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Mescaline Analogs. V. *p*-Dialkylamino-β-phenethylamines and 9-(β-Aminoethyl)julolidine

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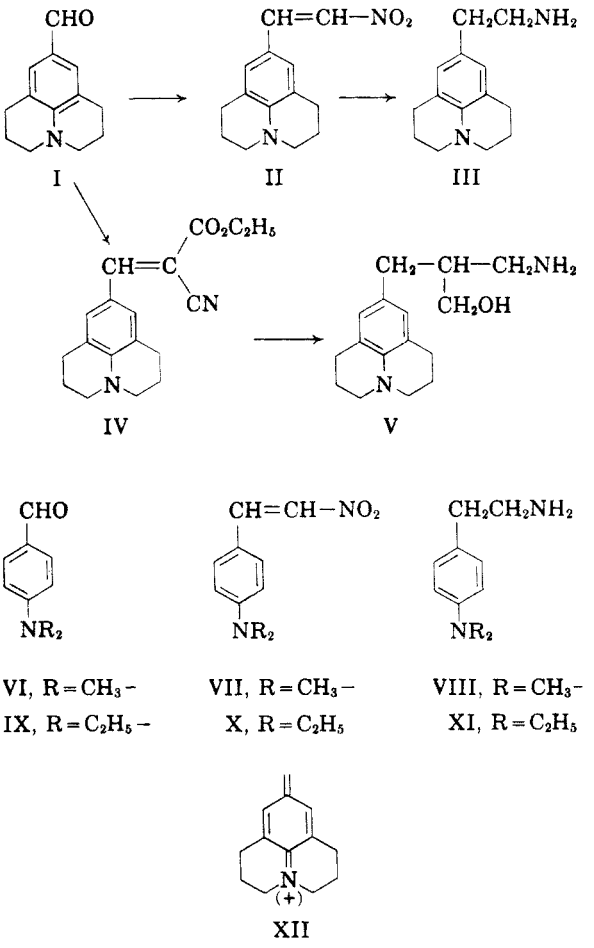
The syntheses of several new substituted dialkylamino-β-phenethylamines having potential physiological interest have been described.

4-Dimethylamino- and 4-diethylamino-β-phenethylamine, and 9-(β-aminoethyl)julolidine were synthesized to examine the influence of 4-dialkylamino groups on the psychochemical activity of ring-substituted β-phenethylamines. The effects of the position and number of methoxyl and hydroxyl groups in the β-phenethylamine nucleus have been reported.[3–6] 9-(β-Aminoethyl)julolidine (III) may be regarded as a mescaline analog in which the 3- and 5-positions are occupied by alkyl groups and the 4-position by a dialkylamino group.

The synthetic routes employed are outlined in Chart I. Julolidine, obtained from the action of trimethylene chlorobromide on 1,2,3,4-tetrahydroquinoline,[7] was converted to aldehyde I in 91 per cent yield by treatment with dimethylformamide in the presence of phosphorus oxychloride.[8] Smith and Yu[9] have reported the preparation of I in 75 per cent yield by treatment of julolidine with N-methylformanilide and phosphorus oxychloride. The procedure of Worrall and Cohen[10] was found to be effective in converting aldehydes I, VI, and IX respectively to nitrovinyl compounds II, VII, and X. In each instance, the particular aldehyde was dissolved in an excess of nitromethane, treated with an aliphatic primary amine which acted as an alkaline condensation catalyst, and then was heated for a short time; the reaction was usually completed by keeping the reaction mixture at room temperature for about 48 hours. It was somewhat surprising to find that this procedure was altogether unsatisfactory for condensing 4-di-*n*-propylaminobenzaldehyde with nitromethane. In spite of the fact that a distinct color change occurred upon adding either an amine catalyst or sodium methoxide to the reactants, only unreacted aldehyde could be isolated from the final reaction mixture.

CHART I



Anhydrous sodium methoxide, which failed to bring about the condensation of I with nitromethane, was found to be an excellent catalyst for the reaction of I with ethyl cyanoacetate under conditions similar to those employed for preparing II, VII, and X. In this manner, it was found that 3 - (9 - julolidyl) - 2 - carbethoxyacrylonitrile (IV) could be obtained in 90 per cent yield.

The reduction of II, VII, and X to the corresponding β-arylethylamines III, VIII, and XI

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(3) Benington, Morin, and Clark, *J. Org. Chem.*, **19**, 11 (1954).
(4) Benington, Morin, and Clark, *J. Org. Chem.*, **20**, 102 (1955).
(5) Benington, Morin, and Clark, *J. Org. Chem.*, **20**, 292 (1955).
(6) Clark, Fox, Benington, and Morin, *Federation Proc.*, **13**, 27 (1954).
(7) Glass and Weissberger, *Org. Syntheses*, **26**, 40 (1946).
(8) British Patent 607,920 (1948); *Chem. Abstr.*, **43**, 2232 (1949).
(9) Smith and Yu, *J. Org. Chem.*, **17**, 1281 (1952).
(10) Worrall and Cohen, *J. Am. Chem. Soc.*, **66**, 842 (1944).

was accomplished with lithium aluminum hydride.[11] The hydrochlorides of these bases were found to undergo darkening on exposure to air and light. It was particularly noticed that the hydrochloride of III, which was isolated initially as colorless crystals, underwent a color change to a pink solid upon exposure to air and light for a period of several days. Smith and Yu[9] have commented that many 9-substituted julolidines undergo photoxidation to highly colored compounds which are probably quinoidal structures derived from an ionic form such as XII. It is believed that the color change which takes place in the hydrochloride of III is limited to a surface reaction, because the colored compound can be recrystallized to give again colorless material.

dl - 3 - (9 - Julolidyl) - 2 - hydroxymethyl - 1 - aminopropane (V) was prepared by reduction of IV with lithium aluminum hydride.[11] Dornow, Messwarb, and Frey[12] have shown that cross-conjugated —CH=C(CN)(CO_2R) groups present in a number of similar 3-aryl-2-carbethoxyacrylonitriles undergo complete reduction to the saturated amino alcohols. Considerable difficulty was met in attempting to purify the hydrochloride of V. Both the compound and its solutions in organic solvents undergo extensive darkening during manipulations in air. Analytical data obtained from a sample of the colorless product are only in fair agreement with the calculated values for the hydrochlorides of V.

Both *in vivo* and *in vitro* biochemical studies have been undertaken to determine whether these amino compounds possess mescaline-like activity. The results of this phase of the investigation will be reported in an appropriate journal at some later date.

EXPERIMENTAL[13]

9-(β-Nitrovinyl)julolidine (II). Julolidine was obtained from the reaction of 1,2,3,4-tetrahydroquinoline with trimethylene chlorobromide following the procedure of Glass and Weissberger;[7] the vacuum distilled product, b.p. 121–122°/2.5 mm., was used to prepare the aldehyde. To a precooled mixture of 57 g. of phosphorus oxychloride and 13.5 g. of dimethylformamide was added a cold solution of 24.5 g. of julolidine in 15 ml. of dry ether. The reaction mixture was heated on a steam-bath for 1.5 hours and then was hydrolyzed by pouring into an ice-water mixture. The resulting clear green solution was made alkaline with 20% sodium hydroxide solution and cooled. The crude aldehyde, which separated as a green solid, was collected, washed with water, and air-dried. After recrystallization from ethanol-water pure 9-julolidinecarboxaldehyde (I) was obtained; yield, 26 g. (91%); m.p. 83–84° (reported,[9] 83°).

To a warm solution of 6.0 g. of I in 6.3 ml. of redistilled nitromethane was added 0.16 ml. of *n*-amylamine (5 mole-%). The deep-red solution was heated on a steam-bath for one minute and then kept at room temperature for 48 hours. The red crystalline mass was collected and washed with ethyl acetate-petroleum ether; when combined with a second crop of crystals, obtained by concentrating the mother liquor and washings, the total product amounted to 5.9 g. of deep-red plates. Recrystallization from benzene-petroleum ether afforded 3.5 g. (48%) of pure 9-(β-nitrovinyl)-julolidine melting at 142–143°.

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: C, 68.9; H, 6.55; N, 11.5. Found: C, 68.7; H, 6.65; N, 11.8.

9-(β-Aminoethyl)julolidine (III). Reduction of II with lithium aluminum hydride by the procedure of Ramirez and Burger[11] gave the 9-(β-aminoethyl)julolidine. Using the Soxhlet extraction technique, 3 g. of II and 2.6 g. of lithium aluminum hydride in 250 ml. of absolute ether gave 3.3 g. (40%) of *9-(β-aminoethyl)julolidine dipicrate* as small yellow prisms, m.p. 166–167° (dec.), from ethanol.

Anal. Calc'd for $C_{26}H_{26}N_8O_{14}$: C, 46.6; H, 3.9; N, 16.6. Found: C, 46.8; H, 3.8; N; 16.4.

The *dipicrate* was converted to the *dihydrochloride* by dissolving 2.8 g. of the dipicrate in about 250 ml. of boiling water and then adding 10 ml. of hydrochloric acid; after cooling and filtering off the precipitated picric acid, the filtrate was extracted with three 15-ml. portions of nitrobenzene to remove dissolved picric acid and finally twice extracted with ether. Concentration of the aqueous solution under reduced pressure gave 1.0 g. (83%) of 9-(β-aminoethyl)julolidine dihydrochloride, m.p. 246–248°, from methanol-ether-ethyl acetate.

Anal. Calc'd for $C_{12}H_{22}Cl_2N_2$: Cl, 24.6; N, 9.7. Found: Cl, 24.3; N, 9.8.

3-(9-Julolidyl)-2-carbethoxyacrylonitrile (IV). To 4 g. of I, 2.5 g. of ethyl cyanoacetate, and sufficient methanol to give a clear solution was added 50 mg. of anhydrous sodium methoxide. The reaction mixture was refluxed for three minutes and then allowed to remain at room temperature for about 12 hours. On cooling, the product crystallized as bright-orange plates, melting at 190–191°; yield, 5.3 g. (90%). The melting point was unchanged after recrystallization from a methanol–chloroform mixture.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.9; H, 6.8; N, 9.5. Found: C, 72.5; H, 6.5; N, 9.7.

Reduction of IV *to dl-3-(9-julolidyl)-2-hydroxymethyl-1-aminopropane* (V). The reduction 4.7 g. of IV with 3.8 g. of lithium aluminum hydride in 250 ml. of absolute ether was carried out in the same manner as described for the conversion of II to III. The product was worked up by first adding sufficient water to the reaction mixture to cause the precipitation of lithium aluminate and then decanting the ether layer. After drying the etheral solution over magnesium sulphate, the crude hydrochloride of V precipitated upon treatment with anhydrous hydrogen chloride. The colorless crude product, m.p. 170–175°, gradually darkened on exposure to air and light and was found difficult to purify by conventional methods.

Anal. Calc'd for $C_{16}H_{25}ClN_2O$: C, 64.8; H, 8.4; N, 9.4; Cl, 12.0. Found: C, 65.0; H, 7.9; N, 9.21; Cl, 11.9.

p-Dimethylamino-β-phenethylamine (VIII). Following the procedure of Worrall and Cohen,[10] a mixture of 15 g. of purified *p*-dimethylaminobenzaldehyde (VI), 15 ml. of redistilled nitromethane, and 0.5 ml. of *n*-butylamine was warmed on a steam-bath for one minute and then allowed to stand at room temperature for two days. The crude β-nitrostyrene (VII) was collected on a filter and washed with methanol to remove dark-colored impurities; yield, 16.8 g. (87%); ruby-red plates, m.p. 182–183° [reported[10] 179–180.5°] from a large volume of methanol.

The crude nitrostyrene (16.7 g.) was reduced in the manner described above using 15.5 g. of lithium aluminum hydride in 850 ml. of absolute ether. The product was isolated as the *dipicrate;* yield 25.9 g. (56%); m.p. 177–178° (dec.) from ethanol-ethyl acetate.

Anal. Calc'd for $C_{22}H_{22}N_8O_{14}$: C, 42.4; H, 3.5. Found: C, 42.6; H, 3.7.

(11) Ramirez and Burger, *J. Am. Chem. Soc.*, **72**, 2782 (1950).

(12) Dornow, Messwarb, and Frey, *Ber.*, **83**, 445 (1950).

(13) Melting points are uncorrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill.

The picrate (24 g.) was converted to the *dihydrochloride* of VIII by essentially the procedure described for the preparation of the hydrochloride of base III; yield 8.0 g. (88%); m.p. 224–225° (dec.)[14] after recrystallization from methanol-ethyl acetate ether.

Anal. Calc'd for $C_{10}H_{18}Cl_2N_2$: Cl, 30.0; N, 11.8. Found: Cl, 29.9; N, 11.7.

p-Diethylamino-β-nitrostyrene (X). A mixture of 14 g. of *p*-diethylaminobenzaldehyde (IX), 10 ml. of redistilled nitromethane, and 0.4 ml. of *n*-butylamine was first warmed for one minute (steam-bath) and then kept at room temperature for 20 hours. The semisolid, dark reaction product was triturated with methanol, cooled, and the crude β-nitrostyrene was collected. After recrystallization from the minimum quantity of methanol, 10.6 g. (60%) of pure X was obtained as ruby-red prismatic plates melting at 99–100°.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: C, 65.5; H, 7.3; N, 12.7. Found: C, 65.4; H, 7.1; N, 12.6.

p-Diethylamino-β-phenethylamine (XI). Reduction of 2.2 g. of *p*-diethylamino-β-nitrostyrene with 1.9 g. of lithium aluminum hydride in 100 ml. of absolute ether and treatment as described previously gave 1.8 g. (66%) of the crude dihydrochloride of XI. Repeated recrystallizations from methanol-ethyl acetate-ether solutions were required to obtain 500 mg. (19%) of the pure salt, m.p 206–208° (dec.).

Anal. Calc'd for $C_{12}H_{22}Cl_2N_2$: Cl, 26.8; N, 10.6. Found: Cl, 26.6; N, 10.5.

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(14) von Braun and Blessing, *Ber.*, 56, 2153 (1923) have reported a preparation of VIII by reduction of *p*-dimethylaminobenzyl cyanide with sodium and alcohol. These workers describe the hydrochloride of VIII as an oil; their reported analysis of the picrate of VIII, m.p. 133–135°, corresponds to a product containing 1 mole of picric acid per mole of VIII.