroxy

---

[8] The ultraviolet absorption spectrum of the compound was taken in dilute alcoholic solution with a Beckman spectrophotometer. The oximes absorbed in the same region as the corresponding ketones.

ester (dimethyl ester of V) in 35 cc. of anhydrous ether. After the first few drops, a pyridine salt precipitated. The addition required about fifteen minutes, after which the solution was half filled with a fluffy white precipitate. The mixture was allowed to stand for one hour at 0°. It was poured on cracked ice and, after all the solid had dissolved, the aqueous layer was discarded. The excess thionyl chloride in the organic layer was decomposed by the cautious addition of sodium bicarbonate solution. When no more carbon dioxide was evolved, the solution was extracted with 10% sodium carbonate and water. After drying and filtering, the solvent was removed in a stream of dry air. The residual pale yellow oil was refluxed in a solution of 240 cc. of 18% methanolic potassium hydroxide for twelve hours. About half of the methanol was removed in a stream of dry air and replaced by water. The resulting clear amber solution was heated on a steam-bath for two hours and acidified cold by pouring it into a cold mixture of 150 cc. of 10% hydrochloric acid and 50 cc. of ether. The aqueous layer was drawn off and extracted again with ether. The combined organic layers were washed with water, dried, and concentrated. The crude unsaturated acid was obtained as a viscous oil; yield, 16.2 g.

The above mentioned oil was dissolved in 150 cc. of glacial acetic acid and shaken under 30 lbs. of hydrogen at room temperature in the presence of 0.2 g. of Adams' catalyst for twenty-four hours. Only a small amount of hydrogen was consumed and 0.2 g. of fresh catalyst was added. After further hydrogenation for twenty-four hours, almost the theoretical amount of hydrogen had been taken up. Continued hydrogenation with an additional batch of 0.2 g. of fresh catalyst caused the reduction to reach completion. The catalyst was filtered off and the colorless filtrate was concentrated in a stream of dry air on a steam-bath. The residual colorless oil was dissolved in 100 cc. of methanol, and 100 cc. of water was added. The mixture was heated in the presence of charcoal, filtered, and allowed to cool slowly. On seeding and scratching, *cis-γ-2-methyl-2-carboxycyclohexanebutyric acid (IV)* crystallized in colorless rhombs; yield, 11.92 g. (71%, based on the crude hydroxy ester, and 59%, based on 2-methyl-2-carbomethoxycyclohexanone); m.p. 106–110°. This sample was used for the cyclization experiments described below. A portion, recrystallized from 50% aqueous methanol, melted at 111.5–112° [reported (1) 109–112°].

From the mother liquors, 3.35 g. of an oily acid was obtained. It was not characterized with certainty; it could, however, be cyclized by the methods described below to a camphoraceous ketone.

(*b*) *From the diene acid (III).* A solution of 0.26 g. of the diene acid (III) in 5 cc. of glacial acetic acid was shaken under one atmosphere of hydrogen at room temperature in the presence of a trace of Adams' catalyst. Two mole equivalents of hydrogen were absorbed in twenty minutes. No break after the consumption of one mole could be observed. The catalyst and solvent were removed and the *cis*-acid (IV) crystallized from aqueous methanol; yield, 0.42 g. (92%), m.p. 108–110°. After recrystallization from the same solvent, it melted at 111.5–112° [reported (1) 109–112°]. Hydrogenation of the diene acid in the form of its sodium salt in aqueous solution with Adams' catalyst also yielded only the *cis*-acid (IV), m.p. 111.5–112°.

(*c*) *In form of its dimethyl ester through an Arndt-Eistert reaction.* The dimethyl ester of *cis*-β-2-methyl-2-carboxycyclohexanepropionic acid (7) (1.05 g.) was half-hydrolyzed and the product subjected to an Arndt-Eistert reaction according to the procedure described for the lower homolog (7). In this manner the dimethyl ester of *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid (IV) was obtained. It was evaporatively distilled, b.p. 105–110° (0.02 mm.); yield, 0.62 g. (56%). When this ester was cyclized according to the Dieckmann method, described below, 0.31 g. (77%) of *cis*-9-methyl-1-decalone was obtained. The melting points, mixed melting points, and crystalline forms of the oxime and of the 2,4-dinitrophenylhydrazone showed that this sample of the ketone was identical with the one obtained by the method involving the methyl γ-bromocrotonate Reformatsky reaction.

cis-9-Methyl-1-decalone. (*a*) *By a Dieckmann condensation on the dimethyl ester of IV.* The procedure described here represents a modification and improvement of the one reported (1). The dimethyl ester (27.97 g.) was made from 25.6 g. of the diacid (IV) [m.p. 106–110°; this sample was made by the method described in (a) of the previous experiment] with diazomethane and distilled; b.p. 124–125° (0.4 mm.). Dry sodium methoxide, made from 6.15 g. of clean sodium, was covered with a solution of the ester in 45 cc. of dry reagent benzene. The flask, which was kept filled with nitrogen, was fitted with a gooseneck tube and a receiver. Heat was supplied at such a rate that the benzene distilled into the receiver at a very slow rate. After five hours of heating, the residual light-brown cake was treated with a chilled mixture of 150 cc. of water and 40 cc. of glacial acetic acid. The oil which separated was taken up in ether, washed with sodium bicarbonate solution and water, dried, and concentrated. The residual *cis-9-methyl-2-carbomethoxy-1-decalone* was a pale yellow oil, sufficiently pure for the next step. In some runs, it was evaporatively distilled, b.p. 90–100° (0.4 mm.). The distillate was a colorless oil which gave a purple color with alcoholic ferric chloride.

The crude keto ester was heated up slowly in a solution of 230 cc. of glacial acetic acid, 130 cc. of concentrated hydrochloric acid, and 30 cc. of water in an atmosphere of nitrogen. When the temperature of the solution reached 90–95°, the decarboxylation started, proceeded very vigorously for twenty minutes, more slowly for another twenty minutes, and then ceased. The mixture was diluted with an equal amount of water, saturated with salt, and extracted with ether. The ethereal solution was washed with 10% sodium hydroxide solution until all the acidic material was removed and then with water. After it was dried, the solvent was removed and the residue distilled; b.p. 68–70° (0.2 mm.); yield, 16.23 g. (90%), n_D^{25} 1.4890. On acidification of the alkaline extracts, 2.65 g. of *cis*-γ-2-methyl-2-carbomethoxycyclohexanebutyric acid (monomethyl ester of IV) was obtained as an oil. It was evaporatively distilled at 110–120° (0.3 mm.). This accounted for the 10% of the diester which did not cyclize, and which was half-hydrolyzed under the conditions of the decarboxylation. It was re-esterified and made to undergo the Dieckmann reaction, hydrolysis, and decarboxylation. In this manner an additional 1.65 g. of *cis*-9-methyl-1-decalone was obtained, increasing the yield to 17.88 g. (99%).

(b) By the action of acetic anhydride on the diacid (IV) and pyrolysis of the product.[9] A solution of 1 g. of the *cis*-dibasic acid (IV) in 10 cc. of acetic anhydride was refluxed for two hours. The acetic acid and anhydride were distilled at atmospheric pressure, the residue was heated at 200° for twenty minutes, and the crude product was distilled at 215–225°. The yellow distillate was heated in 10 cc. of glacial acetic acid, 4 cc. of concentrated hydrochloric acid, and 1 cc. of water for one hour. The solution was cooled, saturated with salt, and extracted with ether. The acidic material was removed by extraction with alkali and water. Colorless ketone was obtained by evaporative distillation at 60–70° (0.08 mm.); yield, 0.31 g. (41%). Its oxime melted at 114–115°.

Methyl γ-2-methyl-1-hydroxycyclohexanecrotonate (II). The Reformatsky reaction between 10 g. of 2-methylcyclohexanone and 20 cc. of methyl γ-bromocrotonate in the presence of 10 g. of granulated zinc was conducted in the manner described for the reaction on the 2-carbomethoxy derivative. The crude oil was fractionally distilled through a two-inch column, b.p. 112–116° (0.02 mm.); yield, 15.03 g.(80%). The colorless distillate decolorized bromine in carbon tetrachloride.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.82; H, 9.47.
Found: C, 67.21; H, 9.24.

Methyl ester of γ-2-methyl-1-hydroxycyclohexanebutyric acid (VI). A solution of 13 g. of the above Reformatsky ester (II) in 50 cc. of absolute methanol was shaken in the presence of 0.1 g. of Adams' catalyst under 30 lbs. of hydrogen at room temperature. The theoretical amount of hydrogen was consumed in thirty minutes. The colorless solution was filtered and concentrated *in vacuo* at room temperature. The residual hydroxy ester was distilled through a two-inch column at 85–95° (0.05 mm.); weight, 11.8 g. (90%). The

---

[9] Kon, Linstead, and Simon, *J. Chem. Soc.*, 814 (1937) cyclized this acid (prepared in non-crystalline form by another method) by pyrolyzing it with barium oxide.

colorless distillate did not affect a solution of bromine in carbon tetrachloride. A small fraction was cut at 90° (0.05 mm.) for analysis.

Anal. Calc'd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35.
Found: C, 67.25; H, 9.91.

γ-2-Methyl-Δ¹-cyclohexenebutyric acid. A mixture of 9.1 g. of the above hydroxy ester and 20 g. of powdered fused anhydrous potassium acid sulfate was heated on a steam-bath under nitrogen for thirty minutes. The unsaturated ester, isolated by ether extraction, was distilled through a small fractionating column, b.p. 72–76° (0.02 mm.); yield, 7.48 g. (91%). It immediately decolorized aqueous potassium permanganate.

A solution of the above distillate in 20 cc. of 50% potassium hydroxide and 50 cc. of methanol was refluxed for one hour in an atmosphere of nitrogen. Some of the methanol was removed *in vacuo* and the solution was acidified with chilled dilute hydrochloric acid. The yellow oil which partially solidified was extracted with ether and, after drying and removal of the solvent, was distilled *in vacuo* with slight decomposition, b.p. 110–115° (0.05 mm.) yield, 4.95 g. (72%). A portion of the viscous distillate was dissolved in hot aqueous methanol. On cooling, colorless plates appeared, which, after several recrystallizations, melted at 45–46° (3c). The acid instantly decolorized bromine in carbon tetrachloride and aqueous potassium permangante.

9-Methyl-1-octalone. A solution of 3.74 g. of the above unrecrystallized acid in 37 cc. of acetic anhydride and 7.5 cc. of a 5% solution of fused anhydrous zinc chloride in glacial acetic acid was allowed to stand at room temperature for forty-eight hours and then heated on a water-bath at 70–80° for thirty minutes. The wine red solution was diluted with ether and extracted with ice-cold 5% sodium hydroxide solution until all the anhydride was decomposed and the acid was removed. The ketone, obtained by removal of the solvent, was evaporatively distilled at 70–80° (0.2 mm.); yield, 2.53 g. (75%). The oxime, m.p. 95–95.5° [reported (3a) 99–100° for this oxime or its isomer with the double bond in the alternative position], was prepared in 72% yield, and the semicarbazone, m.p. 227.5–229° [reported, 226–227° (3a), 222–223° (3b), and 228–229° (3c)], in 75% yield. The pure ketone was regenerated by acid hydrolysis of the semicarbazone in 88% yield; b.p. 70–75° (0.2 mm.).[8] The ultraviolet absorption spectrum showed no maximum in the region of 220–340 mμ, and the intensity of absorption in that region was low (log $\epsilon < 3$). This showed that the unsaturation was not conjugated with the keto group.

Methyl γ-9-methyl-1-hydroxy-1-cis-decalincrotonate. A mixture of 5 g. of *cis*-9-methyl-1-decalone, 2.5 g. of methyl γ-bromocrotonate, and 5.5 g. of clean zinc turnings in 15 cc. of anhydrous ether and 15 cc. of dry reagent benzene was heated. Before the solution started to boil, a few small crystals of iodine were added and were allowed to rest on the zinc without agitation. Within a short while, the reaction started, as evidenced by the disappearance of the iodine color and the rising of a white cloud from the zinc. The reaction became slightly exothermic and remained so while an additional 7.5 g. of methyl γ-bromocrotonate was added slowly from a dropping-funnel. When the reaction was well under way, stirring was started at moderate speed. The addition of bromo ester took about three hours; after this, the solution was kept refluxing for another two hours. During the reaction, batches of 2.5 g. of fresh zinc were added at hourly intervals. The yellow complex was decomposed by the addition of excess glacial acetic acid. Cold water and ether were added and the organic layer was washed with as many portions of 1% ammonium hydroxide as needed to remove the zinc salts, and then with water. From the ethereal solution was obtained 8.8 g. of the crude Reformatsky ester. It contained some unreacted ketone, as will be shown below. In some experiments it was distilled with some decomposition, b.p. 160–170° (0.1 mm.). The distillate was a slightly yellow viscous oil. For the continuation of the synthesis a purification was not necessary; the unreacted ketone could be recovered at a later stage.

γ-9-Methyl-Δ¹-1-cis-octalinbutyric acid (VII). The crude Reformatsky ester (8.8 g.) was catalytically reduced in 35 cc. of absolute methanol at room temperature under one atmosphere of hydrogen in the presence of 0.2 g. of Adams' catalyst. The solution was filtered, the solvent was removed, and the oily residue was heated with 20 g. of powdered fused anhydrous potassium acid sulfate in an atmosphere of nitrogen for one hour on a steam-bath. The product, which was isolated by use of ether, and a solution of 13 cc. of 40% potassium hydroxide and 25 cc. of methanol were refluxed for one and one-half hours on a steam-bath under nitrogen. The solution was diluted with water, saturated with salt, and extracted with ether. From the ethereal solution 1.95 g. (39%) of unreacted *cis*-9-methyl-1-decalone was recovered; after evaporative distillation at 0.4 mm. it gave the same yield of Reformatsky product as did the starting ketone. The alkaline solution was acidified with cold dilute hydrochloric acid. The unsaturated acid (VII) was extracted with ether, and the ethereal solution was washed with water, dried, and concentrated *in vacuo* at room temperature; yield of pale yellow oil, 3.14 g. This crude acid was usually used directly for the cyclization. In some experiments it was evaporatively distilled at 143–150° (0.02 mm.). The distillate was a colorless viscous oil which resisted attempts at crystallization. It decolorized both bromine in carbon tetrachloride and aqueous potassium permanganate slowly. The *p-bromophenacyl ester* crystallized in fine colorless needles from aqueous ethanol, m.p. 67–69°.

Anal. Calc'd for $C_{23}H_{29}BrO_3$: C, 63.74; H, 6.74; Br, 18.44.
Found: C, 63.17; H, 6.85; Br, 18.97.

cis-1-Keto-4b-methyl-Δ^{4a-10a}-dodecahydrophenanthrene (IX). A solution of 3.14 g. of the crude unsaturated acid (VII) in 43 cc. of reagent acetic anhydride and 8.6 cc. of a 5% solution of anhydrous fused zinc chloride in glacial acetic acid was allowed to stand at room temperature under nitrogen for twenty hours. The wine red solution was heated at 70° for one hour. Ether was added and the acetic anhydride was decomposed by extraction with chilled 5% sodium hydroxide. From the alkaline extracts a small amount of uncyclized acid could be recovered. The crude ketone (IX), obtained from the ethereal solution, was evaporatively distilled at 105–115° (0.2 mm.); yield, 2.44 g. (84%).[8] The colorless distillate decolorized aqueous potassium permanganate solution slowly. The derivatives were obtained by standard methods. The *oxime* crystallized from aqueous methanol in clusters of colorless needles, m.p. 134–135.5°.

Anal. Calc'd for $C_{15}H_{23}NO$: C, 77.20; H, 9.95; N, 6.00.
Found: C, 77.01; H, 9.72; N, 6.33.

The *semicarbazone* crystallized from methanol in clusters of colorless prisms, m.p. 229–231°.

Anal. Calc'd for $C_{16}H_{25}N_3O$: C, 69.78; H, 9.15.
Found: C, 69.82; H, 9.63.

The *2,4-dinitrophenylhydrazone* crystallized from ethyl acetate in scarlet threads, m.p. 228.5–229.5°.

Anal. Calc'd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06.
Found: C, 63.10; H, 6.46; N, 13.91.

1-Keto-Δ^{4a-10a}-dodecahydrophenanthrene (X). The crude unsaturated acid (VIII) (1) (2.5 g.) was cyclized in the manner described for IX. The crude ketone was evaporatively distilled at 80–100° (0.05 mm.); yield, 1.42 g. (62%). The scarlet 2,4-dinitrophenylhydrazone, after recrystallization from ethyl acetate, melted at 229–230° d. [reported (1) 215–216° d.]. The *oxime*, m.p. 142–145°, was prepared in 88% yield. A small portion, recrystallized from dilute methanol and then from petroleum ether (b.p. 65–70°), formed glistening elongated prisms, m.p. 171.5–173.5°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39.
Found: C, 76.81; H, 9.22; N, 6.40.

The pure ketone was obtained from a boiling (three hours) solution of 0.31 g. of the oxime (m.p. 144–146°) in 3.8 cc. of 15% hydrochloric acid and 10 cc. of ethanol. The ketone was extracted and evaporatively distilled at 100–109° (0.05 mm.);[8] yield, 0.28 g. (90%).

Cyclization of γ-3,4-dihydro-1-naphthalenebutyric acid by acetic anhydride and zinc chloride. The acid (1) (0.66 g.) was cyclized in the manner described for IX. The crude *1-keto-1,2,3,4,9,10-hexahydrophenanthrene (Xa)* was evaporatively distilled at 90–100°

(0.02 mm.); yield, 0.58 g. (96%). The *2,4-dinitrophenylhydrazone*, m.p. 238–242°, was obtained in quantitative yield. After two recrystallizations from ethyl acetate, it formed fine magenta needles, m.p. 259–260°.

Anal. Calc'd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.80; N, 14.81.
Found: C, 63.27; H, 4.88; N, 14.77.

The oxime crystallized from aqueous methanol in stout colorless needles, m.p. 142-143° [reported, 140.5–141.5° (1), 141.5–142° (8)]. The semicarbazone, after recrystallization from aqueous methanol, melted at 254–258° d. [reported (8) 257–258°]. The crystalline ketone was obtained by hydrolyzing 0.31 g. of the oxime (m.p. 142–143°) in 3.8 cc. of 15% hydrochloric acid and 10 cc. of ethanol on a steam-bath for three hours under nitrogen. The ketone was extracted with ether, evaporatively distilled (at 85–95° and 0.02 mm.; yield, 0.25 g.) and recrystallized twice from ether-petroleum ether; m.p. 48–49°[8] [reported 48–49° (1), 49–50° (8)]; yield, 0.20 g. (65%).

cis-Methyl 1-keto-4b-methyl-Δ^{4a-10a}*-dodecahydro-2-phenanthreneglyoxalate* (*XI*). Dry sodium methoxide (from 0.25 g. of sodium) and 1 g. dimethyl oxalate were suspended in 56 cc. of dry benzene. A solution of 0.82 g. of the unsaturated ketone (IX) in 4 cc. benzene was added dropwise while the mixture was kept under nitrogen at 0°. After standing at room temperature for two hours, the solution was treated with cold water, a little 5% sodium hydroxide, and ether. The aqueous layer was drawn off and the organic layer extracted with some more alkali. From the ethereal solution, about 3% of unreacted ketone could be recovered. The combined alkaline layers were washed with ether and acidified with cold 10% hydrochloric acid. The precipitate was taken up in ether and, after concentrating, a golden viscous oil was obtained; yield, 1.10 g. (95%). The glyoxalate solidified upon standing in the cold; it was placed on a Büchner funnel, pressed, and washed with a few drops of cold methanol; m.p. 75–78°; weight, 1 g. From the mother liquor, another 0.08 g. of solid glyoxalate was obtained by evaporating and treating with a few drops of methanol; total yield, 1.08 g. (94%). A sample crystallized from absolute methanol in elongated cream colored prisms, m.p. 76.5–77.5°.

Anal. Calc'd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95.
Found: C, 71.24; H, 8.04.

The glyoxalate gives a dark red-brown color with alcoholic ferric chloride. It is insoluble in sodium bicarbonate but soluble in 5% sodium hydroxide solution. When an alkaline solution of the glyoxalate was allowed to stand at room temperature for several days, the parent ketone (IX) precipitated.

cis-2-Carbomethoxy-1-keto-2,4b-dimethyl-Δ^{4a-10a}*-dodecahydrophenanthrene* (*XIV*). A mixture of 0.61 g. of the glyoxalate and 2 g. of powdered glass (9) was slowly heated in a test-tube under an atmosphere of nitrogen. At a bath temperature of 158° the evolution of carbon monoxide started and continued until the temperature had reached 170° after ten minutes. During the next three minutes the bath temperature rose to 175° but no additional gas was evolved. Exactly the theoretical amount (48 cc. at 22°) of gas was collected in a gas burette. The gas burned with a dull blue flame. The residue was taken up in ether and the ethereal solution washed with 5% sodium hydroxide solution to remove any unreacted glyoxalate. After removal of the ether, the keto ester (XII) was obtained as a dark viscous oil; yield, 0.53 g. It gave a green color with alcoholic ferric chloride.

This oil, dissolved in 4 cc. of dry benzene, was added to a cold solution of 0.47 g. of sodium methoxide in 6.0 cc. anhydrous methanol. Methyl iodide (1.8 cc.) was added and the mixture was allowed to stand at 0° for one hour. Another 0.8 cc. of methyl iodide was added and the solution again allowed to stand at 0° for one-half hour and then at room temperature for fifteen hours. The solution, which was now neutral to moist litmus paper, was concentrated and water, ether, and salt were added. The ethereal solution was washed with 5% sodium hydroxide and water, dried, and filtered through a small column of activated alumina. The filtrate was concentrated and the residue evaporatively distilled at 125–135° (0.05 mm.); yield, 0.55 g. (87%). The colorless viscous keto ester (XIV) slowly decolorized aqueous potassium permanganate.

cis-1-Keto-2,4b-dimethyl-Δ^{4a-10a}-dodecahydrophenanthrene (XIII). For the decarboxylation, 0.235 g. of the methylated keto ester (XI) was dissolved in a solution of 5 cc. of 20% potassium hydroxide and 10 cc. of methanol. The mixture was refluxed under nitrogen for fifteen hours. After cooling, it was diluted with water, saturated with salt and extracted with ether. The crude ketone was evaporatively distilled at 90–100° (0.02 mm.); yield, 0.177 g. (94%).[8] The colorless oil slowly decolorized aqueous potassium permanganate. The *oxime*, which formed readily, crystallized from methanol with a little water in colorless rhombs; m.p. 196–197°.

Anal. Calc'd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66.
Found: C, 78.02; H, 9.99; N, 5.86.

The *2,4-dinitrophenylhydrazone*, which formed more sluggishly than with the two lower homologs (IX and X), crystallized from methanol-ethyl acetate in fine scarlet needles, m.p. 159–161°.

Anal. Calc'd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58.
Found: C, 64.30; H, 6.72; N, 13.30.

cis-2,4b-Dimethyl-Δ^{4a-10a}-dodecahydro-1-phenanthrylideneacetic acid (XV). A mixture of 0.12 g. of the unsaturated ketone (XIII), 0.3 g. of cleaned granulated (20 mesh) zinc, and 0.1 cc. of methyl bromoacetate in 1.5 cc. of ether and 2.0 cc. of reagent benzene was heated to reflux with a crystal of iodine. The Reformatsky reaction started after ten minutes. Reflux was continued for twenty-four hours during which time four equal portions of fresh zinc and methyl bromoacetate were added. The yellow complex was decomposed with acetic acid and water. The Reformatsky ester was purified by extraction with 1% ammonium hydroxide solution. The crude product was treated with 0.18 cc. of thionyl chloride in benzene in the presence of 0.12 cc. of pyridine at 0°. After an hour, the excess thionyl chloride was decomposed by the addition of ice and extraction with sodium bicarbonate solution. The solvents were removed *in vacuo*, and the residue was refluxed in 4 cc. of 10% methanolic potassium hydroxide for five hours. Extraction with ether afforded 0.03 g. of unreacted ketone (XIII). The alkaline solution was acidified cold and extracted with ether. The ethereal solution was dried and concentrated. Upon addition of a few drops of absolute methanol, the crude residue crystallized; yield, 0.08 g. (57%); m.p. 188–194°. It crystallized in almost quantitative yield from glacial acetic acid in clusters of colorless leaflets,[8] m.p. 212–213° (soon after melting, the clear liquid evolved bubbles).

Anal. Calc'd $C_{18}H_{26}O_2$: C, 78.79; H, 9.55.
Found: C, 78.97; H, 9.54.

The acid immediately decolorized aqueous potassium permanganate.

All analyses were performed by Micro-Tech Laboratory, Skokie, Ill.

SUMMARY

The Reformatsky reaction with methyl γ-bromocrotonate was applied to *cis*-9-methyl-1-decalone and 2-methylcyclohexanone. From the products, δ,ϵ-unsaturated acids were obtained. These and two others were cyclized by zinc chloride-acetic anhydride to unsaturated ketones in good yields. Evidence for the structure of some of these ketones was obtained by demonstrating by their ultraviolet absorption spectra, that the double bond was located α,β to the keto group. In the same manner, two doubly unsaturated acids were shown to be $\alpha,\beta,\gamma,\delta$-diene acids.

Several important intermediates for the synthesis of the desoxyandrosterone structure, containing the first three rings and functional groups for the attachment of the fourth ring, were synthesized.

ANN ARBOR, MICHIGAN

REFERENCES

(1) Bachmann and Wendler, *J. Am. Chem. Soc.*, **68**, 2580 (1946).

(2) Hausser, Kuhn, Smakula, and Hoffer, *Z. phys. Chem.*, **29B**, 371 (1935).

(3) (a) Chuang, Tien, and Ma, *Ber.*, **69**, 1494 (1936); (b) Cook and Lawrence, *J. Chem. Soc.*, 817 (1937); (c) Elliott and Linstead, *J. Chem. Soc.*, 660 (1938).

(4) Braude, *Ann. Reports Chem. Soc.*, **42**, 120, 126 (1945).

(5) Footnote 4 in Reference 1.

(6) Snyder, Brooks, and Shapiro, *Org. Syntheses*, Coll. Vol. II, 531 (1943).

(7) Bachmann and Kushner, *J. Am. Chem. Soc.*, **65**, 1963 (1943).

(8) Johnson, Johnson, and Peterson, *J. Am. Chem. Soc.*, **68**, 1926 (1946).

(9) Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).