[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohols Derived from Carbazole[1]

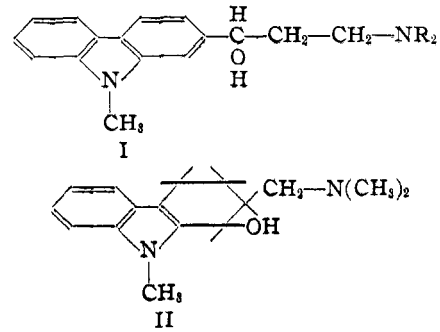
BY LEONE RUBERG AND LYNDON SMALL

In previous reports from this Laboratory the synthesis of numerous derivatives of the phenanthrene and dibenzofuran series has been described.[2] Many of these compounds bear a superficial resemblance to morphine in containing a portion of the morphine nucleus, to which is attached one or more of the peripheral groups that appear to be important for the analgesic action and other physiological effects of morphine. Those derivatives carrying an amino group and an alcoholic hydroxyl group, attached directly to the nucleus or in a side chain, have proved to be particularly active.[3] Diethylaminomethyl-3-phenanthrylcarbinol, for example, produces in the cat marked analgesia and a physiological picture very like that of morphine.[4]

Certain substitution products derived from dibenzofuran show analgesic action even stronger than the analogous derivatives of phenanthrene,[3b] and, as a working hypothesis, the assumption seems justified that various carbocyclic or heterocyclic nuclei, in themselves indifferent, may be activated by, or serve to carry, groups conferring the desired type of physiological effect.

We were therefore led to extend our investigations to the simple amino and amino-9-methylcarbazoles, which were found to possess definite and prolonged analgesic action, combined with relatively low toxicity.[5] Systematic studies on a series of alkylamino and alkyldiamino carbazoles will be presented in a later paper. The present communication deals with the preparation of carbazole amino alcohols resembling the phenanthrene amino alcohols that have been found to possess the most desirable physiological action.

The two types of amino alcohols that have been synthesized are represented by formulas I and II.



I

II

In formula I, $-NR_2$ represents the dimethylamino, diethylamino, or tetrahydroisoquinolino group. These compounds were prepared by application of the Mannich reaction to 2-acetyl-9-methylcarbazole, using the modification of van de Kamp and Mosettig,[6] *i. e.*, by treatment of the ketone with paraformaldehyde and the hydrochlorides of the respective secondary amines. The amino ketones were then reduced catalytically to the corresponding amino alcohols. The compound of formula II was prepared by analogous reactions, starting with 1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole.

Whereas 2-(3-dimethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (I, R = CH_3) yielded a well crystallized hydrochloride, for reasons which are not obvious the diethylamino and tetrahydroisoquinolino analogs were decomposed by alcoholic hydrogen chloride. The cyclic alcohol II apparently suffered loss of water in the presence of alcoholic hydrogen chloride to yield a compound that we believe to be 2-dimethylaminomethyl-9-methyl-3,4-dihydrocarbazole hydrochloride. The tendency of similar amino alcohols in the tetrahydrophenanthrene series to split out water has been pointed out by Burger and Mosettig.[7]

The experimental work in this series will be extended to the resolution of the diethylamino alcohol of type I, and to the preparation of similar compounds in the benzocarbazole series.

The most active of the substances here described is 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (I, R = C_2H_5). This approaches codeine in analgesic action, but has a

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

(2) Mosettig, Burger, van de Kamp and co-workers, THIS JOURNAL, 1930–1938.

(3) (a) Eddy, *J. Pharmacol.*, **55**, 419 (1935); (b) **58**, 159 (1936).

(4) Eddy, *ibid.*, (Proc.), **54**, 140 (1935).

(5) Eddy, *ibid.*, **60**, 105 (1937).

(6) Van de Kamp and Mosettig, THIS JOURNAL, **58**, 1568 (1936).

(7) Burger and Mosettig, *ibid.*, **58**, 1570 (1936).

disadvantageous convulsant effect. In experiments on mice, it may be remarked that some of the animals showed the Straub reaction (erection of the tail in S form) that is so typical of morphine derivatives.

Experimental

Amino Ketones.—The method of Plant and Williams[8] for the preparation of 2-acetyl-9-methylcarbazole proved to be so laborious for making the ketone on a large scale that the following procedure was used. A suspension of 2,9-diacetylcarbazole (once recrystallized) in acetone, mechanically stirred, was treated dropwise with dimethyl sulfate and excess concentrated potassium hydroxide solution. Hydrolysis and methylation took place in a single step, and the product was easily purified by recrystallization from dilute acetic acid (70% by volume). The yield averaged 77% of the calculated amount. The amino ketones were all prepared in the same general way, by treating under reflux for fifteen or twenty minutes a mixture of 2-acetyl-9-methylcarbazole or 1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole (1 mole), the amine hydrochloride (1.2 moles), and paraformaldehyde (2.5 moles) in isoamyl alcohol. The quantity of ketone was usually 10 to 15 g., in 100 to 150 cc. of isoamyl alcohol. In some experiments the amino ketone hydrochloride precipitated from the reaction mixture when it was cooled, or diluted with ether. In these instances the precipitate was filtered out and washed with ether or acetone. In other reactions, dilution with ether caused the hydrochloride to separate as an oil, which was then extracted into water. The free bases were obtained by treating the aqueous solution of the hydrochloride with dilute ammonia, and filtering or extracting with ether, according to the consistency of the precipitate.

2-(3-Dimethylamino-1-oxopropyl)-9-methylcarbazole.—The yield of pure ketone obtained was 18% of the calculated amount. A large amount of starting material was recovered, but was very difficult to purify. The amino ketone crystallized from ethyl acetate in transparent, colorless plates of m. p. 111.5–113.5°.

Anal. Calcd. for $C_{18}H_{20}ON_2$: N, 10.00. Found: N, 10.00.

The hydrochloride precipitated as fine silky needles, m. p. 191.5–193°, when alcoholic hydrogen chloride was added to a solution of the base in absolute alcohol.

Anal. Calcd. for $C_{18}H_{21}ON_2Cl$: C, 68.22; H, 6.68. Found: C, 68.17; H, 6.61.

2-(3-Diethylamino-1-oxopropyl)-9-methylcarbazole.—The yield of purified amino ketone was from 20 to 25% of the calculated amount; it is rather unstable. It crystallized from ligroin (b. p. 70–90°) in creamy-white irregular crystals that sintered at 69° and melted at 70.5–72.5°.

Anal. Calcd. for $C_{20}H_{24}ON_2$: C, 77.87; H, 7.85. Found: C, 77.72, 77.49; H, 7.41, 7.93.

The hydrochloride crystallized from absolute alcohol in glistening leaflets that softened at about 160° and melted at 163.5–166°.

Anal. Calcd. for $C_{20}H_{25}ON_2Cl$: Cl, 10.29. Found: Cl, 10.11.

2-(3-Tetrahydroisoquinolino-1-oxopropyl)-9-methylcarbazole.—The hydrochloride of this amino ketone precipitated after the reaction mixture had been boiled for two to three minutes, and heating was then discontinued. The salt was only slightly soluble in water, and was converted to the base by trituration with dilute ammonia. The base crystallized from ethyl acetate in glistening leaflets of m. p. 123–125°; yield 37% of the theoretical amount.

Anal. Calcd. for $C_{25}H_{24}ON_2$: C, 81.48; H, 6.56. Found: C, 81.62; H, 6.77.

The hydrochloride crystallized from absolute alcohol–acetone mixture in short colorless rods that sintered at 209° and melted at 211–213°.

Anal. Calcd. for $C_{25}H_{25}ON_2Cl$: Cl, 8.76. Found: Cl, 8.89.

2-Dimethylaminomethyl-1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole.—The starting material for this synthesis was obtained by methylation of 1-keto-1,2,3,4-tetrahydrocarbazole according to the method of Smith and Tucker;[9] yield nearly quantitative. 1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole crystallized from methanol in long colorless prisms, m. p. 101.5–103.5°

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.35; H, 6.58. Found: C, 78.16; H, 6.21.

By the Mannich reaction with dimethylamine hydrochloride the above ketone was transformed in 10–15% yields to (crude) 2-dimethylaminomethyl-1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole. This compound crystallized from petroleum ether in almost colorless transparent plates that sintered at 72.5° and melted at 74–75°.

Anal. Calcd. for $C_{16}H_{20}ON_2$: C, 74.95; H, 7.87. Found: C, 74.90; H, 8.12.

The hydrochloride of the amino ketone crystallized from a mixture of absolute alcohol and acetone in short, colorless rods, which sintered at about 180°, and melted with decomposition at about 190°. Both the base and the hydrochloride were unstable and became colored after a few weeks.

Anal. Calcd. for $C_{16}H_{21}ON_2Cl$: C, 65.61; H, 7.23; N, 9.58. Found: C, 65.74; H, 7.44; N, 9.47.

Amino Alcohols.—The hydrochlorides of the amino ketones were hydrogenated in solution in 60% alcohol, using platinum oxide catalyst. It was found to be essential for the success of the hydrogenation that the salts be of a high degree of purity. In most instances reduction stopped after slightly more than one mole of hydrogen had been absorbed.

2-(3-Dimethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—The reduction of 5.3 g. of the amino ketone in the presence of 0.25 g. of platinum oxide required about three hours. The catalyst was removed, and the solvent was distilled off under diminished pressure, leaving a residue which was taken up in water, treated with ammonia, and extracted with ether. The residue from distillation of the ether crystallized from ligroin (b. p. 90–120°) in colorless rosets, of m. p. 96.5–99°; yield of purified amino alcohol, 80% of the calculated amount.

(8) Plant and Williams, *J. Chem. Soc.*, 1142 (1934).

(9) Smith and Tucker, *ibid.*, **123**, 2140 (1923).

Anal. Calcd. for $C_{15}H_{22}ON_2$: C, 76.55; H, 7.86. Found: C, 76.37; H, 7.71.

The hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride; it crystallized as fine colorless needles of m. p. 195–196.2°. It is very soluble in water.

Anal. Calcd. for $C_{15}H_{23}ON_2Cl$: Cl, 11.13. Found: Cl, 11.24.

The *p*-nitrobenzoate hydrochloride was prepared by combining equivalent amounts of the amino alcohol and *p*-nitrobenzoyl chloride in dry benzene. The yellow amorphous compound was washed with absolute ether and was recrystallized from a mixture of absolute alcohol and ether. It formed short yellow rods that softened at 164° and melted at 165–166.5°.

Anal. Calcd. for $C_{25}H_{26}O_4N_3Cl$: N, 8.99; Cl, 7.58. Found: N, 8.93; Cl, 7.24.

2-(3-Diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—Reduction of the diethylamino ketone (11 g.) with platinum oxide (0.55 g.) proceeded like that of the dimethylamino derivative, and the product was isolated in the same way. The amino alcohol was purified by fractional crystallization from petroleum ether, from which it separated as soft, glistening irregular crystals that sintered at 73° and melted at 75.2–76°; yield 80% of the calculated amount.

Anal. Calcd. for $C_{20}H_{26}ON_2$: C, 77.36; H, 8.45. Found: C, 77.14; H, 8.47.

It is particularly important in this reduction that the amino ketone salt be pure. In one reduction, apparently with less pure material, absorption of hydrogen proceeded slowly and a precipitate formed. This was warmed into solution, the catalyst removed, and the solution was permitted to crystallize. Long yellow needles were deposited, which were purified from alcohol and melted at 133–135°. The new compound was not basic, and formed an oxime, colorless prisms from alcohol, m. p. 172–173°; its nature has not been determined. From the mother liquors, the amino alcohol could be obtained, but was very difficult to purify.

The amino alcohol did not form a crystalline hydrochloride, but was extensively decomposed by alcoholic hydrogen chloride.

The picrate crystallized from alcohol in golden-yellow needles of m. p. 136–138.5°.

Anal. Calcd. for $C_{26}H_{29}O_8N_5$: C, 57.86; H, 5.42. Found: C, 57.98; H, 5.63.

The *p*-nitrobenzoate hydrochloride crystallized from a mixture of absolute alcohol and ether in short yellow rods, which sintered at 177° and melted at 179–180.5°.

Anal. Calcd. for $C_{27}H_{30}O_4N_3Cl$: C, 65.36; H, 6.10; N, 8.48. Found: C, 65.57; H, 6.03; N, 8.25.

2-(3-Tetrahydroisoquinolino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—After reduction of the amino ketone hydrochloride, the reaction mixture was warmed with additional solvent until the separated material redissolved, and the catalyst was removed. A small amount of amino alcohol base crystallized from the cooled solution. The solution was concentrated under diminished pressure and made alkaline with ammonia. The yield of crude product (m. p. 148–152°) was 90% of the calculated amount. It crystallized from alcohol in long colorless prisms of m. p. 151.5–153°. Repeated recrystallization and sublimation did not effect further purification. The following analyses were made on different samples.

Anal. Calcd. for $C_{25}H_{26}ON_2$: C, 81.03; H, 7.08. Found: C, 81.23, 81.52, 81.64, 81.43, 81.37, 81.73; H, 6.64, 7.29, 7.22, 7.03, 6.96, 7.07.

The amino alcohol was insoluble in dilute hydrochloric acid, and was decomposed by alcoholic hydrogen chloride.

The styphnate crystallized from alcohol in small orange clusters that sintered above 135° and melted with decomposition at 171–175°.

Anal. Calcd. for $C_{31}H_{29}O_9N_5$: C, 60.46; H, 4.75. Found: C, 60.21; H, 4.75.

The *p*-nitrobenzoate hydrochloride crystallized from absolute alcohol in small yellow prisms that sintered at 153° and melted at 159.5–161°.

Anal. Calcd. for $C_{32}H_{30}O_4N_3Cl$: C, 69.10; H, 5.44. Found: C, 69.13; H, 5.73.

2-Dimethylaminomethyl-1-hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole.—After reduction of the amino ketone hydrochloride and removal of the catalyst and solvent as described above, the residue was dissolved in water, and the solution was extracted with ether. The base was liberated from the aqueous layer with ammonia, and extracted into ether. The product was recrystallized successively from dilute alcohol and from ethyl acetate petroleum ether mixture (1:15), and consisted of colorless six-sided plates of m. p. 123.5–125°. The yield of pure amino alcohol was 46% of the calculated amount.

Anal. Calcd. for $C_{16}H_{22}ON_2$: C, 74.36; H, 8.59; N, 10.85. Found: C, 74.36, 74.50; H, 8.38, 8.63; N, 10.89.

Attempts to prepare the hydrochloride of this amino alcohol resulted in the formation of a hydrochloride which analysis showed to lack the elements of water from the expected formula. The compound, tentatively designated as 2-dimethylaminomethyl-9-methyl-3,4-dihydrocarbazole hydrochloride, crystallized from absolute alcohol on addition of ether as colorless irregular crystals that sintered at about 180° and melted with decomposition at 192–194°. It was somewhat unstable, and showed a lower melting point after a few weeks.

Anal. Calcd. for $C_{16}H_{23}ON_2Cl$: C, 65.16; H, 7.87; N, 9.51. Calcd. for $C_{16}H_{21}N_2Cl$: C, 69.41; H, 7.65; N, 10.13. Found: C, 69.71; H, 7.67; N, 10.21.

Summary

The preparation of amino alcohols derived from 9-methylcarbazole and from 1-keto-9-methyltetrahydrocarbazole is described. Several of these amino alcohols show marked analgesic action, the most effective being 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.

UNIVERSITY, VIRGINIA RECEIVED MAY 19, 1938