

THE PREPARATION OF MANNICH BASES RELATED TO GRAMINE

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Recent interest in the chemistry of Mannich bases derivable from indole (1, 2) and its derivatives (3, 4) prompts us to report on work done in this field some years ago. At that time it was deemed desirable to add the indole nucleus to the list of basically substituted heterocyclic systems under investigation as potential antimalarials.

The compounds studied were all tertiary amines prepared from indole, 2-methylindole, or ethyl indole-2-carboxylate by treatment with formaldehyde and a secondary amine in glacial acetic acid solution. This procedure was the same as that used by Kuhn and Stein (5) and Supniewski and Serafin-Gajewski (6) in the preparation of gramine and 2-methylgramine respectively.

Indole and 2-methylindole were reactive enough to require the cooling of their reaction mixtures to avoid the formation of insoluble polymeric gums. However the electronegativity of the carbethoxyl group sufficiently lowered the reactivity of the indole nucleus to allow heating the reaction mixtures during the preparation of derivatives of 2-carbethoxyindole.

EXPERIMENTAL

A. *Materials.* Save as otherwise described below all starting materials were commercial products.

Ethyl indole-2-carboxylate. *o*-Nitrophenylpyruvic acid was prepared by the condensation of ethyl oxalate and *o*-nitrotoluene according to the method of DiCarlo (7). Reduction of this material with sodium hydrosulfite gave indole-2-carboxylic acid as described by Cornforth and Robinson (8). Refluxing the acid in ethanol solution for several hours gave a 90% yield of crystalline (m.p. 119–120°) ethyl indole-2-carboxylate after cooling the mixture.

1-Diethylamino-4-n-propylaminopentane. Over a period of two hours 24 g. of propionaldehyde was added dropwise with stirring to 64 g. of Noval diamine (1-diethylamino-4-aminopentane) kept at 0° in an ice-salt bath. A small amount of solid potassium hydroxide was added to the clear solution, and after standing for one hour the aqueous layer was removed. The organic layer was dried over crushed potassium hydroxide in the refrigerator overnight. The dried aldimine was distilled from fresh pellets of alkali, b.p. 124–128°/34–35 mm. The freshly distilled, colorless Schiff base was dissolved in 100 cc. of ethanol and reduced with hydrogen at a pressure of 3 atm. over a 5% palladium-charcoal catalyst. After removing the ethanol *in vacuo* the product was distilled; yield, 54.4 g. (68%), b.p. 128–135°/30–32 mm. Before being used the product was redistilled at atmospheric pressure, b.p. 234–236°.

When dry hydrogen chloride gas was bubbled through a solution of this diamine in dry ether a solid *dihydrochloride* precipitated. After recrystallization from ethanol and isopropyl alcohol the slightly hygroscopic white crystals melted at 219.5–220.5°.

Anal. Calc'd for $C_{12}H_{30}Cl_2N_2$: N, 10.27; Found: N, 10.14.

B. *The Mannich bases.* A solution of the indole compound in glacial acetic acid (about 5 cc./0.01 mole) was treated with a slight excess (about 10% over the equimolecular quantity) of a secondary amine and then with 37% aqueous formaldehyde solution. In those cases where the reaction mixture was initially homogeneous, *i.e.* when indole (I) or 2-methylindole (II) was used, considerable heat was evolved and external cooling was applied. With 2-carbethoxyindole (III), insoluble in the reaction mixture described here, the mix-

CHART I
COMPOUNDS PREPARED

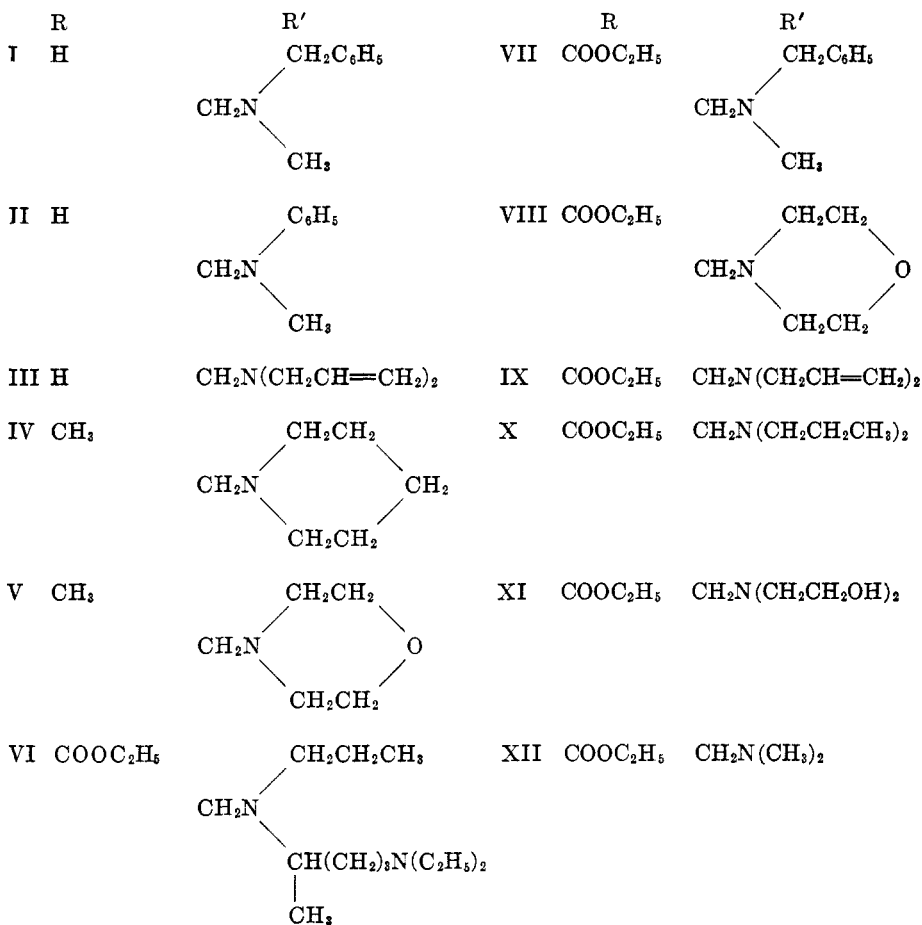
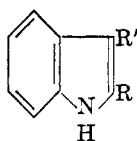


TABLE I
MANNICH BASES RELATED TO GRAMINE

COMPOUND NUMBER	EMPIRICAL FORMULA	M.P., °C.	YIELD, %	ANALYSIS	
				N	
				Calc'd	Found
I	C ₁₇ H ₁₈ N ₂	114	90	11.19	11.43, 10.95
II	C ₁₆ H ₁₆ N ₂	126-127	7	11.86	11.97
III	C ₁₅ H ₁₅ N ₂	77.5-78	60	12.38	12.47
IV	C ₁₅ H ₂₀ N ₂	156-157	79	12.27	12.36
V	C ₁₄ H ₁₈ N ₂ O	175-176	92	12.17	12.37
VI	C ₂₄ H ₂₉ N ₃ O ₂	78-79	80	10.47	10.19
VII	C ₂₀ H ₂₂ N ₂ O ₂	104-105	93	8.69	8.77
VIII	C ₁₆ H ₂₀ N ₂ O ₂	152-153	94	10.29	10.53
IX	C ₁₈ H ₂₂ N ₂ O ₂	100-101	88	9.39	9.59
X	C ₁₈ H ₂₆ N ₂ O ₂	78-79	94	9.26	9.46
XI	C ₁₆ H ₂₂ N ₂ O ₄	105-107	70	9.15	9.31
XII	C ₁₄ H ₁₈ N ₂ O ₂	86-87	83	11.38	11.28

ture was heated on the steam-bath for several hours until complete solution was attained. After dilution with an excess of water and removal of non-basic material by extraction with ether the solution was made basic with an excess of aqueous alkali. The precipitated product was then collected by filtration or extraction with ether and purified by crystallization from a suitable solvent. A summary of the properties of the compounds prepared in this manner is given in the accompanying table.

SUMMARY

A series of compounds resembling gramine have been prepared by the use of the Mannich reaction. The reagents employed were indole, 2-methylindole or 2-carbethoxyindole, formaldehyde, and various secondary amines.

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