Acknowledgment.—The authors wish to express their appreciation to The Wm. S. Merrell Company through whose generous support this work was carried out.

Summary

1. 2-Nitro-4-chlorobenzonitrile has been reduced to the corresponding amino nitrile.
2. The cleavage of 5-chloroisatoic anhydride by ammonia has been more fully investigated.
3. From these intermediates, two new basically substituted quinazolines have been prepared.

CHAPEL HILL, NORTH CAROLINA
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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

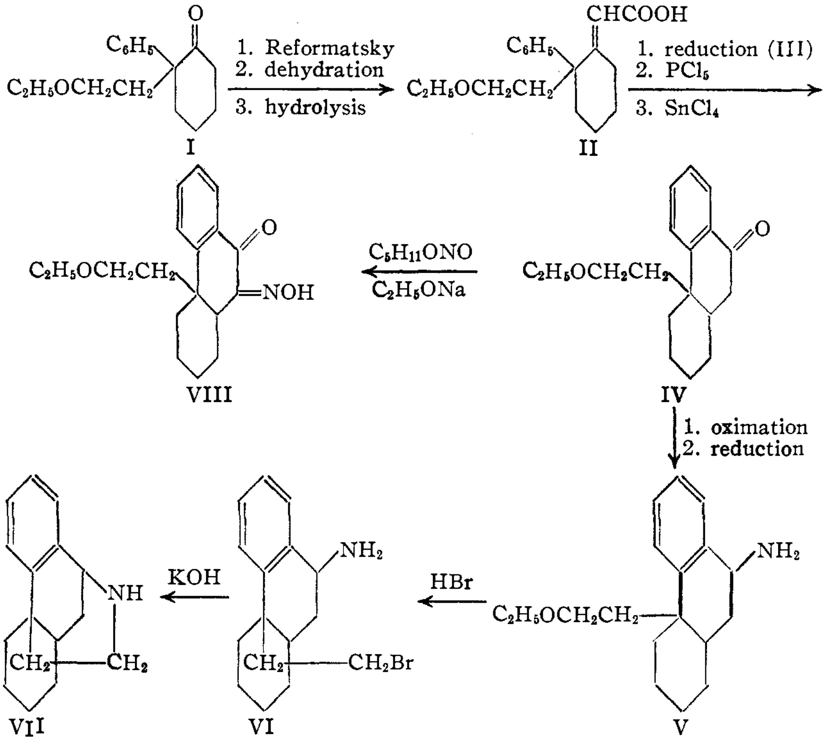
The Synthesis of Hydroaromatic Compounds Containing Angular Groups. III. 9,4a(2)-Iminoethanohydrophenanthrene Series[1]

BY MELVIN S. NEWMAN AND BARNEY J. MAGERLEIN[2]

The present work was undertaken with the object of exploring methods for the synthesis of heterocyclic compounds similar to those found in morphine and related alkaloids. Although this work is only partially completed, it seems worth while to present the results obtained to date. Evidence is given for the successful synthesis of 1,3,4,9,10,10a - hexahydro - 9,4a(2) - iminoethanophenanthrene,[3] although it was not isolated in a pure state. A lack of material prevented further work at this stage. We have also made some progress as indicated by formula VIII toward the synthesis of 1,3,4,9,10,10a-hexahydro-10,4a(2)-iminoethanophenanthrene which contains a ring system more nearly analogous to that of morphine.

The synthetic scheme follows closely along the lines previously developed[4] and is outlined in the chart.

The work was made difficult by the fact that none of the compounds was obtained in a crystalline form. For the most part they were fairly viscous oily mixtures of stereoisomers. In the case of ketones I and IV crystalline semicarbazones were obtained. A small amount of a crystalline oxime of IV was also isolated but the regenerated ketones failed to crystallize.



Accurate molecular models show that the ring closure involved in proceeding from VI to VII is possible with only two of the four possible inactive isomers of VI. Isomers incapable of cyclization might either polymerize or dehydrobrominate to yield a primary 12-vinylamine isomeric with the desired secondary amine, VII.

The monomolecular product we obtained in very small yield was not sufficient for further work. The analysis for carbon, hydrogen, and nitrogen agreed with the theoretical values for VII. However, a Van Slyke amino nitrogen determination[5]

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(1) The material herein presented was taken from the Ph.D. Thesis of Barney J. Magerlein, Ohio State University, June, 1946.

(2) The authors wish to take this opportunity to acknowledge with thanks a grant-in-aid from a special fund donated by the Ohio State University Research Foundation and administrated by the Graduate School.

(3) The nomenclature is consistent with that used by *Chemical Abstracts*. The parent substance is 9,4a(2)-iminoethanophenanthrene, a 2,4a-dihydrophenanthrene derivative. The number 9 comes first to indicate the position of the nitrogen linkage of the bridge.

(4) M. S. Newman and M. D. Farbman, THIS JOURNAL, 66, 1550 (1944), article I, this series.

(5) We wish to thank Drs. D. D. Van Slyke and Paul B. Hamilton of the Rockefeller Institute for Medical Research for this analysis.

indicated that our product contained approximately 56% of primary amine. The remainder was undoubtedly the desired amine, VII.

Experimental[6]

2-Ethoxyethyl Methanesulfonate.—To a solution at −10° of 114 g. of methanesulfonyl chloride and 81 g. of 2-ethoxyethyl alcohol (ethyl cellosolve) in 200 cc. of dry ether was added 112 g. of dry pyridine over a period of four hours. After two hours at 0° the water soluble product was isolated by ether extraction and distilled to give 102 g. (67%) of a colorless liquid, b. p. 122–124° at 7 mm. This procedure[7] was superior to others we tried.[8]

Anal.[a] Calcd. for $C_5H_{12}O_4S$: C, 35.7; N, 7.2; S, 19.1. Found: C, 36.2, 35.9; H, 7.2, 7.2; S, 19.0, 19.1.

2-(2′-Ethoxyethyl)-2-phenylcyclohexanone, I.—To a stirred suspension at 50° of 41 g. of sodamide in 100 cc. dry benzene was added over a period of one hour a solution of 174 g. of 2-phenylcyclohexanone[4] in 500 cc. of benzene. After refluxing for three hours the evolution of ammonia had almost stopped and the mixture was then treated with a solution of 190 g. of 2-ethoxyethyl methanesulfonate in 100 cc. of benzene. After warming for one hour, the organic product was isolated and, on vacuum fractionation, there was obtained 135 g. (54%) of pure I, b. p. 129–134° at 0.5 mm., $n^{20}{}_D$ 1.5227, as a viscous colorless oil. When 5-ethoxyethyl iodide was used, the yield was 25% and with the tosyl derivative, 44–54%. In the latter case isolation of a pure ketone was more difficult. The semicarbazone, formed in 39% yield by conventional procedure, melted at 168.0–168.4°.

Anal.[b] Calcd. for $C_{16}H_{22}O$: C, 78.0; H, 9.0. Found: C, 78.2, 77.8; H, 9.1, 9.0. Calcd. for $C_{17}H_{25}ON$: C, 67.3; H, 8.3; N, 13.9. Found: C, 67.0, 67.0; H, 8.4, 8.2; N, 13.7, 13.6.

2-(2′-Ethoxyethyl)-2-phenylcyclohexeneacetic Acid, II.—The Reformatsky reaction between 126 g. of I and 167 g. of ethyl bromoacetate was run in ether–benzene using 98 g. of zinc foil. After the vigor of the reaction subsided the mixture was treated with four additions of 83 g. of bromoester and 32.5 g. of zinc at half hour intervals with refluxing after each addition.[9] After hydrolysis the organic matter was vacuum distilled and to the distillate in 400 cc. of dry ether and 64 cc. of dry pyridine was added 60 g. of pure thionyl chloride. After two hours at 5° the mixture was treated with water and the organic reaction product was subjected to alkaline hydrolysis. The neutral fraction afforded 8.5 g. (7%) of recovered ketone, I. The acid fraction was rapidly distilled at 1 mm. with a bath temperature not exceeding 250° to yield 116 g. (79%) of an amber-colored unsaturated acid. The position of the double bond was not determined. When the Reformatsky reaction was carried out without extra additions of bromoester and zinc the yield dropped to 20% with 56% of recovered ketone, I.

Anal.[a] Calcd. for $C_{18}H_{24}O$: C, 75.0; H, 8.4; neut. equiv., 288. Found: C, 75.0, 75.4; H, 8.4, 8.2; neut. equiv., 290.

In an attempt to secure a crystalline acid the 2,4,6-tribromoanilides[10] were made and the small crystalline portion was recrystallized to a melting point of 146.4–147.7°. However, the acid fraction regenerated by refluxing for twenty hours with 28% sulfuric acid failed to crystallize.

Anal.[b] Calcd. for $C_{24}H_{26}O_2NBr_3$: C, 48.0; H, 4.4. Found: C, 48.4, 48.4; H, 4.4, 4.5.

The ethyl ester was prepared in high yield and formed a pale yellow viscous oil, b. p. 159–168° at 1 mm., $n^{25}{}_D$ 1.5303.

Anal.[b] Calcd. for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.1, 76.0; H, 9.0, 9.0.

2-(2′-Ethoxyethyl)-2-phenylcyclohexaneacetic Acid, III.[11]—To a hot solution of 57 g. of II in 100 cc. of alcohol, 1600 cc. of water and 160 g. of sodium hydroxide was added 155 g. of Raney nickel over a period of nine hours.[12] Octyl alcohol was added as needed to prevent excessive foaming. The reduced saturated acids were almost colorless and formed a viscous oil on rapid vacuum distillation (0.5 mm.) with a heating bath at 230°. The yield was 83%. The acid did not decolorize permanganate and the tribromoanilide failed to crystallize. Attempts to reduce the unsaturated acid or its ethyl ester by catalytic means failed. The analyses given represent two cuts.

Anal.[a] Calcd. for $C_{18}H_{26}O_2$: C, 74.4; H, 9.0. Found: C, 73.7, 75.4; H, 8.4, 9.0.

12-(2′-Ethoxyethyl)-9-keto-1,2,3,4,9,10,11,12-octahydrophenanthrene, IV.—A solution of 92 g. (0.32 mole) of III in 200 cc. of dry sulfur-free benzene was added to a mixture of 69.5 g. (0.34 mole) of phosphorus pentachloride and 50 cc. of benzene at a moderate rate and the whole then warmed at 50° for fifteen minutes. The resulting solution was cooled until the benzene was partly crystallized and 125 g. (0.48 mole) of stannic chloride was added rapidly with vigorous stirring. After stirring in the cold for five minutes, the mixture was hydrolyzed by shaking with cold dilute hydrochloric acid and a little ether. The ketone formed a slightly yellow oil, b. p. 158–165° at 0.5 mm., $n^{20}{}_D$ 1.5530, and weighed 82 g. (95%). Ring closure using aluminum chloride afforded a 68% yield of a similar product. A small portion of this crude ketone was purified by means of Girard reagent "P."[13] Both the crude and pure ketone had the same index of refraction but the analytical figures from the crude ketone were not consistent with the theoretical.

Anal.[a] Calcd. for $C_{18}H_{24}O_2$: C, 79.4; H, 8.9; C_2H_5O, 16.5. Found: C, 79.1, 79.3; H, 8.8, 8.6; C_2H_5O, 16.0.

The crude ketone afforded a semicarbazone, m. p. 219–220° with dec., and a 2,4-dinitrophenylhydrazone, m. p. 213.0–214.5° uncor.

Anal. Calcd. for $C_{19}H_{27}O_2N_3$: C, 69.3; H, 8.3; N, 12.8. Found:[a] C, 69.3, 69.3; H, 8.2, 8.4; N, 12.9, 12.9. Calcd. for $C_{24}H_{28}O_5N_4$: C, 63.7; H, 6.2; N, 12.4. Found:[b] C, 63.5, 63.3; H, 6.3, 6.1; N, 12.1, 12.1.

The oxime was obtained either by reaction with an excess of hydroxylamine in aqueous alcohol (63%) or in pyridine (84%). However, the noncrystalline oxime gave low nitrogen analyses. On long standing in benzene–petroleum ether a small quantity of crystalline oxime, m. p. 137.4–138.3° separated.

Anal.[a] Calcd. for $C_{18}H_{25}O_2N$: C, 75.2; H, 8.8; N, 4.9. Found: C, 75.1, 75.0; H, 9.1, 8.9; N, 4.9, 4.8.

On treatment of the crude oxime with acetyl chloride in pyridine there was obtained in 41% yield a crystalline acetate, m. p. 151–155°. Seven recrystallizations from benzene–petroleum ether (Skellysolve B) raised the melting point to 155.1–156.4°.

Anal.[a] Calcd. for $C_{20}H_{27}O_3N$: C, 72.9; H, 8.3; N, 4.3. Found: C, 72.7, 72.9; H, 8.1, 8.5; N, 4.5, 4.4.

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(6) All melting points corrected except those otherwise designated. Analyses marked [a] by Arlington Laboratories, [b] by J. A. Curtiss.

(7) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(8) P. Ruggli, O. Levpin and A. Businger, *Helv. Chim. Acta*, **24**, 339 (1941); H. Gilman and N. Beaber, THIS JOURNAL, **47**, 518 (1925).

(9) W. E. Bachmann and R. O. Edgerton, *ibid.*, **62**, 2970 (1940).

(10) M. Kuehn and S. M. McElvain, *ibid.*, **53**, 1173 (1931).

(11) These compounds formed mixture of stereoisomers which were not separated. Mostly these substances were quite viscous and were usually contaminated with closely related products. Hence, the analyses of the distilled materials were usually somewhat different from theory. However, analyses of carefully purified portions gave the expected results. For the most part the crude mixtures were used for the subsequent operations.

(12) E. Schwenk, D. Papa, B. Whitman and H. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(13) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

12-(2′-Ethoxyethyl)-9-amino-1,2,3,4,9,10,11,12-octahydrophenanthrene, V.—In the best of several attempts, 9.08 g. of oxime, purified by extraction from petroleum ether solution with Claisen alkali and precipitation with acid, in 200 cc. of pure anhydrous butyl alcohol at 80° was treated with 14 g. of sodium. The mixture rapidly heated up enough to melt the sodium and was shaken occasionally to break up the molten globules of sodium. At the end additional heat was required to complete the reaction. The crude amine thus obtained was purified by dissolving in dry petroleum ether to which dry hydrogen chloride was added. The precipitated hydrochloride was collected, washed, and treated with alkali. There was thus obtained 5.5 g. (64%) of faintly yellow viscous amine, n^{25}_D 1.5518, which distilled at 0.5 mm. when the bath temperature was about 190°. More of a similar product was obtained in 21% yield from the non-crystalline material remaining after the separation of the crystalline oxime acetate described above.

Anal.[a] Calcd. for $C_{18}H_{27}ON$: C, 79.1; H, 10.0; N, 5.1. Found: C, 78.1, 78.4; H, 9.8, 9.9; N, 4.9, 4.9.

The neutral fraction remaining after removal of the amine hydrochloride yielded a small amount of an oily liquid which distilled at 0.5 mm. when the bath temperature was about 190°. This fraction was larger when oxime not purified by the Claisen alkali treatment was used. Treatment with methylmagnesium iodide showed that this substance contained an active hydrogen, and on analysis, figures consistent with the formulation as 12-(2′-ethoxyethyl)-9-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene were obtained.

Anal.[a] Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6. Found: C, 79.1, 78.7; H, 9.1, 8.9.

1,3,4,9,10,10a-Hexahydro-9,4a(2)-iminoethanophenanthrene, VII.—On refluxing a solution of 3.35 g. of the above amine in 60 cc. of 48% hydrobromic acid, an insoluble compound separated. On extraction, washing, and removal of solvent, 3.25 g. of a brittle resin-like substance was obtained. Since this product could not be distilled or crystallized readily, it was immediately subjected to cyclization attempts. An analysis of the crude material is given.

Anal.[a] Calcd. for $C_{16}H_{22}NBr$: C, 62.3; H, 7.2; N, 4.5; Br, 25.9. Found: C, 56.2; H, 6.7; N, 3.8; Br, 26.2.

In the best of several attempts at cyclization, 1.88 g. of bromoamine in 50 cc. of 95% ethyl alcohol was added to 500 cc. of 10% sodium hydroxide containing 200 cc. of ethyl alcohol.[14] After keeping at 60° for three days, the alcohol was largely removed and the organic material extracted to yield 1.63 g. of a substance which was much more fluid than the starting material. On triturating with Skellysolve B 0.37 g. remained undissolved. Analysis showed it to contain 6% of bromine so it was not further studied. On treatment of the Skellysolve B soluble fraction with dry hydrogen chloride, a crude hydrochloride fraction was obtained which was only partially soluble in water. The water insoluble fraction was discarded after preliminary examination and the soluble fraction was made alkaline. The amine thus obtained was vacuum distilled (bath temperature, 180°, pressure 0.5 mm.) to yield 25 mg. of almost colorless, rather fluid product.

Anal.[a] Calcd. for $C_{16}H_{21}N$: C, 84.5; H, 9.3; N, 6.2. Found: C, 84.0; H, 9.4; N, 5.8.

A small amount of solid chloroplatinate was made and analyzed for platinum.

Anal. Calcd. for $C_{32}H_{44}N_2PtCl_6$: Pt, 22.6. Found: Pt, 22.2.

A Van Slyke amino-nitrogen determination[5] showed that 56.2% of this product was primary (undesired) amine, probably 9-amino-12-vinyl-1,2,3,4,9,10,11,12-octahydrophenanthrene. The remainder was probably the desired secondary amine, VII, but further work must be done before this synthesis is firmly established.

12-(2′-Ethoxyethyl)-9-keto-10-oximino-1,2,3,4,9,10,11,-12-octahydrophenanthrene, VIII.—The ketone, IV, was nitrosated with *i*-amyl nitrite and potassium ethoxide[15] to yield 62% of a yellow-orange oil soluble in Claisen alkali. This material could not be vacuum distilled or crystallized but gave the expected analytical figures for VIII after partial purification by chromatographic adsorption over a mixture of 5 parts calcium silicate (Silene, Pittsburgh Plate Glass Co.) and 1 part celite No. 535 (Johns Manville Co.) had removed a dark colored impurity.

Anal.[a] Calcd. for $C_{18}H_{23}O_3N$: C, 71.7; H, 7.7; N, 4.6. Found: C, 71.7; H, 7.9; N, 4.7.

Summary

Steps in the attempted synthesis of 1,3,4,9,10,-10a-hexahydro-9,4a(2)-iminoethanophenanthrene are described.

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[14] Compare J. von Braun, W. Haensel and F. Zobel, *Ann.*, **462**, 283 (1928); J. von Braun and K. Schwarz, *ibid.*, **481**, 56 (1930) V. Prelog, *ibid.*, **545**, 229 (1940).

[15] A. Pictet and A. Gams, *Ber.*, **42**, 2943 (1909); L. Claisen *ibid.*, **20**, 655 (1887).

Columbus 10, Ohio Received December 16, 1946

[Contribution from the Department of Chemistry and the Purdue Research Foundation, Purdue University]

Fluorinated Derivatives of Propane[1]

By E. T. McBee, H. B. Hass, R. M. Thomas,[2] W. G. Toland, Jr.,[3] and A. Truchan

This work is an extension of the research undertaken for the purpose of synthesizing fluorine-containing compounds for pharmacological tests. The synthesis of certain fluoro derivatives of propane has been described in a previous paper.[4] The investigation has now been extended to include additional derivatives of propane.

The fluorination of $CCl_3CH_2CH_3$ with antimony fluoride gives a 5–10% yield of $CF_3CH_2CH_3$.[5] Three new syntheses for the preparation of 1,1,1-trifluoropropane have been developed, namely, fluorination of $CCl_3CH_2CH_3$, $CCl_2{=}CHCH_3$ and 1,1-dichloro-cyclopropane with hydrogen fluoride. These reactions also yielded $CClF_2CH_2CH_3$ and $CCl_2FCH_2CH_3$. This same fluorination procedure

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[1] The major portion of this paper is taken from the Ph. D. Thesis submitted to the faculty of Purdue University by R. M. Thomas in 1942.

[2] Present address: Firestone Tire and Rubber Co., Akron, Ohio.

[3] Present address: California Research Corporation, Richmond, California.

[4] E. T. McBee, A. L. Henne, H. B. Hass and N. Elmore, This Journal, **62**, 3340 (1940).

[5] A. L. Henne and A. M. Whaley, *ibid.*, **64**, 1157–1159 (1942).