3-Pyridyl-ω-benzamidopropyl Ketone.—A portion of the above picrate was treated with an excess of 6 *N* HCl, and the precipitated picric acid was filtered off. The acid filtrate was extracted with ether to remove traces of picric acid. The aqueous layer was chilled in ice, and enough sodium hydroxide was added to make the mixture just alkaline. The white precipitate, filtered off and crystallized from 40% ethanol, melted at 117.0–117.8° (yield 6.3 g.). The melting point and analytical result agree with those of the myosmine benzoylation product which Späth, Wenusch and Zajic[3] reported to be 3-pyridyl-ω-benzamidopropyl ketone. The picrate of this base melted at 151.0–152.0°. When mixed with the picrate of N-benzoylmyosmine, the melting point was depressed.

Anal. Calcd. for $C_{22}H_{19}N_5O_9$: C, 53.12; H, 3.82; N, 14.08. Found: C, 52.87; H, 4.14; N, 13.70.

The base also formed a hydrochloride melting at 195.0–196.0°.

Acknowledgment.—The authors are indebted to Ruth Brand, Frances J. Cooper and Alice G. Finley for the analyses herein reported, and to Clyde L. Ogg for the modification of the micro-Dumas procedure by which the nitrogen analyses were obtained.

Summary

Myosmine hydrolyzes readily to 3-pyridyl-ω-aminopropyl ketone in aqueous solution, whereas N-methylmyosmine is resistant to hydrolysis.

Nornicotine, hexahydronornicotine and octahydronornicotine were prepared by the reduction of myosmine and by confirmatory syntheses. 3-(1,4-Diaminobutyl)-pyridine, 3-(4-aminobutyl)-pyridine, and 2-(3-pyridyl)-3-(2-aminoethyl)-indole dihydrochloride were also prepared.

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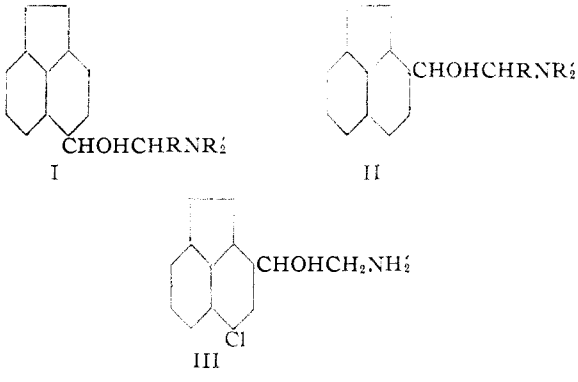
The Preparation of α-(Dialkylaminoalkyl)-acenaphthene-methanols[1]

BY DOROTHY NIGHTINGALE, H. E. UNGNADE AND H. E. FRENCH

This paper deals with the preparation of a series of amino alcohols of the general type (I), (II) and (III).



R = H or CH_3, R′ = CH_3 to C_6H_{13}

These amino alcohols were obtained from acenaphthenyl ketones through the following series of reactions

$$\mathrm{ArCOCH_2R} \xrightarrow{\mathrm{Br_2}} \mathrm{ArCOCHBrR} \xrightarrow{\mathrm{R'_2NH}} \mathrm{ArCOCHRNR'_2} \xrightarrow{\mathrm{Al(OC_3H_7)_3}} \mathrm{ArCHOHCHRNR'_2}$$

It has been established that acetylation of acenaphthene yields two isomeric ketones with the acetyl group in the 5- and 3-positions.[2] The 3-isomer is formed in small amounts. The two isomers have been separated by fractional crystallization of the picrate.[2] The 5-isomer could be isolated by distribution between petroleum ether and aqueous methanol but losses were high by either procedure. Fortunately the solubilities of the α-bromo ketones in ether differed sufficiently so that most of the 3-isomer could be separated after bromination. The 3-α-bromoacetylacenaphthene crystallized from the ether solution on standing. The identity of the two α-bromo ketones was established by oxidation to the two known acenaphthoic acids.

Fleischer and Wolff[3] acetylated acenaphthene with bromoacetyl bromide. They report one of the products as 5-α-bromoacetylacenaphthene, m. p. 180°, and an unidentified compound melting at 94–96° which was not isomeric with 5-α-bromoacetylacenaphthene. They did not establish the structures of their compounds. Actually, their unidentified compound appears to be the 5-isomer since it does not depress the melting point of 5-α-bromoacetylacenaphthene prepared by bromination of 5-acetylacenaphthene. Their compound melting at 180° may be the 3-isomer. Acylation of acenaphthene with chloroacetyl chloride or bromoacetyl bromide was not practical as a means of obtaining the α-halogen ketones directly. The products were complex mixtures.

The acylation of acenaphthene with propionyl chloride likewise yielded a mixture of isomeric ketones which could be separated by crystallization of the reaction product from ether, in which the higher melting isomer (m. p. 122–123°) was only slightly soluble. Analysse of the compound agreed with a monopropionylacenaphthene. Dziewonski and Moszew[4] report 5-propionyl-

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Missouri.

(2) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939).

(3) Fleischer and Wolff, *Ber.*, **53**, 925 (1920).

(4) Dziewonski and Moszew, *Bull. intern. acad. polon. sci.*, 1931A 158

acenaphthene as melting at 69–70° and accompanied by a by-product melting at 122–123°. In a subsequent paper they report 5,6-dipropionylacenaphthene as melting at 122–123°.[4a]

Acetylation of 5-chloroacenaphthene could yield a mixture of three isomeric ketones with the acyl group in the 3,6 or 8 position. By analogy with acetylacenaphthene the 6-isomer should predominate. Two isomeric acetylchloroacenaphthenes were isolated by fractional crystallization of the acylation product. Their structures were not established since most of the necessary reference compounds were unknown. These two ketones were converted to the corresponding α-bromoacetyl-5-chloroacenaphthenes.

The α-bromo ketones have been converted to α-amino ketones which in turn have been reduced to α-amino alcohols by aluminum isopropoxide.

Experimental[5]

5-Acetylacenaphthene.—Acenaphthene (154 g., 1 mole) and acetyl chloride (78 g.) were dissolved in 900 cc. of nitrobenzene. Aluminum chloride (140 g.) was added to the iced reaction mixture at such a rate that the temperature did not rise above 5°. The flask was packed with ice, allowed to come to room temperature and left to stand overnight. The complex was decomposed in the usual manner. The nitrobenzene was removed by distillation with superheated steam, and the residue distilled at reduced pressure; yield 157 g., b. p. 212–214° (18 mm.).

The crude ketone (25 g.) was shaken with 250 cc. of 80% aqueous methanol and 500 cc. of petroleum ether (30–100°). Crystals separated from both solvents on standing in the refrigerator, 2.5 g. from the methanol and 6.5 g. from the petroleum ether. Both melted at 65.5–66°. The crystals were combined and redistributed between the same solvents. The crystals from both solvents melted at 69–70°; yield, 4 g.

Acetylation of Acenaphthene with Bromoacetyl Bromide.—Aluminum chloride (40 g.) was added slowly with stirring to a solution of 40 g. of acenaphthene and 50 g. of bromoacetyl bromide in 150 cc. of carbon disulfide at −15°. The mixture was allowed to come to room temperature, decomposed as usual, and extracted with chloroform. Removal of the solvent left 72 g. of tarry residue which solidified on standing.

A portion (30 g.) of this material was extracted with ether in a Soxhlet extractor. The solid (1.5 g.) which separated from the ether was recrystallized from methanol and chloroform and melted at 174–175°. Mixed melting points and analyses indicated that this material was mainly di-(α-bromoacetyl)-acenaphthene.

Evaporation of the ether solution yielded 17 g. of an oil which solidified on standing. A portion of this solid was crystallized from aqueous methanol and melted at 90–91°. Mixed with 5-α-bromoacetylacenaphthene (m. p. 94–95°) the melting point was 93–94°. Analyses indicated the presence of a small amount of impurity. This fraction corresponds to the unidentified compound reported by Fleischer and Wolff[3] as melting at 94–96°.

The Propionylacenaphthenes.—When the mixture of 3- and 5-propionylacenaphthene was dissolved in boiling ether, a solid m. p. 115–118° separated in 10% yield on standing. It formed an unstable picrate, which decomposed to yield a pure ketone, m. p. 122-123°, which should be 3-propionylacenaphthene.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.72; H, 6.66. Found: C, 85.70; H, 6.73.

5-Propionylacenaphthene, m. p. 69–70°,[4] could be obtained by repeated recrystallization of the ether-soluble fraction.

Acetyl-5-chloroacenaphthene.—5-Chloroacenaphthene was prepared from acenaphthene and sulfuryl chloride by the procedure of Crompton and Walker.[6] It was not advisable to use more than 100 g. of acenaphthene at a time. The reaction product was distilled with superheated steam. The fractions of distillate melting above 63° were combined and crystallized from aqueous alcohol to yield a product melting at 67–67.5°, which corresponds to a mixture of 92% of 5-chloroacenaphthene and 8% of acenaphthene. This material is suitable for acylation.

For reference, 5-chloroacenaphthene, m. p. 65.5–66°, was prepared by diazotization of 5-aminoacenaphthene.[7]

5-Chloroacenaphthene was acetylated with acetyl chloride as described above, to yield acetyl-5-chloroacenaphthene (61%), b. p. 191–195° (1 mm.). The thick, sirupy distillate was dissolved in hot petroleum ether (60–70°). On standing overnight at room temperature, a solid separated which melted at 102–118°. Fractional crystallization of this material from petroleum ether (60–70°) yielded the ketone (A), m. p. 121–122°.

Anal. Calcd. for $C_{14}H_{11}OCl$: C, 72.88; H, 4.78. Found: C, 72.70; H, 4.95.

A solid, m. p. 75–92°, separated from the concentrated filtrate. This material was fractionally crystallized from a chloroform–ether mixture and yielded the ketone (B), m. p. 99–100°.

Anal. Calcd. for $C_{14}H_{11}OCl$: C, 72.88; H, 4.78. Found: C, 72.97; H, 5.05.

These isomers formed a eutectic mixture, m. p. 73–74°. Approximately 30% of the distillate remained as a viscous oil which would not crystallize.

For bromination in quantity, the crude ketone was separated roughly into two fractions of melting range 72–96° and 96–118°. These fractions were brominated separately.

The α-Bromoacetylacenaphthenes. — Acetylacenaphthene (38.5 g., 0.2 mole) was dissolved in 450 cc. of dry peroxide-free ether and 32 g. (0.2 mole) of bromine added dropwise with stirring at room temperature. The reaction mixture was allowed to stand overnight.

The solid (6–8 g.) which separated was collected on a filter, washed, dried, and recrystallized from chloroform, m. p. 163–164°.

Anal. Calcd. for $C_{14}H_{11}OBr$: C, 61.09; H, 4.00. Found: C, 61.13; H, 4.08.

Oxidation of this α-bromoketone yielded an acid, m. p. 251–252°, neut. eq. 199 (calculated 198), which would identify the acid as 3-acenaphthoic acid, recorded melting point 256–257°.[8]

The ether filtrate was washed with water and sodium bicarbonate until free from acid and dried. Evaporation of the solvent left an oil (34 g.) which solidified on standing. Recrystallization of the solid from methanol gave colorless needles which melted at 87°, solidified and melted again at 94–95°.

Anal. Calcd. for $C_{14}H_{11}OBr$: C, 61.09; H, 4.00. Found: C, 60.88; H, 4.29.

Oxidation of this α-bromo ketone yielded an acid, m. p. 214–215°. The recorded melting point of 5-acenaphthoic acid is 217°.[8]

The crude 5-α-bromoacetylacenaphthene was used without further purification for the preparation of the amino ketones. The accumulated 3-α-bromoacetylacenaphthene was crystallized from chloroform.

The α-Bromoacetyl-5-chloroacenaphthenes.—Bromination of acetyl-5-chloroacenapthene (A) in a 1:1 chloroform–ether solution yielded α-bromoacetyl-5-chloroacenaphthene (C), m. p. 151–152° (from chloroform).

Anal. Calcd. for $C_{14}H_{10}OClBr$: C, 54.28; H, 3.23. Found: C, 54.18; H, 3.28.

(4a) Dziewonski and Moszew, *Bull. intern. acad. polon. sci.*, 1931A, 242.

(5) Semimicro-analyses by D. R. Smith, University of Missouri, Lois May and Frances Marx, Columbia University.

(6) Crompton and Walker, *J. Chem. Soc.*, **101**, 959 (1912).

(7) Sachs and Mosebach, *Ber.*, **43**, 2474 (1910).

(8) Grignard, Bellet and Courtot, *Ann. chim.*, [9] **4**, 52 (1915).

TABLE I

α-(DIALKYLAMINOALKYL)-5-ACENAPHTHENEMETHANOLS

R′ (R = H)	M. p., °C.	B. p.,[a] °C. 1 × 10⁻⁶ mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3	99–100	130	$C_{18}H_{19}ON$	79.68	79.38	7.88	8.13		
C_2H_5	77– 78	150	$C_{18}H_{23}ON$	80.30	80.12	8.55	8.67		
n-C_3H_7	69– 70	130	$C_{20}H_{27}ON$	80.80	80.68	9.52	9.36		
n-C_4H_9		170	$C_{22}H_{31}ON$	81.23	81.38	9.54	9.58		
C_6H_{13}		160	$C_{26}H_{39}ON$	81.82	81.78	10.31	10.14		
$C_5H_{10}N$	126.5–127	180	$C_{19}H_{23}ON$	81.13	81.16	8.18	8.72		
R = CH_3									
C_2H_5	76– 76.5	155	$C_{19}H_{25}ON$	80.56	80.76	8.83	9.09	4.94	5.30
C_4H_9		160	$C_{23}H_{33}ON$					4.12	3.90
α-(DIALKYLAMINOALKYL)-3-ACENAPHTHENEMETHANOLS									
R = H									
C_3H_7	52– 52.5	150	$C_{20}H_{27}ON$	80.80	80.26	9.09	9.12	4.71	4.97

[a] Bath temperature.

Bromination of acetyl-5-chloroacenaphthene (B) yielded α-bromoacetyl-5-chloroacenaphthene (D) which melted at 103–103.5°, solidified, and melted again at 121–122°.

Anal. Calcd. for $C_{14}H_{10}OClBr$: C, 54.28; H, 3.23. Found: C, 54.08; H, 3.34.

Bromination of the eutectic mixture of ketones (A) and (B) (m. p. 72–73°) yielded a mixture of bromo ketones melting at 104–130°.

The high-melting fraction of acetyl-5-chloroacenaphthene (m. p. 96–118°) was brominated in chloroform–ether solution. On standing overnight at room temperature, a solid, m. p. 136–144°, separated in 34% yield. This product was recrystallized once to raise the melting point to 147–149° and was used for the preparation of the amino ketones. The pure α-bromoacetyl-5-chloroacenaphthene (C) could be obtained by fractional crystallization of the product obtained by the bromination of the low-melting fraction of acetyl-5-chloroacenaphthene (m. p. 72–96°) but not enough of it could be separated for the preparation of amino alcohols.

The α-Bromopropionylacenaphthenes.—The 5-propionylacenaphthene remaining in ether solution after removal of the 3-isomer was brominated in the usual manner. A small amount of heavy oil separated and was removed. The ether solution was washed, dried, and used directly for the preparation of amino ketones.

5-(α-Di-*n*-hexylaminoacetyl)-acenaphthene.—The preparation of this amino ketone and its reduction to the corresponding amino alcohol is typical of the entire series.

Crude 5-α-bromoacetylacenaphthene (59 g., 0.21 mole) was dissolved in 250 cc. of dry benzene and added to 79.2 g. (0.42 mole) of di-*n*-hexylamine in 100 cc. of dry benzene. After standing overnight, the di-*n*-hexylamine hydrobromide (40 g.) was separated by filtration. The filtrate was warmed on a water-bath and after standing several hours an additional 6 g. of amine salt separated. The benzene was removed under reduced pressure, leaving 9 g. of crude amino ketone.

α-(Di-*n*-hexylaminomethyl)-5-acenaphthenemethanol.—The crude amino ketone was added to a solution of 50 g. of aluminum isopropoxide in 230 cc. of absolute isopropyl alcohol. The reduction was carried out by the usual procedure for Meerwein reductions,[9] while nitrogen was passed through the apparatus.[10]

After reduction was complete, the solvent was removed in a partial vacuum and the complex decomposed with 40% sodium hydroxide. The oily layer was extracted with peroxide-free ether, the ether solution was washed with water and dried over magnesium sulfate.

After removal of the ether, the crude amino alcohol (79 g.) was dissolved in petroleum ether (60–70°) and washed through a column of aluminum oxide (General Chemical Company, reagent). Some impurities were adsorbed on the aluminum oxide. The solvent was removed, leaving 74 g. of product which was distilled from a molecular pot still at 160–165° (1 × 10⁻⁶ mm.); yield, 41 g. (50%).

When low molecular weight amines were used, the dry ether solution of α-bromo ketone was used directly for the amination rather than a benzene solution.

The amino alcohols are listed in Table I.

5-(α-Tetrahydroquinolinoacetyl)-acenaphthene.—This amino ketone was prepared by warming equivalent amounts of 5-α-bromoacetylacenaphthene and tetrahydroquinoline on a water-bath. The solid was digested with hot alcohol and ether. The yellow solid was crystallized from di-*n*-butyl ether, m. p. 160–161°.

Anal. Calcd. for $C_{23}H_{21}ON$: C, 83.91; H, 6.6. Found: C, 83.6; H, 6.7.

The amino ketone was insoluble in isopropyl alcohol and could not be reduced to the amino alcohol with aluminum isopropoxide.

x-(α-Diethylaminomethyl)-5-chloroacenaphthenemethanol.—The amino alcohol distilled at 160° (1 × 10⁻⁶ mm.) and solidified on standing. The compound was crystallized from petroleum ether (60–80°), m. p. 87–88°.

Anal. Calcd. for $C_{18}H_{22}ONCl$: C, 71.15; H, 7.28. Found: C, 70.84; H, 7.21.

Summary

3-α-Bromoacetylacenaphthene and 5-α-bromoacetylacenaphthene have been prepared and their structures established.

Two isomeric ketones were isolated from the acetylation of 5-chloroacenaphthene and were converted to the corresponding α-bromoacetyl-5-chloroacenaphthene.

3-Propionylacenaphthene has been isolated from the reaction product of propionyl chloride and acenaphthene.

Ten α-dialkylaminoalkylacenaphthenemethanols have been prepared.

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(9) Wilds, "Organic Reactions," Vol. II, p. 178 (1944).

(10) The use of a nitrogen atmosphere is essential for good yields in these reductions and was suggested by Dr. T. L. Jacobs and Dr. S. Winstein, University of California at Los Angeles.