[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

Synthesis of Phenanthrenes. III. 5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene

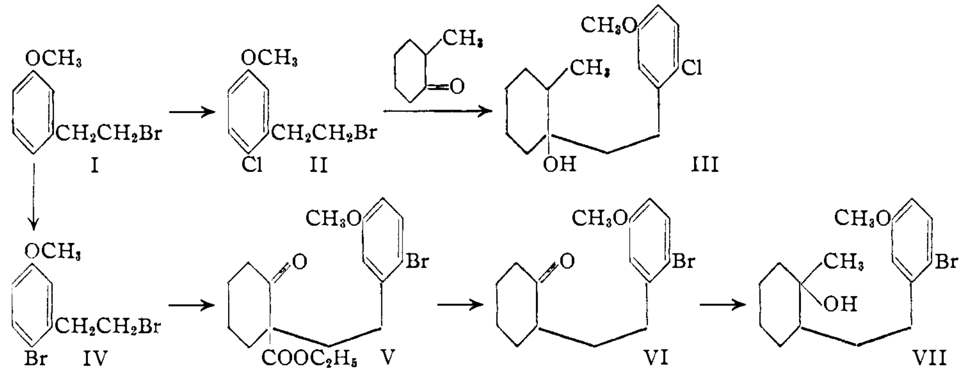
BY RODERICK A. BARNES, H. PETER HIRSCHLER AND BERNARD R. BLUESTEIN

RECEIVED FEBRUARY 18, 1952

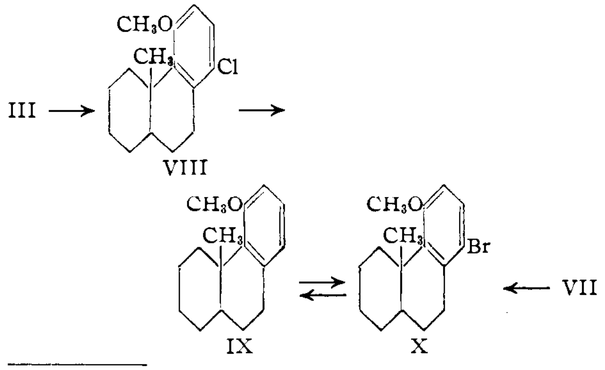
Two tertiary alcohols have been cyclized to yield 8-chloro- and 8-bromo-5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. The halogen atoms were replaced by hydrogen and the resulting methoxyoctahydrophenanthrene was found to brominate at the 8-position but to undergo a Friedel–Crafts reaction with succinic anhydride mainly at the 6-position.

In a previous paper[1] octahydrophenanthrenes were prepared in which a methoxyl group was in the 5-position but these substances also had an angular carboxyl group. The purpose of the present work was to prepare the carboxyl-free octahydrophenanthrenes which are of greater interest as possible intermediates for the synthesis of steroids.

In order to obtain a 5-methoxyoctahydrophenanthrene by cyclization of a β-arylethylcyclohexanol it is necessary to have a blocking group to prevent cyclization para to the methoxyl group. Tertiary alcohols III and IV, prepared by different procedures, had a chlorine and a bromine atom, respectively, as blocking groups.



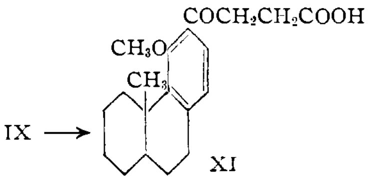
The chlorination of I with sulfuryl chloride proved to be remarkably dependent on the exact composition of the solvent. When II was treated with one equivalent of magnesium a coupling product, 1,4-di-(2′-chloro-5′-methoxyphenyl)-butane was formed in 26% yield. With ten moles of magnesium the amount of coupling product was reduced to 17%.



An attempt to purify alcohol III by evaporative distillation caused extensive dehydration, therefore, the crude alcohols were cyclized directly without distillation in subsequent experiments. Both III and VII produced as the major product a single stereoisomeric form of the desired octahydrophenanthrenes[2] VIII and X.

The halogen atoms could be reductively removed either with sodium and alcohol or by shaking with hydrogen and Raney nickel in alkaline solution. Both VIII and X have the same stereochemical configuration of the two saturated rings because a sample of IX prepared from VIII could be brominated to yield X identical with the sample prepared by cyclization of VII. This bromination also established that the preferred position of attack by bromine on the aromatic nucleus of IX was the 8-position.

It was anticipated that IX would also undergo the Friedel–Crafts reaction at the 8-position.[3] However, the ketoacid obtained from the reaction of IX with succinic anhydride was different than the acid obtained when the bromine atom of X was replaced by a succinoyl group.

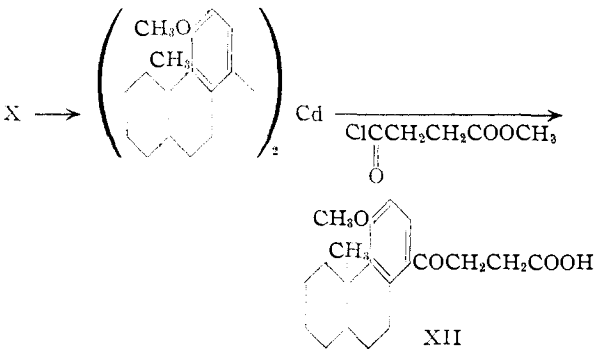


---

[1] R. A. Barnes, H. P. Hirschler and B. R. Bluestein, THIS JOURNAL, **74**, 32 (1952).

[2] R. A. Barnes and R. T. Gottesman, *ibid.*, **74**, 35 (1952), have presented evidence to indicate that 4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene is also obtained as one stereoisomer from a similar cyclization reaction.

[3] The observation of W. E. Bachmann and A. B. Ness, *ibid.*, **64**, 536 (1942), that 5-methoxy-1,2,3,4-tetrahydronaphthalene reacts with succinic anhydride in nitrobenzene to introduce a succinoyl group at the 8-position is a closely related example to support this expectation.



XII

The position of the succinoyl group in acid XII is established by its method of synthesis, therefore, it is believed that XI represents the structure of the acid obtained by direct succinoylation. In a previous paper[2] it was noted that the succinoyl group also enters the 6-position of the octahydrophenanthrene lacking a methoxyl group.

Acknowledgment.—We wish to express our appreciation to the Research Corporation for a Frederick Gardner Cottrell Grant which made this work possible. We also wish to acknowledge the assistance of Doris E. Barnes in preparing many of the compounds used in this research.

Experimental[4]

β-(2-Chloro-5-methoxyphenyl)-ethyl Bromide (II).—Sulfuryl chloride (65 g.) was added to a cold solution of β-(3-methoxyphenyl)-ethyl bromide[5] (100 g.) dissolved in unpurified commercial carbon tetrachloride (1000 ml.). The reaction flask was placed in a large crock of ice and allowed to stand overnight as the ice melted. After an additional 32 hours at room temperature the cherry-red reaction mixture was processed by washing with water, removing the solvent and vacuum distilling the residue. There was obtained 104.3 g. (90%) of II which boiled at 98–102° at 0.1 mm., n^{22}_{D} 1.5724.

Anal. Calcd. for $C_9H_{10}OClBr$: C, 43.32; H, 4.04. Found: C, 43.36; H, 4.02.

Oxidation of II by boiling with potassium permanganate solution produced 2-chloro-5-methoxybenzoic acid which melted at 169–171°.[6]

When carbon tetrachloride purified by distillation over phosphorus pentoxide was used as a solvent for the chlorination the reaction was very slow and incomplete; 80–85% of unchanged II could be recovered by careful fractionation. In acetic acid as a solvent the reaction was rapid but chlorination took place ortho to the methoxyl group as well as at the desired position. This was indicated by the melting point, 188–202°, of the permanganate oxidation product.[7]

Two other commercial samples of carbon tetrachloride were unsatisfactory solvents for the chlorination but a solvent prepared by adding 1 ml. of methanol per 100 ml. of pure carbon tetrachloride could be used to prepare II in 68% yield.

8-Chloro-5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VIII).—A Grignard reagent was prepared in the usual manner from II (50 g.), magnesium (48 g.) and dry ether (500 ml.). The reaction mixture was stirred and heated at reflux temperature for 3 hours after the addition of the halide was complete.

A solution of 2-methylcyclohexanone (22 g.) in dry ether (30 ml.) was added dropwise to the cold (0°) Grignard reagent and the mixture allowed to stand overnight. After the addition of excess ammonium chloride solution, the ether layer was separated, dried and concentrated. The addition of methanol followed by prolonged chilling caused the separation of a crystalline by-product (6 g., 17%). This substance melted at 90–91° after recrystallization from ethanol and gave the correct analysis for 1,4-di-(2'-chloro-5'-methoxyphenyl)-butane.

Anal. Calcd. for $C_{18}H_{20}O_2Cl_2$: C, 63.72; H, 5.94. Found: C, 63.51; H, 6.05.

When the Grignard reagent was prepared from II (18.5 g.) using one equivalent (2.4 g.) of magnesium this product was obtained in 26% yield (3.3 g.).

An attempt to purify alcohol III by evaporative distillation of the crude product obtained by concentrating the methanol soluble material yielded a clear liquid, n^{20}_{D} 1.5459. The analysis of this material indicated it to be a mixture of 30% III and 70% of the corresponding olefin.

Crude undistilled III (39 g., from 50 g. of II) was washed into a dropping funnel with benzene (20 ml.). This solution was added dropwise at 5° to a sulfuric acid solution prepared from concentrated sulfuric acid (425 ml.) and water (45 ml.). When the addition was complete the red-orange reaction mixture was stirred for one hour at 5–10° and then poured onto ice. The product was extracted with ether and the ether layer washed with water and potassium hydroxide solution. The crude product remaining after evaporation of the ether was distilled *in vacuo*. There was obtained 16.5 g. (45%) of product which boiled at 110–118° (0.02 mm.), n^{23}_{D} 1.5653. This material crystallized on standing and could be readily recrystallized from absolute ethanol although it is rather soluble in this solvent. By concentrating mother liquors a total of 13 g. of product of m.p. 75–78° was obtained. The pure compound melted at 77.0–78.8°.

Anal. Calcd. for $C_{16}H_{21}OCl$: C, 72.59; H, 7.99; Cl, 13.40. Found: C, 72.69; H, 7.99; Cl, 13.23.

The liquid residue obtained by combining and concentrating the mother liquors from several preparations was distilled *in vacuo* to yield a forerun[8] (b.p. 90–110°, 0.02 mm.; n^{22}_{D} 1.545 ± 0.005) and some of the desired crystalline product VIII (30–40% of total residue).

5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IX).—Small pieces of sodium (16 g.) were added during 3 hours to a gently refluxing solution of VII (8.7 g.) in absolute ethanol (350 ml.). When all the sodium was dissolved the ethanol was distilled and the residue treated with dilute hydrochloric acid and petroleum ether. The organic layer was separated, dried and concentrated and the residue fractionated. There was obtained 4.5 g. (59%) of product which boiled at 109–114° (0.07 mm.), n^{27}_{D} 1.5550.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.62. Found: C, 83.19; H, 9.49.

The higher boiling fractions (1.97 g., n^{27}_{D} 1.5600 ± 0.0020) still contained chlorine and could be converted to IX by further reduction with sodium and alcohol.

When a solution of VIII (4 g.) and potassium hydroxide (3 g.) in absolute ethanol was shaken with hydrogen (40 lb.) and Raney nickel (3 g.) for 6 hours a sample of IX was obtained (n^{27}_{D} 1.5570) which still gave a Beilstein test for halogen.

2-β-(2'-Bromo-5'-methoxyphenyl)-ethylcyclohexanone (VI).—2-Carbethoxy-2-β-(2'-bromo-5'-methoxyphenyl)-ethylcyclohexanone (V)[1] (10 g.) was boiled with a solution of barium hydroxide (40 g.) in water (600 ml.) and ethanol (200 ml.) for 48 hours. The cold reaction mixture was acidified to congo red and extracted with ether. The ether extract was washed with sodium bicarbonate solution, dried and concentrated. There was obtained 4.65 g. (57%) of ketone VI which boiled at 155–162° (0.1 mm.), n^{25}_{D} 1.5530.

Anal. Calcd. for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.16. Found: C, 58.27; H, 6.07.

The 2,4-dinitrophenylhydrazone melted at 168–169° after recrystallization from ethanol–ethyl acetate.

Anal. Calcd. for $C_{21}H_{22}O_5N_4Br$: N, 11.43. Found: N, 11.52.

The semicarbazone melted at 166.5–168° after recrystallization from ethanol.

---

(4) All melting points are corrected. Analyses were by W. Manser, Zurich, Switzerland.

(5) W. E. Bachmann and D. G. Thomas, This Journal, **64**, 94 (1942).

(6) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 147 (1926), report that this compound melts at 170–171°.

(7) 4-Chloro-3-methoxybenzoic acid is reported in ref. 6 to melt at 215–216°.

(8) We believe this substance is largely a non-chlorinated cyclization product.

Anal. Calcd. for $C_{16}H_{22}O_2N_3Br$: C, 52.18; H, 6.02. Found: C, 51.94; H, 5.95.

8-Bromo-5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (X). **A.**—A solution of ketone VI (57 g.) in ether (100 ml.) was added dropwise to a cold solution of methylmagnesium iodide prepared from magnesium (6.1 g.), methyl iodide (40 g.) and dry ether (300 ml.). After standing overnight the reaction mixture was treated with ammonium chloride solution and the ether layer was separated, washed with water and concentrated. The crude alcohol VII (60 g.) was dissolved in benzene (40 ml.) and cyclized with sulfuric acid (600 ml.) and water (126 ml.) as in the preparation of VIII. The crude cyclized product crystallized when seeded and stirred with a small amount of absolute ethanol. The first crystals were obtained when a small sample purified by evaporative distillation was allowed to stand for six months. There was obtained 45 g. (78%) of X which melted at 85–89°. After recrystallization from ethyl acetate the pure product melted at 93–94°.

Anal. Calcd. for $C_{16}H_{21}OBr$: C, 62.14; H, 6.85; Br, 25.84. Found: C, 62.24; H, 6.93; Br, 25.82.

B.—A solution of 5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IX) (230 mg.) in carbon tetrachloride (10 ml.) was treated with a solution of bromine (160 mg.) in carbon tetrachloride (3.2 ml.) at 0°. The reaction mixture was washed with water and the carbon tetrachloride evaporated. The residue crystallized on standing and was recrystallized from ethyl acetate. The melting points of this product and the mixture with the product from part A were 92–93.5°.

β-6-(5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthroyl)-propionic Acid (XI).—A cold solution of aluminum chloride (6 g.) and succinic anhydride (2.2 g.) in nitrobenzene (80 ml.) was added to a solution of IX (4.5 g.) in nitrobenzene (70 ml.) and the mixture allowed to stand in the refrigerator for 72 hours. The reaction mixture was treated with dilute hydrochloric acid and ether. The ether layer was separated and the acidic products extracted with dilute potassium hydroxide solution. Acidification of the alkaline extract produced 5.6 g. (87%) of crude crystalline acid. The product (4.9 g.) melted at 151.5–153° after purification by recrystallization from methanol.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.90. Found: C, 72.53; H, 8.01.

β-8-(5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthroyl)-propionic Acid (XII).—A solution of X (19.5 g.) and methyl iodide (8 g.) in dry ether (200 ml.) and dry benzene (70 ml.) was added dropwise to magnesium (5 g.). When the addition was complete the reaction mixture was refluxed for an hour to complete the formation of the Grignard reagent. The reaction flask was cooled in an ice-bath and dry cadmium chloride (15 g.) was added. The mixture was stirred and heated for 15 minutes and then 150 ml. of ether was distilled off and replaced by dry benzene. A solution of β-carbomethoxypropionyl chloride (14 g.) in dry benzene (20 ml.) was added quickly and the reaction mixture stirred and refluxed for an hour. After standing for a day at room temperature the contents of the flask was poured into a mixture of ice and hydrochloric acid and the product extracted with ether. The residue remaining after evaporation of the ether was boiled for 8 hours with a solution of potassium hydroxide (10 g.) in water (60 ml.) and ethanol (300 ml.). The ethanol was distilled off and water and ether were added to the residue. The ether layer was concentrated and after distillation 6.3 g. of IX and 1.9 g. of X were recovered. By acidification of the water layer there was obtained 8.8 g. (42%) of acid which solidified after seeding (first crystals were obtained after purification by chromatography on silicic acid). The product was recrystallized from ligroin, m.p. 120–121.5° (yield 6.2 g.). An additional amount (1.1 g.) of less pure material, m.p. 117–120°, was recovered from the mother liquors.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.90. Found: C, 72.94; H, 7.92.

Dehydrogenation of IX.—The bromine atom was removed from X (0.5 g.) by shaking with hydrogen and nickel in alkaline solution. The crude product was heated with palladium-on-charcoal (0.1 g.) for 6 hours at 270–300° and for one hour at 320°. Some crystalline product sublimed out of the reaction mixture. The crude dehydrogenated product was converted to the picrate which after recrystallization melted at 185–187° and was identical with an authentic sample of 4-methoxyphenanthrene picrate.[1] The trinitrobenzene adduct prepared as previously described[1] melted at 206–208°. Some cleavage of the methoxyl group occurred during this dehydrogenation since phenanthrene, m.p. 95–97°, was isolated by concentrating the filtrates after separating 4-methoxyphenanthrene picrate and treating the residual mixture of picric acid and phenanthrene picrate with ammonia and ether.

NEW BRUNSWICK, NEW JERSEY

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY, AND THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Studies on the Mucohalic Acids. II. The Synthesis of Fused γ-Lactam-thiazolidines Related to Penicillin[1]

BY HARRY H. WASSERMAN, FRANK M. PRECOPIO AND TIEN-CHUAN LIU*

RECEIVED FEBRUARY 21, 1952

Mucochloric, mucobromic and mucophenoxychloric acids were condensed with *dl*-penicillamine hydrochloride and its methyl ester to form fused γ-lactam-thiazolidines structurally related to the penicillins. The 2-thiazolidineacrylic acids pictured as intermediates appeared to cyclize to γ-lactams either spontaneously or after mild heating.

The condensation of cysteine and penicillamine with aldehydes and ketones to form thiazolidines takes place under a wide variety of conditons.[2–4] In the case of the reaction with aldehyde-acids, the initial thiazolidine formation may be followed by interaction of the carboxyl group with the cyclic imino group to produce a fused lactam-thiazolidine. Although β-lactam formation by this method, utilizing α-aldehydo-acids, has never been observed, γ-lactams have been prepared successfully by the use of β-aldehydo-acids. Thus, as reported in the recent monograph on the chemistry of penicillin,[5] derivatives of β-formylpropionic acid were condensed with the appropriate α-amino-β-mercapto acids to form thiazolidines which readily cyclized to fused-ring γ-lactams. Among

---

* Mary E. Woolley and Skinner Fellow from Mt. Holyoke College 1951–1952.

(1) In part, from the doctoral dissertation of H. H. Wasserman, Harvard University, 1948.

(2) H. T. Clarke, J. R. Johnson and R. Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 921.

(3) S. Lieberman, P. Brazeau and L. B. Hariton, THIS JOURNAL, **70**, 3094 (1948).

(4) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

(5) Reference 2, p. 1004.