Thermal Decomposition of Cyclononyl S-Methyl Xanthate. (A) Low Temperature Procedure.—Crude cyclononyl S-methyl xanthate (12 g.) was pyrolyzed in a 100-ml. flask at 120–130° according to the procedure previously described.[6] The product, a yellow liquid, was distilled at 56–64° (15 mm.) and weighed 4.1 g. The yellow contaminant was removed by chromatography. Subsequent distillation through a Podbielniak column at atmospheric pressure yield 2.2 g. (34.4%) of II, b.p. 168–173°, $n^{25}D$ 1.4770. **(B). High Temperature Procedure.**—Crude cyclononyl S-methyl xanthate (14 g.) was dropped through a carborundum packed column heated to the desired temperature as described for the acetate pyrolysis. After completion of the pyrolysis, the column was cooled and washed with pentane. The combined pyrolyzate and washes were worked up as in the low temperature procedure.

The results of the pyrolyses at various temperatures are summarized in Table II.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

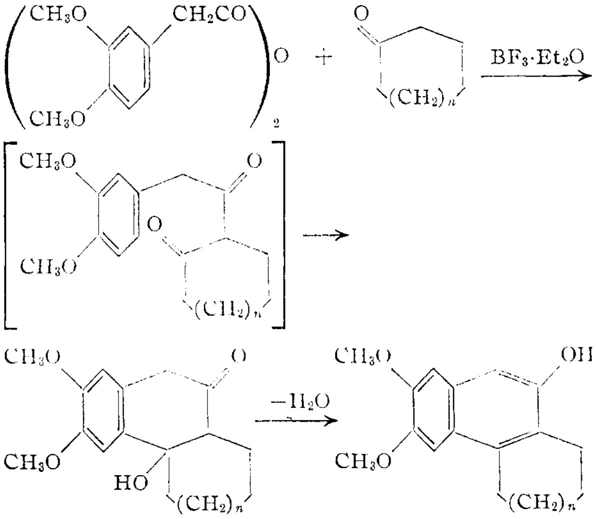
Synthesis of Methoxyhydrophenanthrenes and Methoxyhydrocyclohepta[a]-naphthalenes by Acylation of Ketones with Homoveratric Anhydride

BY GORDON N. WALKER

RECEIVED JANUARY 24, 1957

Acylation of cyclohexanone and cycloheptanone with homoveratric anhydride in the presence of boron trifluoride etherate is accompanied by cyclization, giving, after dehydration, compounds IIa and IIb, respectively. An intermediate hydroxyketone Ia is isolated in the first case. Acylation of cyclohexanone and cycloheptanone with homoveratric anhydride in the presence of boron trifluoride in acetic acid leads to formation of 1-acetyl-2-naphthol derivatives, XIa and XIb, respectively. Evidence confirming the structures of these products is presented, notably oxidation of compounds II to quinones VIII, and hydrogenation of compounds XI to octahydrophenanthrenes, XII. Angular methyl compounds V and VI have also been synthesized by acylation of 2-methylcyclohexanone with homoveratric anhydride.

There are several methods for synthesizing phenanthrenes and hydrophenanthrenes from simple aromatic compounds, depending upon cyclization reactions of appropriate functional groups with benzene carbon–hydrogen. These methods include the classical Pschorr procedure[1] and its modifications, the Haworth method[2] and cyclizations first described by Bardhan and SenGupta[3] and independently by Bogert[4] and Cook[5] and their collaborators. The Pschorr synthesis,[6,7] and another approach, namely, closure of ring B after elaboration of the A/C system,[8,9] have been adapted to synthesis of methoxy tricyclic compounds incorporating seven-membered rings (colchicine relatives). Efforts to circumvent difficulties inherent in these approaches have now led to discovery of a new cyclodehydration[10] reaction, described in this paper,[11] which accomplishes in one step the synthesis of certain hydrophenanthrenes and their C-ring homologs.



Ia, $n = 1$
b, $n = 2$

IIa, $n = 1$
b, $n = 2$

Experimental work was begun, acting upon the premise that if cyclic ketones could be C-acylated with phenylacetic anhydrides, it should be possible to bring about cyclization of resulting β-diketones through interaction of the benzene ring and the cyclic ketone moiety under acid conditions. Exposure of mixtures of phenylacetic anhydride and cyclohexanone to boron trifluoride under various conditions failed to yield recognizable products, an observation which agrees with earlier data.[12] However, it seemed likely that C-acylation did occur, for infrared spectra of the (presumably polymeric) products showed ketone (5.8–5.9 μ) rather than enol ester (5.7 μ) bands. Experiments with homoveratric anhydride were then tried, and these proved to be successful, inasmuch as C-acylation did occur, as supposed, and cyclization of resulting diketones *in situ* took place as well.

---

(1) See P. H. Leake in *Chem. Revs.*, **56**, 27 (1956).

(2) R. D. Haworth, *et al.*, *J. Chem. Soc.*, 1125, 1784, 2248, 2717, 2720 (1932).

(3) J. C. Bardhan and S. C. SenGupta, *ibid.*, 2520, 2798 (1932).

(4) M. T. Bogert, *et al.*, *Science*, **77**, 289 (1933); *J. Org. Chem.*, **1**, 288, 300 (1936); THIS JOURNAL, **56**, 185, 959 (1934).

(5) J. W. Cook and C. L. Hewett, *Chemistry & Industry*, **52**, 451 (1933); *J. Chem. Soc.*, 1098 (1933).

(6) J. W. Cook, J. Jack and J. D. Loudon, *ibid.*, 1397 (1951), and preceding papers.

(7) H. Rapoport, *et al.*, THIS JOURNAL, **73**, 1414 (1951); **77**, 670 (1955).

(8) C. D. Gutsche and F. A. Fleming, *ibid.*, **76**, 1771 (1954).

(9) D. Ginsburg, *ibid.*, **76**, 3628 (1954).

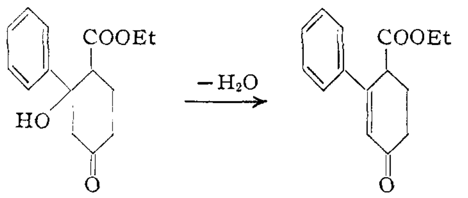
(10) A term used by C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946), to describe formation of aromatic rings through reactions involving loss of water. The synthesis presented here may be considered to fall into this category.

(11) A preliminary report of this work appeared in THIS JOURNAL, **78**, 2340 (1956).

(12) J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1954).

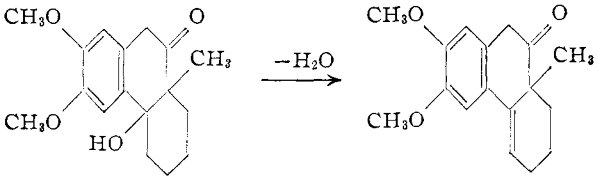
Compound Ia was obtained in 68% yield when a mixture of homoveratric anhydride, cyclohexanone and boron trifluoride etherate was allowed to stand at 0–10° for three days. Evidence leading to assignment of structure Ia and excluding other possibilities was obtained from analysis, spectra and further reactions. While the infrared spectrum of Ia showed only weak absorption at 2.8–2.9 μ, there was present a strong ketone band at 5.79 μ (chloroform solution) or 5.85 μ (mull). A hydroxymethylene derivative was prepared by reaction of Ia with ethyl formate (sodium methoxide), indicating that a methylene position adjacent to a ketone group was present. Attempts to acetylate Ia with acetic anhydride were fruitless, thus making it appear likely that a tertiary alcohol was at hand. As expected, compound Ia lost water rapidly in the presence of mineral acids, polyphosphoric acid being best for the purpose, and formed a β-naphthol, IIa. Infrared and ultraviolet spectra (see Experimental part) showed clearly that IIa was a naphthalene, and the structure was substantiated further by aromatization of IIa to 2,3-dimethoxy-9-phenanthrol in the presence of palladium. O-Acetates of IIa and the phenanthrol again had typical ultraviolet spectra, and the infrared spectra of these compounds disclosed, as anticipated, peaks at 5.70 μ.

Condensation of homoveratric anhydride with cycloheptanone in the presence of boron trifluoride etherate gave IIb directly, and Ib, though perhaps formed first in the reaction, could not be isolated. The fact that the presumed cycloheptanol intermediate Ib dehydrates more readily than does the cyclohexanol Ia is interesting and probably is due to steric effects. Data available at present do not permit an unequivocal statement about the stereochemistry of hydroxyketone Ia. However, it seems likely that rings B and C of Ia are arranged *cis*. A comparable case, compound III, was described earlier.[13] Compound III, in which a presumed equatorial hydroxyl group is located in the benzyl position, beta to a carbonyl group and *cis* with respect to hydrogen at carbon atom 4, is like Ia in being relatively resistant to dehydration, as well as to hydrogenolysis and acetylation. It has now been found that III, like Ia, loses water in the presence of polyphosphoric acid, giving IV.



III IV

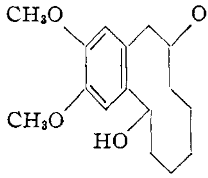
Another compound of the type shown in formula I was synthesized by condensation of homoveratric anhydride with 2-methylcyclohexanone in the presence of boron trifluoride etherate. Reasoning from some data available on methylene *versus* methinyl acylation,[14] it was felt that acylation of a 2-substituted cyclohexanone might as well take place at position 2 as at position 6 of the ketone. This in fact was the case, for the product isolated (63%) was compound V. Dehydration of V did not afford a naphthol, but rather an unsaturated ketone VI, a result readily explained only on the basis of an angularly substituted structure.



V VI

Thus it appears that the synthesis is applicable to preparation of angular-methyl compounds such as V or VI.

The novelty of these condensation–cyclization products makes it desirable that there be some proof of their structures in addition to the facts already presented. Attempts to convert Ia or IIa to a known compound, 2,3-dimethoxyphenanthrene,[15,16] were thwarted by the following events. Reduction of IIa under various conditions gave mixtures of products, and 2,3-dimethoxyphenanthrene could not be isolated after subsequent dehydration and aromatization. Hydrogenation of IIa may have taken place in ring A as well as in ring B, and in this connection some results obtained in hydrogenation of phenanthrene-9,10-quinone (see below) may be relevant. Compounds Ia, V and VI resisted catalytic hydrogenation in the presence of 10% palladium–charcoal. Lithium aluminum hydride (or sodium borohydride) reduction of Ia gave a diol, $C_{16}H_{24}O_4$, m.p. 147–149°, having two hydrogen atoms more than expected for a diol corresponding to Ia; it is thought at present that in this reduction reverse aldol reaction, leading to VII, or possibly some other type of cleavage may also have occurred.



VII

A satisfactory demonstration of the correctness of structures II was achieved eventually in a rather unusual way. Although other oxidizing agents for the most part destroyed IIa and IIb, it was found that *ozone* oxidizes these compounds rapidly to corresponding *o*-quinones, VIIIa and VIIIb, respectively. Compound IIa is oxidized in this manner more rapidly than is IIb, and in the same vein quinone VIIIa appears to be somewhat less stable than VIIIb, although both compounds VIII are rather more stable than 1,2-naphthoquinone and 1,2,3,4 - tetrahydrophenanthrene - 9,10 - quinone. Preparation of quinoxaline derivatives IX from quinones VIII provided confirmation of structures VIII. There seemed to be no tendency toward formation of corresponding quinhydrones during oxidation of compounds II, an observation which

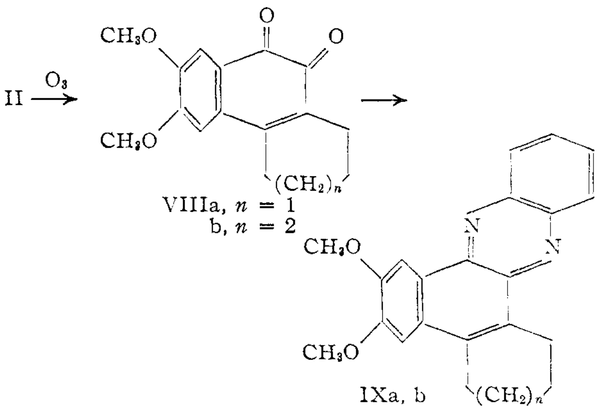
---

[13] G. N. Walker, THIS JOURNAL, **77**, 3664 (1955).

[14] C. R. Hauser and J. T. Adams, *ibid.*, **66**, 345 (1944).

[15] R. Pschorr and W. Buckow, *Ber.*, **33**, 1829 (1900).

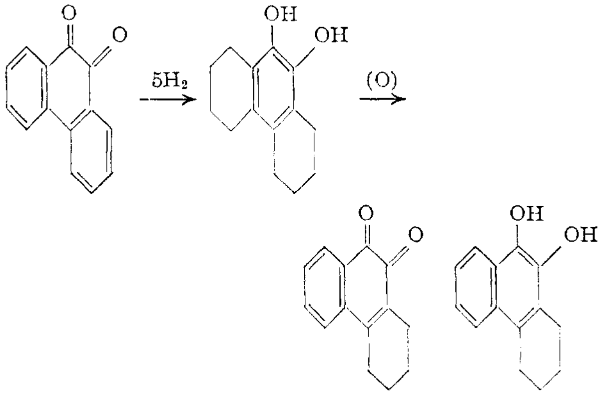
[16] E. Mosettig and A. Burger, THIS JOURNAL, **52**, 2988 (1930).



VIIIa, $n = 1$
b, $n = 2$

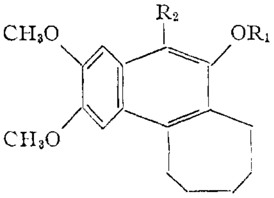
IXa, b

stood in contrast to a report concerning formation of the parent system, 1,2,3,4-tetrahydrophenanthrene-9,10-(quinone-hydroquinone).[17] Therefore, hydrogenation of phenanthrene-9,10-quinone was carried out in an effort to get more information about compounds in this category. After exhaustive hydrogenation of phenanthrene-9,10-quinone in the presence of 10% palladium–charcoal in ethyl acetate at 80°, a diol was obtained which, like the diol described by Skita,[17] oxidized very readily, even upon exposure to air, to tetrahydrophenanthrenequinhydrone. This oxidative transformation appeared at first to be analogous to oxidation of compounds II, and indeed a parallel could be drawn if the unstable reduction product obtained here were 1,2,3,4,9,10-hexahydrophenanthrene-9,10-diol, as supposed earlier,[17] or 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-9,10-diol, as seemed more likely from present analytical results. However, the diol evidently had neither of these structures but was instead 1,2,3,4,5,6,7,8-octahydrophenanthrene-9,10-diol. This conclusion was necessitated by the elementary composition and, more important, the properties, particularly infrared spectrum (5.70 μ, phenol acetate) of a fairly stable monoacetate obtained from the diol (see Experimental part).



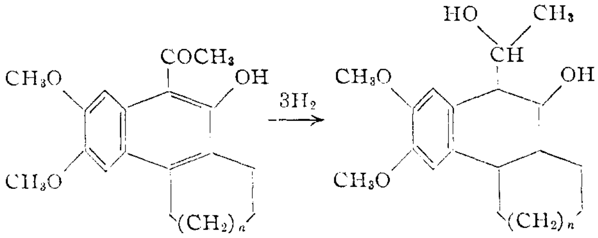
Admittedly, this work is not especially relevant to other results presented here but is included because it has some novelty and represents one attempt to obtain a desired model compound, 1,2,3,4-tetrahydro-10-hydroxyphenanthrene.

Some additional experiments with compound IIb were done in the interest of providing further evidence for the structure and exploring possible means of selectively opening ring B. The O-acetate Xa, methyl ether Xb and a bromo-derivative Xc were prepared by conventional reactions. Nitrous acid converted IIb to the nitroso-compound (quinone monoxime) Xd, catalytic reduction of which, followed by acetylation, provided Xe. Preliminary attempts to carry out inverse Beckmann rearrangement[7] of Xd, and other reactions designed to selectively cleave the 5,6-double bond in IIb and its derivatives, have been unsuccessful.



Xa, $R_1 = COCH_3$, $R_2 = H$
b, $R_1 = CH_3$, $R_2 = H$
c, $R_1 = H$, $R_2 = Br$
d, $R_1 = H$, $R_2 = NO$
e, $R_1 = COCH_3$, $R_2 = NHCOCH_3$

Early in exploratory work, condensations of homoveratric anhydride with cyclohexanone and cycloheptanone were carried out using acetic acid, rather than ether, as solvent and complexing agent. The products when analyzed proved to be acetates of IIa and IIb, respectively, but were yellow rather than colorless compounds, gave strong ferric chloride tests and judging from ultraviolet spectra seemed to be C-acylnaphthalenes. The infrared spectra of the compounds lacked hydroxyl and ordinary carbonyl bands, as in spectra of other 1,3-keto-enols, and thus structures XIa and XIb, consistent with this evidence, were assigned to the compounds. Formation of XIa and XIb may have come about either by direct acetylation of IIa and IIb after cyclization or through Fries reaction[18] of O-acetates. O-Acetylation itself may have occurred either before or after cyclization. These matters require further examination. Confirmation of structures XIa and XIb was provided by hydrogenation in the presence of 10% palladium–charcoal in warm ethyl acetate, under which conditions the phenolic ring in XI was reduced as well as the 1,3-keto-enol system, as shown by disappearance of naphthalene ultraviolet absorption, and diols XIIa and XIIb, respectively, were obtained. These crystalline compounds appeared to



XIa, $n = 1$
b, $n = 2$

XIIa,b

---

[17] A. Skita and W. Rohrmann, *Ber.*, **63**, 1473 (1930).

[18] Boron trifluoride can expedite Fries reaction, according to A. H. Blatt, *Chem. Revs.*, **27**, 413 (1940); *cf.* H. Meerwein, *Ber.*, **66**, 411 (1933), and K. V. Auwers, H. Pötz and W. Noll, *Ann.*, **535**, 228 (1938). For rearrangement of 2-naphthyl acetate see K. Fries, *Ber.*, **54**, 709 (1921).

consist of only one isomer in each case, and at present it seems likely that they are the all-*cis* isomers, formed by way of initial 1,4-addition, or perhaps even 1,6-addition, of hydrogen. Palladium-catalyzed hydrogenation of other 1,3-keto-enols such as *o*-hydroxyacetophenones,[19] dehydroacetic acids[19] and 2-acetylcyclohexanone (see Experimental part of this paper) under neutral conditions also results in reduction of the acetyl group in each case.

It should be mentioned that successful condensation–cyclization reactions of homoveratric anhydride with cyclopentanone and with 1-tetralone were not achieved, although with 2-tetralone a small amount of rather unstable ketone, $C_{20}H_{20}O_4$, was isolated. Even more disappointing was the failure to isolate any tricyclic compounds after reaction of 3,4,5-trimethoxyphenylacetic anhydride with cyclohexanone and cycloheptanone. The synthesis in its present form appears to be limited in practice to use of relatively simple 6- and 7-membered ring ketones and to use of phenylacetic anhydrides in which the benzene ring carbon atom (6) at which cyclization occurs is activated by suitably placed electron-releasing groups and is not hindered by a group at the adjacent position (5). Even with these limitations the method may prove to be useful in synthesizing a number of new polycyclic compounds, especially if improvements in experimental conditions can be found, and it is hoped to pursue further work in this direction.

Experimental[20]

3,4-Dimethoxyphenylacetic Anhydride.—A solution of 56.5 g. of 3,4-dimethoxyphenylacetic acid in 550 ml. of acetic anhydride was treated with 5.5 ml. of pyridine and was refluxed for 4 hr. The solution was evaporated on a steam-cone to a volume of 70 ml. The cooled residue was diluted with 300 ml. of ether and was stirred and chilled in ice until crystallization was complete. The product was collected and washed with 100 ml. of dry ether; first crop, 23 g., m.p. 79–82°. The filtrates were kept at ice temperature for a week, whereupon a second crop, 18 g., m.p. 77–80°, was obtained after trituration with ether. The yield of anhydride was 41 g. (76%). Recrystallization from ethyl acetate gave colorless crystals, m.p. 83–85°. The infrared spectrum (chf.) had an intense doublet, 5.48 and 5.70 μ.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.2; H, 5.92. Found: C, 64.5; H, 6.04.

2,3-Dimethoxy-4b-hydroxy-9-keto-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (Ia).—A mixture of 10.1 g. (0.027 mole) of homoveratric anhydride and 7.3 g. (0.0745 mole) of redistilled cyclohexanone was treated with 74 ml. of ice-cold, commercial 47% boron trifluoride etherate. The mixture was swirled in an ice-bath for an hour until the solid material dissolved, and the dark solution was kept in an ice-box for 3 days. During this time a solid deposited slowly. The mixture was added to a solution of 60 g. of sodium acetate in 300 ml. of water, and this mixture was heated on a steam-cone and stirred for 15 minutes until the ether evaporated and the remaining dark oil began to crystallize. The mixture was chilled in ice and stirred until crystallization was complete. The crude product was collected and was washed with two 50-ml. portions of water. The gummy crystals were triturated with three successive small portions of methanol, which removed dark, oily material and left 5.1 g. (68%) of light-brown crystals, m.p. 133–138°. Recrystallization from aqueous methanol (Norit) gave colorless crystals, m.p. 140–141°. Slow evaporation of solutions of this compound resulted in formation of large, rhombohedral crystals. The infrared spectrum (chf.) showed very weak absorption at 2.8–2.9 μ and an intense peak at 5.79 μ. The infrared spectrum in Nujol mull was devoid of hydroxyl bands, and in this medium the intense carbonyl peak was shifted to 5.85 μ, indicating hydrogen bonding. The ultraviolet spectrum (ethanol) had λ_{max} 232 and 285 mμ (log ε 3.88 and 3.57, respectively).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; mol. wt., 276. Found: C, 69.55; H, 7.34; mol. wt. (Rast), 285.

Although the compound gave a transient positive test with 2,4-dinitrophenylhydrazine, attempts to prepare derivatives using this and other reagents were unsuccessful, apparently owing to decomposition or formation of IIa. The hydroxyketone was insoluble in dilute alkali and did not give a ferric chloride test. It was virtually unchanged after refluxing for an hour in acetic acid or acetic anhydride. Attempted hydrogenolysis in the presence of palladium–charcoal in acetic acid also resulted in recovery of most of the compound.

Another condensation of homoveratric anhydride and cyclohexanone was carried out as described above, except that the solution was allowed to stand at room temperature, rather than 0–10°, for 3 days. In this case the crude product contained very dark, sparingly soluble, gummy material. Compound Ia was isolated from this mixture in 20% yield by recrystallization from aqueous methanol.

The 10-hydroxymethylene derivative was prepared by reaction of 1.0 g. of Ia with excess ethyl formate in the presence of 0.5 g. of dry, freshly prepared sodium methoxide in 300 ml. of dry ether. The product was isolated as usual by acidification of an ether-washed, aqueous solution of the sodium salt. Trituration with ether gave 1.0 g. of pale yellow crystals, m.p. 131–135°. Recrystallization from ethyl acetate afforded 0.85 g. of colorless crystals, m.p. 159–161°. The infrared spectrum (chf.) had a band at 6.00 μ. The ultraviolet spectrum (ethanol) had λ_{max} 257, 288 and 309 mμ (log ε 4.05, 4.08 and 3.95, respectively). The compound was soluble in dilute sodium hydroxide solution and, like 1-hydroxymethylene-2-tetralone, gave a deep-blue color (changing to green) with ferric chloride.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.36; H, 6.87.

Efforts to dehydrate this compound with polyphosphoric acid resulted in formation of tars.

2,3-Dimethoxy-5,6,7,8-tetrahydro-9-phenanthrol (IIa).—A mixture of 1.4 g. of Ia and 18 g. of polyphosphoric acid was heated to 80° and stirred for 10 minutes, until a dark-brown solution was obtained. The chilled solution was treated with ice and water, and the resulting purple solid was extracted with ethyl acetate. The organic solution was washed with successive portions of water, sodium bicarbonate solution and water, and was dried over magnesium sulfate. Evaporation of the solvent and trituration of the crude product (0.8 g.) with methanol gave 0.6 g. (46%) of light-brown crystals, m.p. 211–218° dec. Recrystallization from methanol (Norit) gave colorless crystals, m.p. 219–221° dec. The infrared spectrum (chf.) had a peak at 2.76 μ. The ultraviolet spectrum[21] (ethanol) had $\lambda_{max.}$ 237, 272, 282, 293, 322 and 336 mμ (log ε 4.86, 3.60, 3.59, 3.46, 3.59 and 3.72, respectively).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.50; H, 7.09.

Dehydration of Ia also occurred in the presence of warm sulfuric–acetic acids mixture, as indicated by appearance of a deep-red color, but no crystalline product could be isolated after this reaction. Hydrogenation of IIa in the presence of 10% palladium–charcoal in ethyl acetate at 80° gave glassy material, the infrared spectrum of which showed absorption at 2.76 and 2.9–3.0 μ.

Acetylation of IIa with acetic anhydride (refluxed 2 hr.) gave the **O-acetate**, m.p. 170–171°, after recrystallization from methanol. The infrared spectrum (chf.) had a peak at 5.70 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 235, 264, 273, 282, 293, 314 and 328 mμ (log ε 4.98, 3.68, 3.72, 3.71, 3.54, 3.49 and 3.69, respectively).

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.03; H, 6.69.

2,3-Dimethoxy-9-phenanthrol.—A mixture of 0.5 g. of IIa, 1.5 g. of 10% palladium–charcoal catalyst and 40 ml. of redistilled *p*-cymene was refluxed vigorously for 2.5 hr.

---

[19] G. N. Walker, THIS JOURNAL, **78**, 3201 (1956).

[20] Melting points are corrected.

[21] See R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, especially curve 237.

The catalyst was filtered and was washed with 50 ml. of ethyl acetate. The yellow solution was evaporated to a small volume, and the residual material was taken up in 5 ml. of methanol. The solution was kept at ice temperature overnight, and the product was collected, washed with a small quantity of methanol and air-dried. There was obtained 0.2 g. of nearly colorless crystals, m.p. 244–248° dec. Recrystallization from methanol gave colorless crystals, m.p. 254–256° dec. The infrared spectrum (Nujol) had a strong peak at 2.81–2.87 μ. The ultraviolet spectrum (ethanol) had λ_{max} 241, 265, 282, 323, 338 and 362 mμ (log ε 4.62, 4.36, 4.23, 3.68, 3.64 and 3.28, respectively). The compound was first dried at 80° *in vacuo*.

Anal. Calcd. for $C_{16}H_{14}O_3\cdot{}^1/_2H_2O$: C, 72.99; H, 5.74. Found: C, 73.17; H, 5.70.

When the material was dried at 100° *in vacuo*, it was obtained in anhydrous condition.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.67; H, 5.73.

Acetylation with acetic anhydride (4-hr. reflux) and recrystallization of the product from methanol gave the **O-acetate**, m.p. 197–199°. The infrared spectrum had an intense peak at 5.68 μ. The ultraviolet spectrum (ethanol) had λ_{max} 225, 246, 260, 278, 329, 339 and 355 mμ (log ε 4.42, 4.61, 4.59, 4.45, 3.44, 3.30 and 3.23, respectively).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.68; H, 5.51.

2,3-Dimethoxy-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (IIb).—A mixture of 41 g. (0.110 mole) of homoveratric anhydride and 21.7 g. (0.194 mole) of cycloheptanone was treated with 300 ml. of ice-cold boron trifluoride etherate (47%) in one portion. The solid material dissolved after stirring for 0.5 hr. The solution was allowed to stand at room temperature overnight, then was placed in an ice-box and allowed to stand (at 0–10°) for 24 hr. longer. The mixture was hydrolyzed with a solution of 260 g. of sodium acetate in 500 ml. of water, as described for Ia. Upon chilling the resulting oily mixture, the crude product crystallized. It was collected, washed with cold water and triturated with a small quantity of methanol. Two crops of crystalline product, total weight 8.7 g. (29%), m.p. 198–202°, were obtained. Recrystallization from methanol gave colorless crystals, m.p. 207–208°. The infrared spectrum (chf.) had a peak at 2.76 μ. The ultraviolet spectrum (ethanol) had λ_{max} 237, 274, 285, 296, 324 and 337 mμ (log ε 4.91, 3.61, 3.61, 3.49, 3.58 and 3.72, respectively).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.93; H, 7.45.

Acetylation with boiling acetic anhydride (2 hr.) gave the **O-acetate**, Xa, m.p. 139–141°, after recrystallization from methanol or cyclohexane–ethyl acetate (Norit). The infrared spectrum showed an intense peak at 5.70 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 238, 267, 276, 285, 296, 315 and 329 mμ (log ε 4.78, 3.54, 3.59, 3.58, 3.41, 3.28 and 3.48, respectively).

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.84; H, 7.06.

Methylation with excess dimethyl sulfate and potassium hydroxide afforded the **methyl ether Xb**, which, after recrystallization from methanol, was obtained as colorless crystals, m.p. 122–124°. The ultraviolet spectrum (ethanol) had λ_{max} 238, 272, 282, 321 and 330 mμ (log ε 4.92, 3.66, 3.62, 3.56 and 3.74, respectively).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.43; H, 7.72.

Treatment of IIb with bromine in chloroform at room temperature resulted in rapid consumption of the reagent, hydrogen bromide evolution and formation of **bromo-derivative Xc**. Evaporation of the solvent and recrystallization of the residue from methanol gave colorless crystals, m.p. 164–165°.

Anal. Calcd. for $C_{17}H_{19}O_3Br$: C, 58.13; H, 5.45; Br, 22.75. Found: C, 58.38; H, 5.49; Br, 22.86.

3-Phenyl-4-carbethoxycyclohex-2-ene-1-one (IV).—A mixture of 2 g. of crystalline ethyl benzoylacetate–methyl vinyl ketone adduct,[13] m.p. 127–129°, and 20 g. of polyphosphoric acid was heated on a steam-cone and stirred for 12 minutes. The solid dissolved rapidly and a deep carmine-red color appeared. Hydrolysis of the cooled solution with ice and water and isolation of the neutral product in the usual way gave 1.5 g. of yellow oil, the infrared spectrum of which had intense peaks at 5.80 and 6.01 μ. **The 2,4-dinitrophenylhydrazone** was prepared in 95% yield from this crude product. Recrystallization from ethyl acetate gave red crystals, m.p. 169–171°, which did not depress the m.p. of a sample of the derivative prepared as described earlier.[13]

2,3-Dimethoxy-4b-hydroxy-8a-methyl-9-keto-4b,5,6,7,8,-8a,9,10-octahydrophenanthrene (V).—A mixture of 13.6 g. (0.0364 mole) of homoveratric anhydride and 9.9 g. (0.0883 mole) of 2-methylcyclohexanone was treated with 105 ml. of ice-cold, 47% boron trifluoride etherate (one portion). When the mixture was swirled in an ice-bath, the solid material dissolved gradually. The solution was allowed to stand in an ice-box for 5 days. Hydrolysis with a solution of 100 g. of sodium acetate in 350 ml. of water, as described for Ia, gave viscous, orange oil, which did not crystallize. The oil was extracted with ether, and the organic solution was washed with successive portions of water, sodium bicarbonate solution (excess) and water. Evaporation of the dried solution gave material which crystallized rapidly. Trituration with ether afforded 6.7 g. (63%) of pale-yellow crystals, m.p. 127–129°. Recrystallization from ethyl acetate gave colorless needles, m.p. 129–130°. The infrared spectrum (chf.) was very similar to that of Ia, showing weak hydroxyl band at 2.82–2.90 μ, and an intense carbonyl peak at 5.80 μ. The infrared spectrum in Nujol mull had no hydroxyl band and displayed the intense carbonyl peak at 5.82 μ. The ultraviolet spectrum (ethanol) had λ_{max} 231 and 283–287 mμ (log ε 3.89 and 3.58–3.59, respectively).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.36; H, 7.45.

Like Ia, this compound was insoluble in dilute alkali, gave no ferric chloride test, was inert to acetic anhydride and did not form a 2,4-dinitrophenylhydrazone or semicarbazone. Sodium borohydride reduction (in methanol) gave glassy material, the infrared spectrum of which (chf.) showed fairly strong absorption at 2.7–2.75 and 2.8–2.85 μ, and no carbonyl peak. Attempts to dehydrate this reduction product resulted mainly in decomposition.

2,3-Dimethoxy-8a-methyl-9-keto-6,7,8,8a,9,10-hexahydrophenanthrene 2,4-Dinitrophenylhydrazone.—A mixture of 2.2 g. of V and 30 g. of polyphosphoric acid was heated on a steam-cone and stirred steadily for 7 minutes. The cooled, deep-red solution was hydrolyzed with ice and water and the neutral product was isolated in the usual way. There was obtained 2.1 g. of bright-red, viscous oil which did not crystallize but on standing gradually became dark brown. The infrared spectrum (chf.) still had an intense peak at 5.80–5.83 μ but was rather different in other respects from the spectrum of V. The 2,4-dinitrophenylhydrazone was prepared in the usual way in approximately 70% yield. Recrystallization from ethyl acetate gave orange, small crystals, m.p. 221–223° dec.; λ_{max} (chf.) 365 mμ, 3.00 μ and 6.19 μ.

Anal. Calcd. for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35. Found: C, 61.25; H, 5.14.

Attempts to prepare other derivatives, for example the semicarbazone, from the crude dehydrated ketone were unsuccessful, apparently because of decomposition.

Lithium Aluminum Hydride Reduction of Ia.—Compound Ia (0.6 g.) was stirred with a mixture of 1.2 g. of lithium aluminum hydride and 500 ml. of dry ether at room temperature for 9 hr. Excess hydride and organic complex were then hydrolyzed by cautious addition of 5 ml. of water (stirring), and the suspension was filtered. Evaporation of the colorless ether solution and trituration of the residue with a few ml. of ethyl acetate gave 0.5 g. of colorless crystals, m.p. 147–149°, not raised after recrystallization from the same solvent. The infrared spectrum (chf.) had a moderately strong band at 2.77–2.86 μ. The ultraviolet spectrum (ethanol) had λ_{max} 232 and 282 mμ (log ε 4.07 and 3.59, respectively).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.73.

These analytical figures were obtained with a sample which had been dried at 100° in high vacuum for 5 hr., and thus the material evidently is not a hydrate. The same compound was obtained, although less pure and in lower yield, by reduction of Ia with sodium borohydride in methanol.

2,3-Dimethoxy-5,6,7,8-tetrahydrophenanthrene-9,10-quinone (VIIIa).—A rapid stream of air and ozone from a

Welsbach ozonizer was passed into an ice-cold solution of 0.55 g. of IIa in 250 ml. of ethyl acetate. A bright-red color developed soon and did not appear to become any more intense after 3 minutes; the gas stream was discontinued after 4 minutes, and the solvent was evaporated as rapidly as possible. The partly crystalline residue was triturated with a small quantity of ethyl acetate. There was obtained 0.28 g. of deep-red needles. Neither this material nor that purified further by recrystallization from ethyl acetate had a sharp melting point but rather decomposed gradually when heated above 150°. The infrared spectrum of a purified sample (chf.) had a very sharp, intense peak at 6.01 μ with less intense shoulders at 5.94 and 6.07 μ.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.65; H, 6.23.

A small sample of VIIIa, when treated in warm acetic acid with a solution of *o*-phenylenediamine, gave compound IXa; yellow needles from ethyl acetate, m.p. 228–229°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85. Found: C, 76.99; H, 6.00.

2,3-Dimethoxy-5,6-diketo-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalene (VIIIb).—Compound IIb was exposed to ozone as described in the preceding experiment, except that reaction time was increased to 30 minutes, in view of the fact that the red color developed more slowly. From 0.5 g. of IIb there was obtained 0.4 g. of red crystals, m.p. 140–145°. Recrystallization from ethyl acetate gave deep-red, lustrous needles, m.p. 146–148°. The infrared spectrum (chf.) had a sharp, intense peak at 6.06 μ with shoulders at 5.96 and 6.10 μ.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.35; H, 6.62.

Compound IXb was prepared as described for IXa; yellow crystals from ethyl acetate, m.p. 219–220°.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19. Found: C, 76.85; H, 6.18.

Hydrogenation of 9,10-Phenanthrenequinone.—A mixture of 9.8 g. of 9,10-phenanthrenequinone, 6.5 g. of 10% palladium–charcoal and 450 ml. of ethyl acetate was shaken under hydrogen (40 lb.). Somewhat more than one mole of hydrogen was absorbed rapidly (5 minutes) at room temperature, representing, no doubt, reduction to the hydroquinone. Absorption then ceased and was not resumed until the system was heated to about 80°. Additional hydrogen (3–4 moles) was then absorbed slowly (7 hr.), and finally the consumption of hydrogen became extremely slow, whereupon the cooled contents of the bottle were filtered. The yellowish solution thus obtained became somewhat darker in color during evaporation of the solvent. The residue crystallized readily but continued to acquire a darker color; the exact yield of product could not be ascertained. By rapid, repeated crystallization of the crude material from ethyl acetate and then from cyclohexane, there were obtained colorless crystals, m.p. 127–128°. This material, **1,2,3,4,5,6,7,8-octahydrophenanthrene-9,10-diol**, appeared to be stable when purified and dried, but air-oxidized readily in the presence of solvents, especially if warmed above 70°. The infrared spectrum (chf.) had a fairly strong peak at 2.82 μ. The compound gave a positive ferric chloride test and deteriorated rapidly in the presence of aqueous alkali.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.92; H, 8.21.

Some of the original crude material from hydrogenation was treated with excess acetic anhydride (20 ml.) and ethyl acetate (200 ml.), and the solution was allowed to stand at room temperature overnight. Evaporation of solvent and excess reagent and recrystallization of the residue (cyclohexane–ethyl acetate) gave the **monoacetate** of the diol; colorless crystals, m.p. 169–171°. The infrared spectrum (chf.) had peaks at 2.80 and 5.70 μ. The compound did not give a ferric chloride test but was soluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.60; H, 7.51.

The remainder of the crude diol, upon standing exposed to air, acquired a red-purple color and finally, after a week, became almost black. Trituration with ethyl acetate then afforded (in rather good yield) greenish-black crystals. Recrystallization from the same solvent gave pure **1,2,3,4-tetrahydro-9,10-phenanthrenequinhydrone**[17]; green needles, m.p. 159–161°. Solutions and melts of this compound were deep purple. The infrared spectrum (chf.) had a moderately strong peak at 2.93 μ and a quintet of sharp peaks, 6.07, 6.14, 6.24, 6.29 and 6.40 μ.

Anal. Calcd. for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14. Found: C, 79.12; H, 5.84.

1,2,3,4-Tetrahydrophenanthrenequinone, also prepared by Skita,[17] was found to consist of red-orange needles having no definite m.p. but rather decomposing gradually above 120°. The infrared spectrum of this quinone, after recrystallization from ethyl acetate, showed an intense peak at 6.02 μ with a less intense secondary peak at 5.90 μ.

2,3-Dimethoxy-5-nitroso-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (Xd).—An ice-cold suspension of 1.4 g. of IIb and 2 g. of sodium nitrite in 100 ml. of methanol and 50 ml. of water was treated with 50 ml. of cold 50% sulfuric acid, in 10 portions, over a period of an hour. Additional sodium nitrite (1.5 g.) was added, and the mixture was kept in an ice-box for 4 days, during which time dark red crystals separated gradually. The product was collected and was washed with four 20-ml. portions of water and 20 ml. of methanol. After air-drying, there was obtained 1.4 g. of red crystals, m.p. 170–174°. Recrystallization from ethyl acetate raised the m.p. to 176–178°. The infrared spectrum (chf.), as expected in analogy with 1-nitroso-2-naphthol, showed no absorption near 3 μ and had a peak at 6.23 μ with a shoulder at 6.09–6.13 μ.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.87; H, 6.52.

The corresponding **5-acetylamino-6-acetoxy** compound, Xe, was prepared by hydrogenation of 0.5 g. of Xd in the presence of 1 g. of 10% palladium–charcoal catalyst in ethyl acetate at room temperature for an hour. After filtration, the solution was treated immediately with 30 ml. of acetic anhydride and was allowed to stand at room temperature overnight. Evaporation then gave discolored crystals, trituration of which with ethyl acetate afforded 0.3 g. of product, m.p. 225–227°. Recrystallization from the same solvent gave colorless crystals, m.p. 228–228.5°.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.91; H, 6.79; N, 3.77. Found: C, 68.11; H, 6.76; N, 3.73.

The infrared spectrum (chf.) displayed peaks at 2.96, 5.69, 5.97 and 6.03 μ.

2,3-Dimethoxy-5,6,7,8-tetrahydro-9-hydroxy-10-acetylphenanthrene (XIa).—Glacial acetic acid (50 ml.) was saturated with anhydrous boron trifluoride at ice temperature. There was added 9.6 g. (0.0257 mole) of homoveratric anhydride and 5.5 g. (0.0561 mole) of cyclohexanone. The mixture was stirred steadily and kept at 35–40° for 20 hr. During this time the anhydride dissolved, and later a brown solid separated. The mixture was treated with a solution of 32 g. of sodium acetate in 250 ml. of water, whereupon bright yellow crystals were formed. The material was collected and washed with two small portions of water. Trituration with methanol, in which the crystals were very sparingly soluble, afforded 3.2 g. of a complex, m.p. 239–241° dec., not changed by recrystallization from dry benzene. The complex was taken up in 100 ml. of methanol, and the suspension was boiled 1 hr. The resulting solution was reduced to 20-ml. volume and was cooled. The crystals which separated were collected, washed with a small portion of methanol and dried; 2.9 g. (38%) of yellow needles, m.p. 167–168°. Recrystallization from methanol did not improve this m.p. The infrared spectrum (chf.) showed no hydroxyl or ordinary carbonyl bands, although there was an intense peak at 6.25 μ with shoulders at 6.09 and 6.13 μ. The ultraviolet spectrum (ethanol) had λ_{max} 234, 294 and 340 mμ (log ϵ 4.80, 3.57 and 4.00, respectively). The compound gave a dark-green ferric chloride test.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.75.

Aromatization of a sample of XIa in the presence of 3 parts by weight of 10% palladium–charcoal in *p*-cymene (refluxed 2.5 hr.) gave a small amount of **2,3-dimethoxy-9-hydroxy-10-acetylphenanthrene**, m.p. 161–162° (from methanol). The infrared spectrum (chf.) was similar to but not identical with the spectrum of XIa. The ultraviolet spectrum (ethanol) had λ_{max} 235, 254, 272, 316, 333, 346 and 378 mμ (log ϵ 4.47, 4.57, 4.31, 3.84, 3.80, 3.81 and 3.74, respectively).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.4. Found: C, 72.70; H, 5.7.

2,3-Dimethoxy-5-acetyl-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (XIb).—Condensation of 9.9 g. of homoveratric anhydride and 5.8 g. of cycloheptanone in the presence of 50 ml. of boron-trifluoride-saturated glacial acetic acid, as described in the preceding experiment, and hydrolysis with 33 g. of sodium acetate and 20 g. of sodium bicarbonate in 300 ml. of water (warmed on a steam-cone for 20 minutes) gave, after cooling the mixture, semi-solid brown oil. This material was washed with 2 small portions of water (decanting) and was triturated with a small amount of methanol. There was obtained 0.6 g. of yellow crystals, m.p. 155–157°. Additional product (0.3 g.) was obtained when the original aqueous solution was allowed to stand for a week, bringing the total yield to 0.9 g. (11%). Recrystallization from methanol gave yellow needles, m.p. 157–158°. The infrared spectrum (chf.) was similar to that of XIa, and the ultraviolet spectrum had λ_{max} 235, 291 and 345 mμ (log ε 4.84, 3.56 and 4.02, respectively). The compound gave a dark green ferric chloride test.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.64; H, 7.06.

2,3-Dimethoxy-9-hydroxy-10-(α-hydroxyethyl)-4b,5,6,7,-8,8a,9,10-octahydrophenanthrene (XIIa).—Compound XIa (0.3 g.) in 200 ml. of ethyl acetate with 1.5 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for 1.2 hr. Filtration of the catalyst and evaporation of the solvent gave viscous, pale yellow oil which crystallized rapidly in the presence of methanol. Recrystallization from cyclohexane–ethyl acetate gave 0.25 g. of colorless crystals, m.p. 167–170°. Further recrystallization gave pure material, m.p. 171–173°. The infrared spectrum (chf.) had a moderately strong doublet, 2.76 and 2.98 μ. The ultraviolet spectrum (ethanol) had λ_{max} 288 mμ (log ε 3.34) and an inflection point at 225 mμ (log ε 3.99).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.23.

Similar hydrogenation of the boron complex, m.p. 239–241°, of XIa afforded a monohydroxy compound, probably **2,3-dimethoxy-9-hydroxy-10-ethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene**, m.p. 151–152.5°. after recrystallization from cyclohexane–ether. The infrared spectrum (chf.) of this compound had a single, sharp peak at 2.73 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 280 and 285 mμ (log ε 3.17 and 3.20, respectively).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.72; H, 9.12.

2,3-Dimethoxy-5-(α-hydroxyethyl)-6-hydroxy-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalene (XIIb).—Hydrogenation of 0.4 g. of XIb as described in the preceding experiment gave 0.35 g. of colorless crystals, m.p. 138–140°. Recrystallization from cyclohexane–ethyl acetate gave pure material, m.p. 142–144°. The infrared spectrum (chf.) had a doublet 2.76 and 2.99 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 291 mμ (log ε 3.43) and a point of inflection at 227 mμ (log ε 3.98).

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.44; H, 8.75.

2-Ethylcyclohexanone.—A solution of 5 g. of 2-acetylcyclohexanone[22] in 250 ml. of ethyl acetate containing 4 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for an hour. Two moles of hydrogen were consumed in 0.5 hr., and then the reaction became very slow. Filtration of the catalyst and evaporation of the solvent gave nearly colorless oil. The infrared spectrum (chf.) had an intense peak at 5.87–5.89 μ and a very weak band at 2.90 μ (indicating presence of some hydroxylic material). The **2,4-dinitrophenylhydrazone** was prepared in *ca.* 80% yield from the crude product; recrystallization from ethanol gave orange needles, m.p. 160–161° (lit.[23] m.p. 159–161°).

Condensation of Homoveratric Anhydride with 2-Tetralone.—To a mixture of 7.4 g. of homoveratric anhydride and 4.2 g. of 2-tetralone was added 65 ml. of ice-cold 47% boron trifluoride etherate. The suspension was swirled in an ice-bath for 15 minutes until the anhydride dissolved and was kept in an ice-box for 2 days. Hydrolysis with a solution of 60 g. of sodium acetate in 350 ml. of water at 60–70° for 10 minutes gave oily material, which was extracted with ether–ethyl acetate. The organic solution was washed with successive portions of water, sodium bicarbonate solution (excess) and water and was dried over magnesium sulfate. The solvents were evaporated at 30°, and the residual oil (6.9 g.) was dissolved in 20 ml. of ether. Refrigeration of this solution overnight resulted in formation of 0.85 g. of gummy crystals. Trituration of the crystals with additional ether gave 0.5 g. of product, m.p. 189–192°. Recrystallization from methanol afforded colorless crystals, m.p. 194–195° dec. The infrared spectrum (chf.) showed a weak band at 2.82–2.86 μ and a moderately strong peak at 5.83 μ. The ultraviolet spectrum (ethanol) had λ_{max} 227, 275, 321 and 349 mμ (log ε 4.45, 4.61, 3.96 and 2.96, respectively).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.08; H, 5.90.

Efforts to dehydrate and acetylate this material as with Ia led to decomposition and formation of mixtures of products.

Acknowledgment.—I am indebted to Dr. William C. Alford and his staff for microanalytical data, and to Mr. H. Franklin Byers, Miss Catherine Monaghan and Miss Patricia Wagner for spectra.

---

(22) R. M. Manyik, F. C. Frostick, J. J. Sanderson and C. R. Hauser, THIS JOURNAL, **75**, 5030 (1953).

(23) H. Smith, *J. Chem. Soc.*, 803 (1953).

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MAGGIONI & CO.]

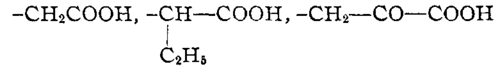
Further Research on Biphenyl, Stilbene and Diphenylethane Derivatives—Potential Anticholesterinemic, Antirheumatic Drugs. VII

BY G. CAVALLINI, E. MASSARANI, D. NARDI AND R. D'AMBROSIO

RECEIVED SEPTEMBER 21, 1956

Derivatives of biphenyl, stilbene and diphenylethane have been prepared with various substituents in the 4-position: alkylacetic acids; oxyacetic acid; and propionic, butyric, acrylic, pyruvic, crotonic, β-hydroxypropionic and γ-ethyl-β-hydroxybutyric acid.

In a previous paper[1] we prepared derivatives of biphenyl, stilbene and diphenylethane with various groups in the 4-position



$$-CH_2COOH,\ -\underset{\displaystyle C_2H_5}{\underset{|}{C}H}-COOH,\ -CH_2-CO-COOH$$

Some of these substances showed a marked anticholesterinemic activity, the most active among them being the 4-biphenylylethylacetic acid[2] which has been used therapeutically with satisfactory results.[3,4]

---

(1) G. Cavallini and E. Massarani, *Il Farmaco, Ed. Scient.*, **11**, 167 (1956).

(2) S. Garattini, C. Morpurgo and N. Passerini, *Giorn. ital. Chem.*, **2**, 60 (1955).

(3) G. Annoni, *Il Farmaco*, **11**, 244 (1956).

(4) E. Sabbadini, N. Campani and M. Gazzaniga, *Minerva Med.*, XLVII, [I], 2048 (1956).