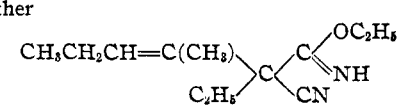
turic acid in yields of 40 to 60% on condensation with urea. Consequently the alkoxyl groups are introduced by addition to the nitrile rather than the alkenyl group, as otherwise a substituted barbituric acid containing alkoxy groups would be produced with urea. Evidence that addition of alcohol to the alkylation product could occur during the alkylation was obtained by refluxing 5.6 g. of relatively pure 1-methyl-1-butenyl ethylmalononitrile (b. p. 119–120° (22 mm.), $n^{25}D$ 1.4448, N analysis 17.0%) with a solution of 0.8 g. of sodium in 30 cc. of absolute ethyl alcohol for twelve hours. The product (5 g.) corresponded in properties to the higher boiling fractions obtained from the alkylations; b. p. 135–148° (28 mm.), $n^{25}D$ 1.4558. N analysis of the middle portion, b. p. 144–146° (28 mm.), 12.2%. A similar experiment in which isopropyl alcohol was employed likewise resulted in addition of the alcohol, giving 4 g. of a mixture, b. p. 120–140° (23 mm.), $n^{25}D$ 1.4508.

The product containing alkoxyl groups was most completely characterized as isolated from an alkylation carried out in ethyl alcohol. 1-Methylbutylidene malononitrile (134 g.) was converted into the sodium derivative by addition to a solution of 23 g. of sodium in 800 cc. of absolute ethyl alcohol at −15° during ten minutes. Ethyl bromide (130 g.) was added in one portion, and the solution was heated to boiling. The reaction was vigorous. After refluxing for thirty minutes the mixture was cooled, poured into ice water containing enough hydrochloric acid to make the mixture slightly acid, extracted and distilled in the usual manner. The crude distillate (78.8 g., b. p. 120–160° (29 mm.)) was shaken overnight with 300 cc. of 20% sodium bisulfite solution and redistilled through a Widmer column. The product (57.1 g.) was separated into four fractions, boiling between 130 and 150° (27 mm.) and having $n^{25}D$ between 1.4440 and 1.4560. Three refractionations partially separated the mixture into a low and high boiling fraction. The middle portion of the high boiling fraction (12 g.) had b. p. 142.5–143° (26 mm.), $n^{25}D$ 1.4541. Analysis showed this fraction to be the impure imino ether



Calcd. for $C_{12}H_{20}ON_2$: N, 13.45; OC_2H_5, 21.63. Found: N, 10.80; OC_2H_5, 20.50. Since both the ethoxyl and nitrogen values on this fraction were low, it contained some impurity other than the corresponding malononitrile. The most likely contaminant is the corresponding cyanoacetic ester, which would be formed by partial hydrolysis of the imino ether during the purification with sodium bisulfite. This impurity would lower the nitrogen without appreciably affecting the ethoxyl content. Indirect evidence that this fraction actually contained the imino ether was obtained in an attempt to prepare a picrate from it. The above product (1.2 g.) and picric acid (1.2 g.) in warm ether gave a bright yellow solid (1.1 g.), which was proved to be ammonium picrate by nitrogen analysis and the liberation of ammonia with sodium hydroxide. Ammonium picrate could be formed under these mild conditions only from a structure very readily cleaved by acids, such as an imino ether.

Summary

Malononitrile has been condensed with four aliphatic ketones to give alkylidene derivatives, $R_2C{=}C(CN)_2$, all of which are liquids. Three of them have been reported previously to be rather high melting solids, which may have been dimers or polymers of the simple compounds. The alkylidene malononitriles form sodium derivatives which can be alkylated to produce substituted vinyl alkylmalononitriles.

BRYN MAWR, PENNSYLVANIA

RECEIVED DECEMBER 16, 1940

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

Amino Alcohols Derived from Carbazole. II[1]

BY LEONE RUBERG AND LYNDON SMALL

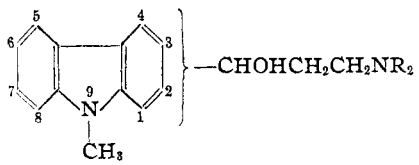
Preliminary investigations of the simple aminocarbazoles and amino-9-methylcarbazoles have shown that some compounds of the series exert definite and prolonged analgesic action, and are of relatively low toxicity. Among the many phenanthrene and dibenzofuran compounds that have been synthesized in our laboratory for analgesia studies, those derivatives carrying an amino group and an alcoholic hydroxyl, attached directly to the nucleus, or in a side chain, are particularly active.[2] These facts led to the selection of amino alcohols derived from carbazole for further study.

In a recent communication[3] we described the preparation of several amino alcohols of types I and II.

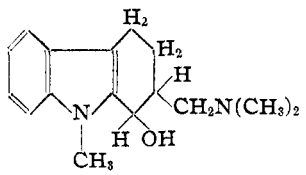
(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, The U. S. Public Health Service, the U.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

(2) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports.

(3) Ruberg and Small, THIS JOURNAL, **60**, 1591 (1938).



I, chain at 2-position
III, chain at 3-position

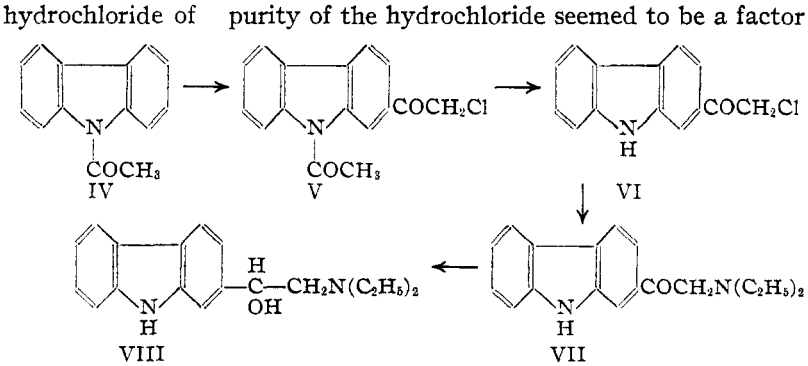


II

The most active of these is 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (I, R = C_2H_5), which approaches codeine in analgesic action, but has a disadvantageous convulsant effect.[4] In mice, this compound frequently caused the erection of the tail in sigmoid form (Straub reaction) that is so characteristic of morphine derivatives.[5]

If the effect of position of substituent on physiological action in the carbazole series is parallel to that observed in the procaine and sulfanilamide types, compounds carrying the amino alcohol group in the 3-position, para to the carbazole nitrogen atom, might be more active than the corresponding 2-derivatives. In this paper the preparation of the 3-isomers is described. In formula III, —NR_2 represents the dimethylamino, diethylamino, or tetrahydroisoquinolino group. These compounds were prepared by application of the Mannich reaction to 3-acetyl-9-methylcarbazole, *i. e.*, by treatment of the ketone with paraformaldehyde and the hydrochloride of the appropriate secondary amine. The amino ketones were then reduced catalytically to the amino alcohols.

A further variation of the amino alcohol portion of the molecule is presented in 2-(2-diethylamino-1-hydroxyethyl)-carbazole (VIII), which was prepared through the following steps:



The work of other investigators has shown that, in general, the Friedel–Crafts reaction with simple acid halides and carbazole or 9-alkylcarbazoles leads to 3,6-disubstituted carbazoles, but that when 9-acyl carbazoles are employed, the product is a 2-substituted derivative.[6] During our study of the Friedel–Crafts reaction with chloroacetyl chloride and 9-acetylcarbazole, from which we believe to have obtained 2-chloroacetyl-9-acetylcarbazole, Sherlin and Berlin[7] reported the preparation, by the same reaction, of a compound which they designated as 3-chloroacetyl-9-acetylcarbazole. They based the structure of their product on the work of Borsche and Feise[8] who claimed to have synthesized 3-acetylcarbazole by the Friedel–Crafts reaction with acetyl bromide and 9-acetylcarbazole, followed by hydrolysis of the 9-acetyl group. The Russian investigators apparently overlooked later work[6] that proved that the compound of Borsche and Feise was actually 2-acetylcarbazole.

In order to clarify this question, the chloroacetylcarbazole VI obtained by acid hydrolysis of V was converted to the corresponding carbazole carboxylic acid by fusion with potassium hydroxide. The acid was transformed to the ethyl ester for convenience in purification. This ethyl carbazolecarboxylate was identical with the ester obtained from authentic 2-acetylcarbazole. Hence, the Friedel–Crafts reaction of chloroacetyl chloride and 9-acetylcarbazole conforms with the generalization mentioned above, and yields the 2-chloroacetyl derivative.

The amination of 2-chloroacetylcarbazole was carried out in benzene at 100°, and was followed by hydrogenation of the amino ketone hydrochloride in the presence of platinum (oxide). The purity of the hydrochloride seemed to be a factor in the success of the reduction, and there was

(4) Eddy, *J. Pharmacol.*, **65**, 308 (1939).

(5) The Straub reaction is rarely encountered outside of the morphine series. For some exceptions see Heinekamp, *J. Pharmacol.*, **20**, 107 (1922); Juul, *Arch. intern. pharmacodynamie*, **62**, 69 (1939).

(6) (a) I. G. Farbenindustrie, German Patent 555,312. (b) Plant and Williams, *J. Chem. Soc.*, 1142 (1934). (c) Plant, Rogers and Williams, *ibid.*, 741 (1935).

(7) Sherlin and Berlin, *J. Gen. Chem.* (U. S. S. R.). **7**, 2275 (1937).

(8) Borsche and Feise, *Ber.*, **40**, 378 (1907).

considerable loss of material in the purification necessary. Sodium amalgam reduction of the crude amino ketone was found to give a better over-all yield of the desired alcohol, and was more dependable than the catalytic method.

Attempted methylation of the imino group in the amino alcohol VIII was unsuccessful. As was expected, alkali and methyl sulfate yielded water-soluble material, probably the metho-methyl sulfate (at the diethylamino group). The basic nitrogen was therefore protected from alkylation by conversion to the amine oxide. From this, however, only starting material was obtained after methylation under various conditions. Treatment of 2-chloroacetylcarbazole with potassium hydroxide and methyl sulfate gave an N-methyl derivative, but the yield was too small to make the reaction practical for the synthesis of the N-methyl derivative of VIII. The possibility of halogenating the side chain in 2-acetyl-9-methylcarbazole will be investigated.

The pharmacological action of the compounds described in this publication will be reported by Dr. N. B. Eddy of this Laboratory.

Experimental

Amino Ketones Derived from 3-Acetyl-9-methylcarbazole.—The required 3-acetylcarbazole was prepared by the Fries–Rosenmund rearrangement of 9-acetylcarbazole, following essentially the methods in the literature.[6c,9] The yield of pure product was considerably less, however, than previously reported. Methylation of 3-acetylcarbazole by the method of Plant and Williams[6b] gave 3-acetyl-9-methylcarbazole in 85 to 96% yields, depending upon the purity of the starting material. The amino ketone hydrochlorides were all prepared in the same general way, by heating under reflux for three to ten hours in an atmosphere of nitrogen a mixture of 3-acetyl-9-methylcarbazole (1 mole), the amine hydrochloride (1.05 moles), and paraformaldehyde (1.75 moles, added in several portions) in absolute ethanol. The quantity of initial ketone was 10 or 20 g. in 50 to 80 cc. of ethanol. The conditions used are essentially those reported by Mannich.[10] While the condensation proceeded more slowly in ethyl alcohol than in isoamyl alcohol,[11] it was not accompanied by as many side reactions. This may be explained by the instability of the amino ketones at the higher temperature. The yields of the amino ketone hydrochlorides are based on the amount of original ketone not recovered from the reactions. The purification of recovered starting material was simpler than its preparation.

3 - (3 - Dimethylamino - 1 - oxopropyl) - 9 - methylcarbazole.—The amino ketone hydrochloride was isolated by addition of acetone to the cooled reaction mixture. It crystallized from absolute ethanol in glistening colorless leaflets, m. p. 193.5–194.5°. The yield was 61% of the theoretical. The hydrochloride could also be obtained from the base.

Anal. Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.22; H, 6.68. Found: C, 68.32; H, 6.67.

The base was obtained by addition of dilute ammonia to an aqueous solution of the hydrochloride and extraction with ether. After distillation of the ether, the pale yellow residue was heated under reflux with petroleum ether (b. p. 30–60°) and methyl acetate (6:1), which dissolved the amino ketone, leaving a considerable amount of resin. After another fractionation with petroleum ether and methyl acetate, the amino ketone crystallized from the filtrate in soft, colorless prisms which sintered at about 70° and melted at 72.5–73°. It crystallized from petroleum ether alone, but required considerable refluxing to obtain solution. Each further recrystallization process seemed to be accompanied by slight decomposition.

3-(3-Tetrahydroisoquinolino-1-oxopropyl)-9-methylcarbazole.—The crude amino ketone hydrochloride was filtered from the reaction mixture and washed with acetone. It was suspended in water, washed with ether to remove a neutral fraction, and converted to the base in the manner described above, yielding a yellow, unstable oil, which could not be crystallized. A 78% yield of pure amino ketone hydrochloride was obtained by addition of concentrated hydrochloric acid to a solution of the base in 95% ethanol. The product crystallized in colorless, silky needles which sintered at 198.5° and melted at 201–202°. A sample was dried at 110° in a vacuum for analysis.

Anal. Calcd. for $C_{25}H_{25}ClN_2O$: C, 74.14; H, 6.23. Found: C, 73.80; H, 6.52.

The picrate crystallized from ethanol in short yellow rods that melted at 177.5–178.5° after sintering at about 170°.

Anal. Calcd. for $C_{31}H_{27}N_5O_9$: C, 62.28; H, 4.56. Found: C, 62.46; H, 4.54.

3 - (3 - Diethylamino - 1 - oxopropyl) - 9 - methylcarbazole.—By extending the reaction time from five to eight hours, the yield of amino ketone hydrochloride was increased from 59 to 83%. After distillation of the solvent under reduced pressure, the semi-solid residue was suspended in water, extracted with ether, and the hydrochloride was converted to the base as previously described. The amino ketone, a yellow oil, was reconverted to the hydrochloride by addition of alcoholic hydrogen chloride to a solution of the base in absolute ethanol and acetone. After one recrystallization from absolute ethanol and absolute ether, the slender, colorless prisms sintered at about 162° and melted at 167–168.5°.

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: Cl, 10.29. Found: Cl, 10.56.

The picrate, prepared by addition of aqueous sodium picrate to a warm solution of the hydrochloride in ethanol, crystallized from absolute ethanol in soft, yellow rods which sintered at about 134° and melted at 143–143.5°.

Anal. Calcd. for $C_{26}H_{27}N_5O_8$: C, 58.07; H, 5.07. Found: C, 58.25; H, 4.91.

Amino Alcohols Derived from 3-Acetyl-9-methylcarbazole.—The amino alcohols represented by formula

(9) Meitzner, THIS JOURNAL, **57**, 2327 (1935).
(10) Mannich and Lammering, *Ber.*, **55**, 3510 (1922).
(11) Van de Kamp and Mosettig, THIS JOURNAL, **58**, 1568 (1936).

III were obtained by hydrogenation of the corresponding amino ketone hydrochlorides in methanol solution or suspension, using platinum oxide catalyst. The reduction stopped after slightly more than one mole of hydrogen had been absorbed.

3 - (3 - Dimethylamino - 1 - hydroxy - *n* - propyl) - 9-methylcarbazole.—The reduction of 7.8 g. of the amino ketone hydrochloride in 125 cc. of methanol with 0.4 g. of platinum oxide required about two days. The catalyst was removed and the solvent was distilled under diminished pressure. The sirupy residue could not be crystallized, so it was suspended in water and extracted with ether to remove the neutral fraction, made alkaline with dilute ammonia, and again extracted with ether. The ether residue was treated under reflux with decolorizing carbon in ligroin (b. p. 70–90°), which left a large portion of yellow impurity undissolved. The amino alcohol crystallized from the filtrate in clusters of colorless, irregular prisms, m. p. 121–123°, yield 65%. After further recrystallization, from ethanol, the amino alcohol melted at 122.5–123°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.55; H, 7.86. Found: C, 76.81; H, 7.65.

The picrate crystallized from ethanol in amber-colored, leaf-shaped plates which sintered slowly above 145° and melted with effervescence at 157.5–158.5°.

Anal. Calcd. for $C_{24}H_{25}N_5O_8$: C, 56.33; H, 4.93. Found: C, 56.61; H, 4.84.

3 - (3 - Tetrahydroisoquinolino - 1 - hydroxy - *n* - propyl) - 9-methylcarbazole.—The reduction of the amino ketone hydrochloride proceeded very slowly. The amino alcohol itself, obtained in the manner described for the dimethylamino alcohol, was an amorphous powder which could not be crystallized nor converted to a crystalline hydrochloride. The salt was obtained crystalline, however, in an 80% yield, by distilling the methanol from the original reduction filtrate and dissolving the sirupy residue in absolute ethanol. The hydrochloride was then recrystallized from an ethanol–ether mixture, yielding colorless prisms that sintered above 177° and melted with effervescence at 187°.

Anal. Calcd. for $C_{25}H_{27}ClN_2O$: C, 73.77; H, 6.69. Found: C, 73.46; H, 6.74.

3 - (3 - Diethylamino - 1 - hydroxy - *n* - propyl) - 9-methylcarbazole.—Methanol as the solvent for the reduction of the parent amino ketone was found to be especially advantageous since it could be removed by diminished pressure distillation without increased temperature; heating decomposed the amino alcohol hydrochloride. The pale yellow sirup which remained after removal of the methanol was dissolved in acetone, from which the hydrochloride crystallized in thick, colorless prisms. After several recrystallizations by addition of absolute ether to a *slightly* warmed solution of the hydrochloride in absolute ethanol, the product sintered above 129° and melted at 132–134°; yield, 74%.

Anal. Calcd. for $C_{20}H_{27}ClN_2O$: C, 69.23; H, 7.85. Found: C, 69.33; H, 7.92.

The amino alcohol itself could be obtained only as an oil. In attempting to reconvert it to the hydrochloride, addition of alcoholic hydrogen chloride and absolute ether to a solution of the base in absolute ethanol gave only a small yield of an unstable crystalline hydrochloride, the analysis of which corresponded with the calculated values for a compound formed by loss of the elements of water from the amino alcohol hydrochloride. The compound crystallized in glistening colorless plates which turned slightly yellow on standing in a desiccator overnight; m. p. 189–190.5° after sintering at about 184°.

Anal. Calcd. for $C_{20}H_{25}ClN_2$: C, 73.02; H, 7.67. Found: C, 72.57; H, 7.45.

Loss of water from similar amino alcohols with such agents as alcoholic hydrogen chloride and acid chlorides has been noted previously.[3,12]

2-Chloroacetyl-9-acetylcarbazole.[13]—The chloro ketone was prepared by the method used by Sherlin and Berlin. Resublimed aluminum chloride (66 g.) was added, with stirring, over a period of twenty minutes to a solution of 22 g. of 9-acetylcarbazole and 37.4 g. of chloroacetyl chloride in 100 cc. of dry carbon disulfide in a 500 cc. three-necked flask fitted with mercury-seal stirrer and reflux condenser. The mixture was heated on a water-bath for one-half hour after the first addition of aluminum chloride and was then allowed to stand at room temperature for two hours before pouring onto ice and water. When the reaction was carried out on a larger scale, using 50 g. of 9-acetylcarbazole, it proceeded more vigorously and the aluminum chloride was added more slowly (1.5 hours); refluxing was sustained by the heat of reaction. The crude crystalline product was too insoluble for recrystallization from ethanol. (The Russian investigators reported use of this solvent for a first recrystallization.) The dried product was dissolved in boiling xylene, and after filtration from a dark, gummy residue, 2-chloroacetyl-9-acetylcarbazole crystallized in pale yellow prisms, m. p. 181–183° (sintering at 178°). The yield of purified product was 94%; Sherlin and Berlin reported a yield of 55%, before recrystallization from xylene.

Anal. Calcd. for $C_{16}H_{12}ClNO_2$: Cl, 12.42. Found: Cl, 12.41.

2-Chloroacetylcarbazole.—Using the conditions reported by Sherlin and Berlin for removal of the N-acetyl group, we obtained only partial hydrolysis; the product melted at 163–178° and could not be purified by recrystallization. The following conditions were more satisfactory. A suspension of 20 g. of 2-chloroacetyl-9-acetylcarbazole in 2400 cc. of ethanol and 720 cc. of 20% sulfuric acid was heated under reflux on a water-bath for 2–2.5 hours, until the original ketone had dissolved. After dilution with water the product was collected, washed well with water, and dried. The pale yellow prisms of 2-chloroacetylcarbazole, which crystallized from ethanol, melted with decomposition at 208–210°. The yield was almost quantitative.

Anal. Calcd. for $C_{14}H_{10}ClNO$: Cl, 14.56. Found: Cl, 14.83.

Fusion with Potassium Hydroxide.—Following the method of Plant, Rogers and Williams,[6c] 2-chloroacetylcarbazole was converted to the corresponding carboxylic acid by fusion with potassium hydroxide. The crude acid was dissolved in absolute ethanol and heated under reflux for one hour while dry hydrogen chloride was passed in.

(12) Burger and Mosettig, THIS JOURNAL, **58**, 1570 (1936).

(13) Preliminary experiments on the following series of compounds were carried out by Dr. Erich Meitzner.

The product was precipitated by dilution with water, and sublimed in a high vacuum. The larger fraction, which sublimed at 145–155°, recrystallized from ethanol in colorless prisms which melted at 183.5–185°. Admixture with an authentic sample of ethyl carbazole-2-carboxylate, prepared in the same manner from 2-acetylcarbazole, caused no depression in melting point.

2-Chloroacetyl-9-methylcarbazole.—Methylation of 2-chloroacetylcarbazole in acetone suspension with dimethyl sulfate and strong aqueous potassium hydroxide[14] in the cold, followed by sublimation of the crude product at 135–140° in a high vacuum and recrystallization from ethanol, yielded 2-chloroacetyl-9-methylcarbazole in yellow needles which melted at 173.5–175°. The yields were very small and not uniform. Attempts to increase the yield by altering conditions, such as temperature and concentration of alkali, were unsuccessful.

Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.89; H, 4.70. Found: C, 69.87; H, 4.92.

2-(2-Diethylamino-1-oxoethyl)carbazole.—Ten grams of 2-chloroacetylcarbazole, 12.7 cc. (3 moles) of diethylamine, and 6.5 cc. of dry benzene were heated in a sealed tube in a boiling water-bath for eight to nine hours; during this time the tube was removed several times and shaken to mix the suspension. The precipitated diethylamine hydrochloride was separated and washed with benzene, and the wash added to the main filtrate. After distillation of the benzene under diminished pressure, the solid residue was suspended in ether and repeatedly extracted with dilute hydrochloric acid. Filtration of the aqueous solution removed a dirty, amorphous fraction. The amino ketone isolated by addition of dilute ammonia to the aqueous hydrochloride solution was a light tan semi-crystalline powder that sintered at about 125° and melted with decomposition at 132–138°; yield 67%. Further purification could be effected only by sublimation at 130–135° in a high vacuum, followed by mechanical separation of the thick, transparent yellow prisms, which were then resublimed. The purified amino ketone sintered above 126° and melted with decomposition at 134–136° (evac. tube, sintering above 150°, m. p. without decomp. 155.5–156.5°).

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19. Found: C, 77.02; H, 7.37.

The amino ketone hydrochloride was prepared by addition of alcoholic hydrogen chloride and absolute ether to a solution of the sublimed base in absolute ethanol and acetone; as soon as precipitation was complete, the salt was separated from the solution, which darkened on standing several hours. The hydrochloride crystallized from absolute ethanol and absolute ether in pale yellow plates which melted with decomposition at 190.5–193° after softening slowly above 100°.

Anal. Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.22; H, 6.68. Found: C, 66.32, 66.23; H, 6.81, 7.09.

The analysis corresponds to a content of one-half mole of hydrate water: Calcd. for $C_{18}H_{21}ClN_2O + 0.5H_2O$: C, 66.34; H, 6.81. The water could not be determined directly because of decomposition, even on gentle heating.

The amino ketone picrate crystallized from ethanol in slender yellow prisms which melted at 164–165° (sintering at 160°).

Anal. Calcd. for $C_{24}H_{23}N_5O_8$: C, 56.56; H, 4.55. Found: C, 56.91; H, 4.67.

2-(2-Diethylamino-1-hydroxyethyl)-carbazole. (A) By Catalytic Reduction.—The amino ketone hydrochloride (0.92 g.) in 20 cc. of 60% ethanol was hydrogenated in the presence of 0.05 g. of platinum oxide. After one and one-half hours the reduction was complete and the amino alcohol was isolated in the usual way. It crystallized from ethanol in silky, colorless needles, which melted at 151–152°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.54; H, 7.86. Found: C, 76.47; H, 7.68.

The yield from the above experiment was 92% of the theoretical (over-all yield from the chloro ketone, 33%), but in a subsequent run the product was more difficult to purify and the yield was considerably lower.

(B) By Sodium Amalgam Reduction.—Four grams of crude amino ketone, dissolved in 75 cc. of ethanol containing 1.2 cc. of concentrated hydrochloric acid and 7 cc. of water, was treated with 34 g. of 5% sodium amalgam, added in several portions. After about an hour, the original amber color of the solution had disappeared, leaving a colorless precipitate in a pale yellow solution. The suspension was decanted from mercury and excess amalgam and concentrated under diminished pressure. The residue was treated with dilute hydrochloric acid and extracted with ether to remove a neutral fraction. The aqueous solution was warmed to remove ether and then treated with decolorizing carbon. Addition of ammonia to the filtrate precipitated the amino alcohol, which melted at 151–152° after recrystallization from ethanol. Admixture with the product from catalytic reduction did not lower the melting point. If the crude amino alcohol was quite impure, sublimation at 130–140° in a high vacuum was found to be more economical since the compound is quite soluble in ethanol. The over-all yield from the chloro ketone was 37%, and the method was much less laborious than the catalytic reduction.

The amino alcohol hydrochloride crystallized from absolute ethanol and absolute ether in colorless, silky clusters, which melted at 182.5–184°. The hydrochlorides prepared from the products of the two reduction methods were identical, as shown by their melting points and the melting point of their mixture.

Anal. Calcd. for $C_{18}H_{23}ClN_2O$: C, 67.78; H, 7.27. Found: C, 67.67; H, 7.46.

The styphnate crystallized from ethanol in long, golden prisms that sintered above 174° and melted with decomposition at 179–180°.

Anal. Calcd. for $C_{24}H_{25}N_5O_9$: C, 54.62; H, 4.78. Found: C, 54.84; H, 4.59.

The amine oxide was obtained in almost quantitative yield by heating under reflux on a water-bath for about thirty minutes a suspension of the amino alcohol in six parts by weight of 30% hydrogen peroxide. During this time the product crystallized from the reaction mixture, which was then diluted with about an equal volume of water. The oxide was collected, washed with acetone, and recrystallized from ethanol. The colorless, transparent

(14) Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

prisms sintered above 176° and melted with strong effervescence at 181°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 72.44; H, 7.44. Found: C, 72.51; H, 7.65.

Summary

By application of the Mannich reaction to 3-acetyl-9-methylcarbazole, followed by reduction, 9-methylcarbazolyl amino alcohols have been prepared, in which the side chain $CHOHCH_2NR_2$ ($-NR_2$ = dimethylamino, diethylamino, tetrahydroisoquinolino) is located at the 3-position. The Friedel–Crafts reaction with 9-acetylcarbazole and chloroacetyl chloride yields 2-chloroacetyl-9-acetylcarbazole, not the 3-derivative as claimed by other investigators. By amination of 2-chloroacetylcarbazole and reduction of the dialkylamino ketone, 2-(2-diethylamino-1-hydroxyethyl)-carbazole was obtained.

WASHINGTON, D. C. RECEIVED OCTOBER 16, 1940

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Catalytic Dehydrogenation of Tetralin and 1,2,3,4-Tetrahydro-naphthol-2 in the Liquid Phase

BY HOMER ADKINS AND WILLIS A. REID

In the course of attempts to develop practical and useful methods for the catalytic dehydrogenation in the liquid phase, a study has been made of the behavior of tetrahydronaphthalene and 1,2,3,4-tetrahydronaphthol-2 over Raney nickel and copper chromite catalysts. Earlier work had shown that ethylene was a useful acceptor for the hydrogen split from alcohols.[1] The irreversibility of the second reaction at 280° made it possible to

$$RCH_2OH \rightleftharpoons RCHO + H_2$$
$$C_2H_4 + H_2 \longrightarrow C_2H_6$$

drive the first reaction to the right and thus enable aldehydes to be obtained in excellent yields.

Attempts thus to use ethylene as an oxidizing agent for hydronaphthalenes were not successful, for ethylene underwent polymerization to a light colored oil in the steel reaction vessel at 300 to 350° under a pressure of 100 to 200 atmospheres. When Raney nickel was present in the reaction vessel carbon was formed from the ethylene.

Tetralin under 60 atm. of nitrogen was stable over copper chromite but underwent dehydrogenation over Raney nickel at 300 to 350°. The reaction mixture might contain four different compounds, decalin, tetralin, dihydronaphthalene, and naphthalene.[2] It is not feasible to separate such a mixture into its components by fractional distillation. However, naphthalene forms a picrate and so may be estimated and separated from the other components of the mixture. The method was carefully worked out using mixtures of tetralin and naphthalene.

The results of typical experiments on the dehydrogenation of tetralin over Raney nickel are recorded in Table I. The figures given show that at 350° from 66 to 78% of the tetralin was converted to naphthalene within four hours. The highest yield was obtained when a rather large ratio of nickel was used. At 300° the yield of naphthalene is considerably lower, being from 31 to 45%.

TABLE I

DATA ON DEHYDROGENATIONS[a]

Moles	Catalyst, g.	Temp., °C.	Original pressure of gas in atm.	% yield of naphthalene[1] or β-naphthol[2]	
	Tetrahydronaphthalene				
0.15	2 Ni	300	33 N_2	45[1]	
.30	4 Ni	300	36 N_2	42[1]	
.15	2 Ni	350	36 N_2	71[1]	
.30	4 Ni	350	30 N_2	67[1]	
.15	8 Ni	350	35 N_2	78[1]	
	1,2,3,4-Tetrahydronaphthol-2				
0.135	8 Ni	350	33 C_2H_4	20[2]	60[1]
.135	8 Ni	250	35 C_2H_4	18[2]	64[1]
.135	10 $CuCr_2O_4$	300	65 N_2	76[2]	
.135	5 $CuCr_2O_4$	300	33 C_2H_4	67[2]	
.135	2.5 $CuCr_2O_4$	300	33 C_2H_4	63[2]	

[a] All of the reaction mixtures were held at the indicated temperature for 4 hours. All of those containing nickel also contained an amount of ethyl alcohol approximately equivalent to the weight of nickel. In addition the reaction mixtures of 1,2,3,4-tetrahydronaphthol-2 contained 20 ml. of dry dioxane.

The mixture of hydrocarbons left after the removal of the naphthalene as the picrate was examined. It was shown, if the picrate method

(1) Reeve and Adkins, THIS JOURNAL, **62**, 2874 (1940).

(2) Zelinski, *Ber.*, **56**, 1924 (1923), stated that over platinum at 300° tetralin disproportionates to decalin and naphthalene. Linstead reported that no decalin was formed in his experiments under similar conditions, *J. Chem. Soc.*, 1146 (1937).