TABLE VI

Hydrochloride of	M. p., °C.	Solvent	Anal., Cl. % Calcd.	Found
$C_6H_5CH(CH_3)CHNH_2CH_3$	136 –139	$C_6H_5CH_3$	19.12	19.25
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (I)	171 –172	$CHCl_3$[a]	17.78	17.89
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (II)	258 –261	$CHCl_3 + C_6H_{14}$[b]	17.78	17.80
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (I)	120 –123	C_6H_6	16.61	16.48
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (II)	250 –253	$(C_2H_5)_2O$[c]	16.61	16.81
$C_6H_5C(CH_3)_2CHNH_2CH_3$	213.5–215	$(CH_3)_2CO$	17.78	17.91
$C_6H_5CH(CH_3)CH(NHCH_3)CH_3$	116 –120	$CH_3CO_2C_2H_5$	17.78	17.78

[a] Dry acetone is also suitable. [b] Very soluble in chloroform, precipitated by petroleum ether. [c] Less soluble than low melting isomer. Further crystallization was from benzene and petroleum ether.

mm.). The total yield from acid and alkaline hydrolyses was 6.45 g. or 63% of the theoretical amount.

In the alkaline hydrolysis of the product from the action of formamide upon methyl α-phenyl-*n*-butyl ketone the yield of amine was only 5.3% while from subsequent acid hydrolysis the amine obtained amounted to an 86% yield, based upon the formyl derivative used.

In the preparation of N, α,β-trimethylphenethylamine methylformamide[5] was substituted for formamide. In Tables IV and V the data for the amines are summarized. They were obtained as clear viscous liquids which were mixtures of diastereoisomers (except for the compound from the dimethyl ketone).

Amine Hydrochlorides.—The five amines were converted into their hydrochlorides by dissolving in ether and passing in dry hydrogen chloride. Fractional crystallization of the precipitates yielded the diastereoisomers in the case of the β-ethyl and β-*n*-propylamines. There was evidence of the existence of two compounds in the case of the methyl homolog but only one was obtained pure. α,β,β-Trimethylphenethylamine gave only one hydrochloride in conformity with the assigned structure. The data for the hydrochlorides are summarized in Table VI.

Summary

1. The monomethylation of phenylacetone is incomplete in the presence of sodium ethoxide in ethyl alcohol but proceeds readily with sodium isopropoxide in isopropyl alcohol. To introduce the second methyl group potassium *t*-butoxide is required.

2. A series of α-methyl-β-alkylphenethylamines has been prepared by the action of formamide upon the corresponding ketones. In two instances both diastereoisomeric forms of the amine hydrochlorides have been isolated by fractional crystallization.

3. The substitution of an alkyl group on the β-carbon of α-methylphenethylamine greatly reduces its toxic properties without a corresponding loss in pressor activity.

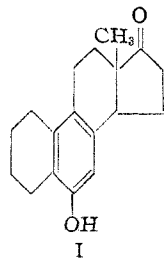
EVANSTON, ILLINOIS RECEIVED DECEMBER 2, 1941

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN

The Synthesis of an Isomer of Estrone Containing a Phenolic B Ring

BY W. E. BACHMANN AND A. B. NESS[1]

In continuation of our work on the synthesis of sex hormones and related compounds,[2] we have prepared 6-hydroxy-1,2,3,4-tetrahydro-17-equilenone (I), an isomer of estrone in which the B ring rather than the A ring is phenolic. We were interested in determining what effect this change in structure would have on the estrogenic activity of the molecule.



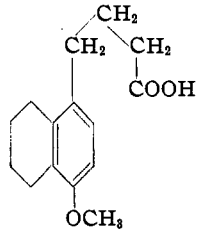
I

For the synthesis of this compound, the methyl ether of 5,6,7,8-tetrahydro-1-naphthol was condensed with succinic anhydride and the resulting keto acid was reduced by the Clemmensen method to II. The structure of the product was established by its conversion to the known γ-4-methoxy-1-naphthylbutyric acid by catalytic dehydrogenation of its methyl ester and hydrolysis of the product. Cyclization of the acid chloride of II yielded 1-keto-9-methoxy-*s*-octahydrophenanthrene (III), whose structure was established

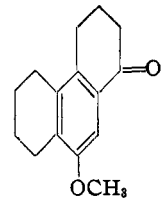
(1) From the Ph.D. dissertation of A. B. Ness.

(2) Previous paper in this series, Bachmann and Thomas, THIS JOURNAL, **64**, 94 (1942).

by reduction to 9-methoxy-*s*-octahydrophenanthrene which was dehydrogenated to the known 9-methoxyphenanthrene.



II



III

From the cyclic ketone (III) the hormone isomer was prepared by the method employed for the synthesis of equilenin.[3] Two series of intermediates were obtained corresponding to the *cis* and *trans* configurations. Since the actual configurations are not known, the stereoisomers are distinguished from each other by the prefixes α and β. In the penultimate step of the synthesis, the α and β forms of the methyl ether of I were obtained in crystalline form. The α methyl ether was smoothly demethylated by hydrobromic acid in acetic acid to the α-form of I, but unexpected difficulties were encountered in the attempted demethylation of the β methyl ether and the β-form of I has not yet been obtained in crystalline form.

The crystalline α form of I (a racemic mixture) failed to induce the estrus response in ovariectomized rats in doses as high as 1000 γ. For this test we are indebted to Miss Helen C. McRae of the Department of Gynecology and Obstetrics of this University.

Experimental

β-5,6,7,8-Tetrahydro-4-methoxy-1-naphthoylpropionic Acid.—5,6,7,8-Tetrahydro-1-naphthol was prepared in 85–87% yields (reported, 65–70%) by reducing 1-naphthol by means of sodium and fusel oil[4]; it was also prepared by catalytic reduction with Raney nickel[5] at 150° and 150 atmospheres pressure for one and one-half to one and three-quarters hours. The methyl ether was prepared in 88% yield by treating 82 g. of the tetrahydronaphthol in a solution of 38 g. of sodium hydroxide in a liter of water with 78.5 cc. of methyl sulfate. When the latter had all reacted, another similar portion of sodium hydroxide and of methyl sulfate was added. The product was extracted with benzene, the benzene solution was washed with aqueous sodium hydroxide (from which 8 g. of unreacted material was isolated), the solvent was removed and the residue was distilled under diminished pressure; yield, 79 g.

To a cold solution of 37.5 g. of aluminum chloride in 107 cc. of nitrobenzene was added 141 g. of succinic anhydride. With the temperature kept at 0–5°, 22.8 g. of 1-methoxy-5,6,7,8-tetrahydronaphthalene was added slowly. After four hours at the same temperature, the mixture was treated with ice and a little hydrochloric acid, the aqueous layer was removed, and the organic layer was washed with water and steam distilled. The residue was dissolved in aqueous sodium hydroxide, and the solution was boiled with Norit and filtered. On acidification, the β-5,6,7,8-tetrahydro-4-methoxy-1-naphthoylpropionic acid precipitated; yield, 30.5 g. (82%); m. p. 174–176.5°. A sample after two recrystallizations from benzene–acetone formed colorless needles; m. p. 176–177°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.9; H, 6.9.

γ-5,6,7,8-Tetrahydro-4-methoxy-1-naphthylbutyric Acid (II).—A mixture of 10 g. of amalgamated zinc (20 mesh), 17.5 cc. of hydrochloric acid, 1 cc. of acetic acid, 7.5 cc. of water, 10 cc. of toluene and 5 g. of the keto acid was refluxed on a sand-bath for twenty-four hours; 5-cc. additions of hydrochloric acid were made at six-hour intervals. The toluene layer was separated, the aqueous solution extracted once with benzene, the combined solutions were evaporated in a current of air and the residue was dissolved in aqueous sodium hydroxide and treated with methyl sulfate. After extraction of the solution with benzene, the aqueous solution was boiled with Norit, filtered and acidified, and the product was recrystallized from benzene–petroleum ether; yield, 3.54 g. (75%); m. p. 121–123°. A sample after two more recrystallizations formed colorless needles; m. p. 122–123°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.6; H, 8.1. Found: C, 72.5; H, 8.2.

A sample of the acid was converted to its methyl ester by means of diazomethane and the ester was heated with one-tenth its weight of palladium–charcoal catalyst at 250–280° for forty-five minutes. The dehydrogenated product was hydrolyzed and the free acid was recrystallized twice from benzene–petroleum ether; m. p. 127–128° alone and when mixed with γ-4-methoxy-1-naphthylbutyric acid (m. p. 127–129°).

1-Keto-9-methoxy-*s*-octahydrophenanthrene (III).—To a cold solution of 7.4 g. of II in 100 cc. of dry benzene was added 7.4 g. of powdered phosphorus pentachloride. After two hours at 10°, during which time the mixture was frequently swirled, the solution was cooled until the benzene began to crystallize, when 7.4 cc. of anhydrous stannic chloride was added with swirling. After two minutes the mixture was poured onto ice and hydrochloric acid and the product was worked up as described in a similar case.[3] Recrystallization of the crude ketone from dilute alcohol gave 5.2–5.9 g. of product melting at 88–90° and about 0.3–0.4 g. of only slightly less pure material; total yield, 80–90%. After three recrystallizations a sample formed colorless needles; m. p. 89.5–90°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.1; H, 7.8. Found: C, 77.7; H, 7.7.

9-Methoxy-*s*-octahydrophenanthrene.—A quantitative yield of the semicarbazone (m. p. 265–270°; colorless needles after three recrystallizations from acetic acid–methanol; m. p. 269–271°) was obtained by refluxing a

(3) Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).
(4) Jacobson and Turnball, *Ber.*, **31**, 897 (1898).
(5) Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

mixture of 1 g. of III, 1.2 g. of semicarbazide hydrochloride, 1.5 cc. of pyridine and 30 cc. of absolute alcohol for seven hours. A mixture of 0.5 g. of the semicarbazone and a solution of sodium ethoxide prepared from 1.05 g. of sodium and 30 cc. of absolute alcohol was heated in a sealed tube at 180° for twenty hours. The product was recrystallized from alcohol; yield, 0.32 g.; m. p. 86.5–90°. After further recrystallization the 9-methoxy-*s*-octahydrophenanthrene formed colorless plates; m. p. 90–91°.

Anal. Calcd. for $C_{16}H_{20}O$: C, 83.3; H, 9.3. Found: C, 83.2; H, 9.6.

Dehydrogenation of the compound by palladium on charcoal at 245–250° for fifteen minutes and at 285–300° for thirty minutes more gave a 50% yield of 9-methoxyphenanthrene, which was identical with a sample prepared by methylation of 9-phenanthrol.

Methyl 1-Keto-9-methoxy-*s*-octahydrophenanthrene-2-glyoxalate.—To the dry sodium ethoxide prepared from 1.19 g. of sodium was added 7.15 g. of dimethyl oxalate and then 3.9 g. of 1-keto-9-methoxy-*s*-octahydrophenanthrene. The apparatus was evacuated and filled with nitrogen and 75 cc. of dry benzene was added. The reaction was carried out and the product was isolated as described.[3] The dry crude glyoxalate was recrystallized from acetone–methanol; yield, 5 g. (92%); m. p. 124–126°. After two more recrystallizations, a sample formed fine yellow needles; m. p. 125–126.5°.

Anal. Calcd. for $C_{18}H_{19}O_5$: C, 68.4; H, 6.3. Found: C, 68.4; H, 6.3.

1-Keto-2-carbomethoxy-9-methoxy-*s*-octahydrophenanthrene.—A mixture of 17.1 g. of the recrystallized glyoxalate and 8.5 g. of powdered soft glass was heated at 180° for one hour. The product was separated from the glass by means of hot acetone, the solution was boiled with Norit, filtered, concentrated and treated with methanol. From the solution 13.8–15.2 g. (88–97%) of product (m. p. 95.5–101°) was obtained. After three recrystallizations from acetone–methanol a sample formed colorless needles; m. p. 103–103.5°. It gave a dark green color with an alcoholic solution of ferric chloride.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0. Found: C, 70.4; H, 6.9.

1-Keto-2-methyl-2-carbomethoxy-9-methoxy-*s*-octahydrophenanthrene.—Ten g. of the aforementioned keto ester was converted to the sodium enolate and the latter treated with methyl iodide by the procedure described,[3] except that the entire reaction was carried out in an atmosphere of nitrogen since the sodium enolate is susceptible to oxidation by the air. The product was recrystallized from acetone–methanol; yield, 9.8 g. (93%); m. p. 136.5–138°. It gave no color with an alcoholic solution of ferric chloride. After two more recrystallizations, a sample formed colorless rods; m. p. 138.5–139°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 71.4; H, 7.3.

Methyl Ester of 1-Hydroxy-2-methyl-2-carbomethoxy-9-methoxy-*s*-octahydrophenanthrene-1-acetic Acid.—The Reformatsky reaction on 5-g. portions of the aforementioned compound was carried out as described for a similar compound[3] except that only one portion (4 cc.) of methyl bromoacetate was employed and six hours were allowed for the reaction. The crude product was recrystallized from methanol; yield, 90–95%; m. p. usually about 141–144°. After three recrystallizations from acetone–methanol, a sample formed colorless needles; m. p. 145–146.5°.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.0; H, 7.4. Found: C, 66.5; H, 7.5.

2-Methyl-2-carboxy-9-methoxy-*s*-octahydrophenanthrene-1-acetic Acid.—Five-gram portions of the Reformatsky ester were treated with thionyl chloride and pyridine in benzene and the resulting chloride was refluxed with methanolic potassium hydroxide exactly as described.[3] The aqueous solution of the potassium salts of the unsaturated acids (geometrical isomers) was shaken with 175 g. of 2% sodium amalgam for one hour; during this time the sodium salts of the reduced acids usually precipitated to some extent. Sufficient hot water was added to the warmed mixture to bring the salts into solution, and the mixture of the α- and β-forms of the reduced acid was precipitated by addition of hydrochloric acid; yield, 4.22 g. (85%).

The mixture of acids was dissolved in 25 cc. of a boiling mixture of xylene-acetic acid (3:1); the solution was allowed to cool to room temperature and after thirty minutes the acid which had crystallized was filtered off. In order to obtain both forms of the acid relatively pure, it is essential that only slightly more than half of the total weight of acids should precipitate at this point; when this did not occur, the precipitate was redissolved in the filtrate, and either a shorter or longer time allowed for crystallization to take place. In a typical experiment 2.13 g. of acid, called the α-form (m. p. 209–210.5°), was obtained. After one recrystallization from 30 cc. of xylene–acetic acid (2:1), it melted at 215° and was suitable for conversion to its dimethyl ester. After two recrystallizations from benzene–petroleum ether, a sample formed clusters of colorless needles; m. p. 219–220°.

The xylene and acetic acid were evaporated from the filtrate and the residue was recrystallized from benzene, whereby 1.24 g. of the β-form of the acid was obtained; m. p. 223–224.5°. Before converting the acid to its dimethyl ester it was recrystallized, with little loss, from benzene until it melted at 226° or higher. After three recrystallizations a sample formed colorless prisms; m. p. 233.5–234°, dec.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.5. Found: (α-form) C, 69.2; H, 7.5; (β-form) C, 68.4; H, 7.3.

Proof of Structure.—In order to establish that no migration of the methyl group took place during the indirect dehydration of the Reformatsky ester, the following experiments were performed. The aqueous solution of the potassium salts of the unsaturated acids obtained from 5 g. of the Reformatsky ester was acidified and the mixture of the *anti* form of the unsaturated acid and the anhydride of the *syn* form was dried at 60–70°. The mixture was digested with 200 cc. of a warm 10% solution of sodium bicarbonate for one hour and the anhydride of *syn*-2-methoxy-2-carboxy-9-methoxy-*s*-octahydrophenanthrylidene-1-acetic acid (2.07 g.; m. p. 226–228) was filtered off. After two recrystallizations from acetic acid it formed colorless prisms; m. p. 227.5–228.5°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.0; H, 6.2.

From the bicarbonate solution there was isolated 2.15 g. of the *anti* **form of the unsaturated acid;** m. p. 206.5–208°. After three recrystallizations from benzene a sample formed colorless prisms; m. p. 208.5–209°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7. Found: C, 68.8; H, 6.9.

The **dimethyl ester of the** *anti* **acid** was prepared by means of diazomethane, decolorized by Norit in acetone solution and recrystallized from methanol; yield, 96%; m. p. 84–85°. After two more recrystallizations, a sample formed colorless prisms; m. p. 85–86°.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.8; H, 7.6. Found: C, 70.4; H, 7.3.

By refluxing a mixture of 1.5 g. of the dimethyl ester, 25 cc. of methanol and 4.3 cc. of *N* sodium hydroxide for two hours, only the acetic ester group was hydrolyzed and a nearly quantitative yield of the *anti* **acid ester** (m. p. 91–99°) was obtained. After three recrystallizations from dilute methanol a sample formed colorless prisms; m. p. 103–104°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.8; H, 7.0. Found: C, 70.3; H, 7.0.

Permanganate oxidation of the sodium salt of 0.6 g. of the acid ester according to the procedure described for an analogous compound[6] gave 0.25 g. (47%) of 1-keto-2-methyl - 2 - carbomethoxy - 9 - methoxy - *s* - octahydrophenanthrene (m. p. 128–132°). After two recrystallizations from methanol it melted at 136–138° alone and when mixed with the same compound described above.

Dimethyl Ester of 2-Methyl-2-carboxy-9-methoxy-*s*-octahydrophenanthrene-1-acetic Acid.—Both forms of this compound were prepared from the reduced acids by means of diazomethane. An acetone solution of the ester was boiled with Norit, filtered and evaporated and the ester was recrystallized from methanol.

From 2.96 g. of the α-acid there was obtained 3.03 g. of the **α-form** of the dimethyl ester; m. p. 113–115°. After three recrystallizations from methanol a sample formed clusters of colorless needles; m. p. 115.6–116°.

From 2.52 g. of the β-acid there was obtained 2.69 g. of the **β-form** melting at 67.5–73°. After four recrystallizations a sample formed colorless prisms melting to a cloudy liquid at 70–71° which became clear at 93–94°.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 70.0; H, 7.8. Found: (α-form) C, 69.5; H, 7.8; (β-form) C, 70.0; H, 7.8.

2-Methyl-2-carbomethoxy-9-methoxy-*s*-octahydrophenanthrene-1-acetic Acid.—A solution of 0.98 g. of the α-form of the dimethyl ester, 40 cc. of methanol and 2.81 cc. of *N* sodium hydroxide was refluxed for two hours; the methanol was removed in a current of air, and the sodium salt of the acid ester was dissolved in the minimum amount of warm water. The solution was filtered from unreacted ester (0.18 g.) and acidified; yield, 0.77 g.; m. p. 153–155°. After four recrystallizations from dilute methanol a sample of the **α-form** formed colorless needles; m. p. 174.5–176°.

Similarly, 2.54 g. of the **β-form** of the acid ester (m. p. 116–124°) was obtained from 2.69 g. of the dimethyl ester, 30 cc. of methanol and 7.9 cc. of *N* sodium hydroxide. After three recrystallizations from dilute alcohol a sample formed colorless prisms; m. p. 118–120°.

(6) Bachmann and Wilds, THIS JOURNAL, **62**, 2084 (1940).

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.4; H, 7.5. Found: (α-form) C, 68.9; H, 7.7; (β-form) C, 69.4; H, 7.7.

Methyl 2-Methyl-2-carbomethoxy-9-methoxy-*s*-octahydrophenanthrene-1-β-propionate.—The aforementioned acid esters were converted to the acid chlorides, the latter treated with diazomethane (prepared from nitrosomethylurea) and the resulting diazoketones were heated with methanol in the presence of silver oxide as described,[3] except that three hours were allowed for the last step.

From 1 g. of the α-acid ester there was obtained 0.72 g. of the **α-form** melting at 89.5–92° and 0.15 g. of only slightly less pure material; total yield, 80%. After four recrystallizations from methanol a sample formed colorless needles; m. p. 94–94.5°.

Similarly, the **β-form** was obtained in yields of 62–82%; m. p. 112–114°. After four recrystallizations from methanol a sample formed colorless prisms; m. p. 115.5–116°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.6; H, 8.0. Found: (α-form) C, 70.1; H, 8.0; (β-form) C, 70.4; H, 8.1.

16-Carbomethoxy-6-methoxy-1,2,3,4-tetrahydro-17-equilenone.—Cyclization of the aforementioned compounds was carried out in an atmosphere of nitrogen by means of sodium methoxide in benzene as described.[3] The cyclic keto esters which were obtained were recrystallized from methanol. The **α-form** was obtained in 69–88% yields; m. p. 138–142°. After three recrystallizations from acetone–methanol a sample formed colorless needles; m. p. 146–147° (vac.) with evolution of gas. It gave a deep violet color with an alcoholic solution of ferric chloride.

The **β-form** was obtained in 57–91% yields; m. p. 121–126°. After four recrystallizations from acetone–methanol a sample formed colorless prisms; m. p. 129.5–130° (vac.). It gave no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.7; H, 7.6. Found: (α-form) C, 73.5; H, 7.5; (β-form) C, 73.2; H, 7.8.

6-Methoxy-1,2,3,4-tetrahydro-17-equilenone.—A mixture of 0.59 g. of the α-form of the cyclic keto ester, 30 cc. of acetic acid, 15 cc. of hydrochloric acid and 3 cc. of water was refluxed in an atmosphere of nitrogen for one hour. Water was added to the hot solution to incipient cloudiness and the solution was cooled, whereupon 0.45 g. of the **α-form** crystallized in needles; m. p. 117–118°. From the filtrate an additional 0.03 g. of the methyl ether was obtained. After three recrystallizations from methanol a sample formed colorless needles; m. p. 118–118.5° (vac.).

In a similar manner 0.56 g. of the β-form of the cyclic keto ester was hydrolyzed and decarboxylated. In this case the liquids were removed under reduced pressure, the residue was dissolved in acetone, the solution was boiled with Norit, filtered and evaporated. By recrystallization from methanol 0.35 g. of colorless prisms of the **β-form** melting at 104–107° and 0.08 g. of only slightly less pure material were obtained. After two more recrystallizations a sample melted at 108–109°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.3; H, 8.5. Found: (α-form) C, 80.3; H, 8.5; (β-form) C, 80.0; H, 8.7.

6-Hydroxy-1,2,3,4-tetrahydro-17-equilenone (I).—A mixture of 0.26 g. of the α-methyl ether, 25 cc. of acetic acid and 25 cc. of 48% aqueous hydrobromic acid was refluxed in an atmosphere of nitrogen for three hours. After re-

moval of the liquids, the residue was heated with 150 cc. of a 1% aqueous solution of potassium hydroxide and the solution was filtered and acidified. A solution of the precipitate in acetone was boiled with Norit, filtered and evaporated, and the product recrystallized from dilute alcohol; yield, 0.15 g.; m. p. 149–150°. From the filtrate an additional 0.05 g. of slightly less pure material was obtained. After two more recrystallizations the α-form formed colorless prisms; m. p. 150–150.5°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 80.1, 80.8; H, 8.2, 8.3.

When the β-methyl ether was heated with the acid mixture for one-half hour or longer and then cooled, about 10% of a crystalline product precipitated, which melted at 203.5–204° (vac.) and crystallized in fine colorless needles from dilute alcohol. Analysis showed that it was not the desired compound (Found: C, 85.1; H, 8.0). From the acid filtrate only an uncrystallizable oil was obtained.

Summary

5,6,7,8-Tetrahydro-1-methoxynaphthalene reacts with succinic anhydride in the 4-position. The keto acid was reduced by the Clemmensen method and the reduced acid was cyclized to 1-keto-9-methoxy-*s*-octahydrophenanthrene. From the latter compound 6-hydroxy-1,2,3,4-tetrahydro-17-equilenone was synthesized.

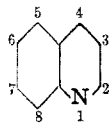
ANN ARBOR, MICHIGAN RECEIVED OCTOBER 8, 1941

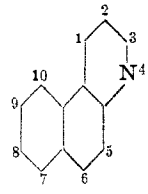
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

5-Amino- and 1-Aminobenzo(f)quinolines and Derivatives

BY EMMETT R. BARNUM[1] AND CLIFF S. HAMILTON

Since a number of the 8-dialkylaminoalkylaminoquinolines, including Plasmoquin, have been found to possess strong antimalarial action,[2] it was believed that the synthesis of benzo(f)quinolines with dialkylaminoalkylamino- or other side chains in the 5-position, analogous to the 8-position in quinoline, should be investigated.





5-Aminobenzo(f)quinoline, obtained from the 5-carboxy- derivative by the Curtius reaction, exhibited reactions similar to those of 8-aminoquinoline. It was diazotized and coupled with 2-naphthol and with R-acid. In addition the amine was condensed with various dialkylaminoalkyl bromides and with 2-bromopyridine to produce the corresponding substituted aminobenzo(f)quinolines. 5-(γ-Diethylaminopropylamino)-benzo(f)quinoline was isolated as the dihydrochloride because the free base was an oil at room temperature.

In order to compare the reactivity of amino groups in the three rings of benzo(f)quinoline, 1-aminobenzo(f)quinoline was synthesized from 5,6-benzocinchoninic acid[3] by the Curtius reaction. The amine was similar to 4-aminoquinoline in that it could not be diazotized and coupled with R-acid and 2-naphthol and like the 7,8 and 10-aminobenzo(f)quinolines[4] could not be alkylated.

(1) Parke, Davis and Company Fellow.

(2) Von Oettingen, Am. Chem. Soc. Mono. **64**, 108 (1933).

(3) Robinson and Bogert, *J. Org. Chem.*, **1**, 65 (1936).

Experimental

5-Carboxybenzo(f)quinoline (I).—Sulfuric acid (106 g.) was carefully added to a mixture of 2-amino-3-naphthoic acid (70 g.), arsenic acid (54 g.) and glycerol (115 g.) and the temperature was slowly raised to 120°. With stirring, the temperature was gradually increased to 135° during a period of four hours, and then to 145–150°, where it was maintained for an additional four hours. The mixture was poured into water (1 liter), allowed to stand overnight, heated to boiling, filtered, and the filtrate made basic with ammonium hydroxide. This mixture was filtered, the filtrate acidified with acetic acid and the very viscous material which formed was separated by filtration. Repeated treatments of the gum-like material with ammonium hydroxide finally gave a solution which, upon filtration, acidification with acetic acid, and concentration produced crude (I). The crude product was recrystallized from cellosolve and then from ethanol; white needles; yield, 26 g. (32%); m. p. 204–205°.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.31; H, 4.07; N, 6.26. Found: C, 75.11; H, 4.09; N, 6.29.

Application of the same reaction to 3-carbomethoxy-2-naphthylamine gave (I) in about the same yield.

5-Carbomethoxybenzo(f)quinoline (II).—Esterification of (I) with absolute methanol in the presence of dry hydrogen chloride gave (II) as white plates; yield, 54%; m. p. 86°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.96; H, 4.68. Found: C, 75.86; H, 4.87.

(4) Clem and Hamilton, THIS JOURNAL, **62**, 2350 (1940).