[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF MADRAS]

N-Mannich Bases of 3-Substituted Indoles and Alkylations with Some N-Indolylmethyltrimethylammonium Iodides[1,1a]

S. SWAMINATHAN, S. RANGANATHAN, AND S. SULOCHANA

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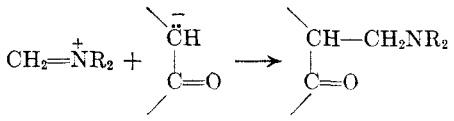
A few selected 3 and 2,3-substituted indoles have been subjected to the Mannich reaction to furnish N-Mannich bases. 1-Dimethylaminomethylskatole methiodide has been shown to have alkylating properties comparable with those of 1-methylgramine methiodide. On the other hand, 1-dimethylaminomethylskatole, 1-dimethylaminomethyl-3-cyanoindole, and the methiodide of the latter have been found to be inert as alkylating agents.

The observation that carbazole[2,3] and skatole[4] participate in the Mannich reaction to give N-Mannich bases prompted the investigation of the Mannich reaction of other 3 and 2,3-substituted indoles. In fact, though considerable work has been reported on the Mannich reaction of compounds containing acidic hydrogen on carbon, only a few examples of Mannich reaction with compounds containing acidic hydrogen on nitrogen are known. Among these compounds are succinimide and phthalimide,[2,3,5-7] benzimidazole,[8] benztriazole,[8] benzthiazole-2-thione,[9] 4-quinazolone,[10] pyrazole,[11] isatin,[3] 2,4-thiazolidinedione,[12] hydantoins,[12] uracil,[12] alkylnitramines,[12] and pyridazones,[13] all of which give N-dialkylaminomethyl bases when subjected to the Mannich reaction.

Indole and indoles substituted in positions other than 3 invariably give 3-dialkylaminomethylindoles. According to Lieberman and Wagner,[14] the Mannich reaction is the result of the addition of a methylene ammonium cation or a protonated dialkyaminomethanol to a carbanion:



The formation of 3-dialkylaminomethylindoles must therefore be due to the attack by one or other of the above cationic intermediates at the 3 carbon which, of course, has a negative charge in one of the resonance forms of indole. It seemed possible that with a substituent present at the 3 carbon the intermediate cation might attack the nitrogen atom itself which has a lone pair of electrons to give rise to an N-Mannich base and a few 3 and 2,3-substituted indoles were therefore subjected to the Mannich reaction.

Skatole which was recently reported[4] to give an excellent yield of N-dimethylaminomethylskatole (I) also furnished the piperidino and the morpholino bases, although in lower yields. With formaldehyde and dimethylamine under more drastic conditions than those employed for the preparation of N-Mannich bases of skatole, 3-ethylindole, 3-cyanoindole, 2,3-dimethylindole, and 2-methyl-3-ethylindole gave the corresponding N-dimethylaminomethyl bases in yields varying from 12 to 49%. With the same reactants 3-benzylindole, 2-methyl-3-benzylindole, and tetrahydrocarbazole did not furnish basic products; however neutral products were isolated which on the basis of their analytical values and infrared spectra are considered to be substituted bis-N-indolylmethanes.

In view of the ease of formation of C-Mannich bases from pyrrole[15] it was also of interest to see if 2,5-dimethylpyrrole would undergo the Mannich reaction. Indeed, under relatively mild conditions, it gave a 51% yield of 1-dimethylaminomethyl-2,5-dimethyl pyrrole.

C-Mannich bases of the type of gramine and their quaternary salts have been found[16] to be excellent alkylating agents and it was considered desirable to study alkylations using some of the above N-Mannich bases and their methiodides. 1-Di-

(1) From theses presented by S. Ranganathan and S. Sulochana to the University of Madras in partial fulfillment of the requirements for the M.Sc. degree.

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(2) J. R. Feldman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942).

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(5) W. I. Weaver, J. K. Simons, and W. E. Baldwin, *J. Am. Chem. Soc.*, **66**, 222 (1944).

(6) M. B. Moore and R. T. Rapela, *J. Am. Chem. Soc.*, **68**, 1657 (1946).

(7) R. O. Atkinson, *J. Chem. Soc.*, 1329 (1954).

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(11) R. Huttel and P. Jochum, *Ber.*, **85**, 820 (1952).

(12) C. C. Bombardieri and A. Taurins, *Can. J. Chem.*, **33**, 923 (1955).

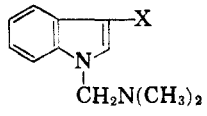
(13) H. Hellmann and I. Löschmann, *Ber.*, **89**, 594 (1956).

(14) S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

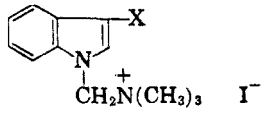
(15) W. Hertz, K. Dittmer, and J. Cristol, *J. Am. Chem. Soc.*, **69**, 1698 (1947).

(16) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

methylaminomethylskatole (I) and 1-dimethylaminomethyl-3-cyanoindole (III) were selected for this purpose so that the effect of such oppositely polar substituents as methyl and cyano on the ease of alkylation may be ascertained.



I, X = CH_3 III, X = CN



II, X = CH_3 IV, X = CN

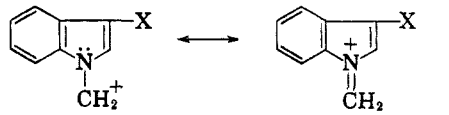
The base I and its methiodide (II) furthermore, as pointed out in an earlier publication,[4] bear a close structural resemblance to 1-methylgramine and its methiodide respectively and it was of interest to compare their reactivities as alkylating agents.

Alkylations of sodium cyanide and ethyl acetamidocyanoacetate with II have been reported.[4] Whereas the reaction of II with sodium cyanide was found to give 1-skatylacetamide and 1-skatylacetic acid in addition to some skatole, the reaction of sodium cyanide with the free base (I) itself gave only skatole and none of the other products. The base (I) was, in fact, found to reverse to skatole by merely heating with water, differing in this respect from gramine and 1-methylgramine. This reversal to skatole was more pronounced in the presence of alkali. With a view to isolating 1-skatylacetonitrile, if formed, the base (I) was treated with a mixture of sodium cyanide and acetic acid, conditions under which 7-azagramine has been converted[17] to the corresponding nitrile. Only skatole was obtained again and no nitrile.

Like 1-methylgraminemethiodide,[18] the methiodide (II) reacted readily with the sodio derivative of diethylmalonate to give the expected alkylated ester which was hydrolyzed to give a 36% yield of β-(1-skatyl)-α-carboxypropionic acid. The latter was decarboxylated in 74% yield to β-(1-skatyl)-propionic acid. The same alkylation when done with the free base (I) did not give the expected product; the product isolated after treatment with alkali was skatole formed by hydrolysis of I. The methiodide (II) resembled[19] 1-methylgramine methiodide also in its reaction with phenylmagnesium bromide whereby 1-benzylskatole was obtained in 63% yield. The same parallelism in alkylating properties between the two sets of compounds was noted with some amine exchange reactions[20] that were run. The methiodide (II) underwent amine exchange readily with piperidine and morpholine to give 1-piperidinomethylskatole and 1-morpholinomethylskatole, respectively. The free base (I) did not undergo any exchange when refluxed with piperidine.

As regards III and its methiodide (IV), both of them proved extremely unreactive as alkylating agents. The base (III) reacted sluggishly toward methyl iodide and IV was obtained only after prolonged treatment. When IV was treated with sodium cyanide either the starting methiodide or 3-cyanoindole was obtained depending upon the conditions of the reaction but no alkylation product. The inertness of IV was further emphasized by failure to effect any reaction between it and the sodio derivative of ethyl acetamidocyanoacetate, both in refluxing ethanol and in refluxing *n*-butyl ether. As in the case of I, III was found to reverse to the parent 3-cyanoindole when refluxed with alkali. Similar treatment of IV furnished after acidification 3-carboxy-1-dimethylaminomethylindole methiodide. In connection with the attempted alkylation of ethyl acetamidocyanoacetate with IV it was also of interest to condense a Mannich base of ethyl acetamidomalonate with 3-cyanoindole under conditions worked out by Butenandt *et al.*[21] for a similar condensation with indole. When ethyl α-piperidinomethyl-α-acetamidomalonate was allowed to react with 3-cyanoindole, only unreacted 3-cyanoindole and 1-piperidinomethyl-3-cyanoindole were obtained and no condensation product.

Structurally, II and IV belong to the class of quaternary ammonium salts which cannot alkylate by a mechanism of elimination and addition;[16] if they alkylate at all, they must do so by a direct substitution mechanism as is the case with 1-methylgramine methiodide. The intermediate in such a mechanism is a carbonium ion of the type V which may be stabilized by resonance with the form VI.



Va, X = CH_3 b, X = CN

VIa, X = CH_3 b, X = CN

Its formation depends on the ease of scission of the bond linking the quaternary nitrogen to the adjacent methylene carbon in the parent quaternary salt. The difference in alkylating properties of II and IV may then be attributed to this scission which, as may be expected, will be favored when X is electron-releasing methyl group and retarded when X is the electron-withdrawing cyano group.

EXPERIMENTAL

1-Piperidinomethylskatole. Acetic acid (4.5 ml.), piperidine (2.6 ml., 0.026 mole), formalin (36%; 3 ml., 0.036 mole), and skatole (4 g., 0.030 mole) reacted together as described[4] in

(17) M. Robison and B. Robison, *J. Am. Chem. Soc.*, **78**, 1247 (1956).

(18) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 663 (1949).

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(21) A. Butenandt, H. Hellmann, and E. Renz, *Z. Physiol. Chem.*, **284**, 175 (1949).

the preparation of 1-dimethylaminomethylskatole. The reaction mixture was then made alkaline and extracted with ether. The base was then extracted from the ether solution with *N* hydrochloric acid and regenerated with alkali. Ether extraction furnished the crude base which was distilled *in vacuo;* b.p. 162°/2 mm.; yield 3.6 g. (51%). The picrate was crystallized from methanol; m.p. 162–165°.

Anal. Calcd. for $C_{21}H_{23}O_7N_5$: C, 55.1; H, 5.1. Found: C, 55.4; H, 5.3.

The base also furnished a methiodide which in spite of several crystallizations had m.p. 160–180° but which analyzed correctly.

Anal. Calcd. for $C_{16}H_{23}N_2I$: C, 51.8; H, 6.2. Found: C, 51.5; H, 6.3.

1-Morpholinomethylskatole obtained similarly was a viscous liquid; b.p. 160°/1 mm.; yield, 31%. It gave a picrate, m.p. 192–193°, after crystallization from methanol.

Anal. Calcd. for $C_{20}H_{21}O_8N_5$: C, 52.3; H, 4.6. Found: C, 52.7; H, 4.7.

1-Dimethylaminomethyl-3-ethylindole. To an ice cold aqueous solution of dimethylamine (17 ml., 16%, 0.060 mole) was added successively glacial acetic acid (11.5 ml.) and formalin (5.5 ml., 36%, 0.066 mole) at such a rate that the temperature did not rise above 0°. The solution was then mixed with 3-ethylindole[19,22,23] (8.4 g., 0.058 mole) and stirred for 4 hr. at room temperature when an additional amount of acetic acid (10 ml.) was added. The mixture was then heated for 4 hr. on a water bath, cooled, made alkaline, and extracted with ether. The ether solution was extracted with an excess of *N* hydrochloric acid, the acid extract made alkaline with 20% sodium hydroxide solution and extracted with ether. The ether extract was dried, the ether was removed and the residual liquid was distilled *in vacuo;* b.p. 132–136°/1.5 mm., yield 2 g. (18%). The base furnished a yellow picrate which was crystallized from methanol; m.p. 204–205°.

Anal. Calcd. for $C_{19}H_{21}O_7N_5$: C, 52.9; H, 4.9. Found: C, 52.8; H, 5.0.

3-Cyanoindole. The following method of preparation proved superior to those previously reported.[24,25] A solution of indole-3-aldoxime (18 g.) in 98% formic acid (100 ml.) was heated on a water bath for 1.5 hr., poured into iced water (600 ml.) and the product filtered and dried; m.p. 170–172°; yield, 10.3 g. (64%).

1-Dimethylaminomethyl-3-cyanoindole (III). To an ice cold aqueous solution of dimethylamine (20 ml., 27%, 0.12 mole) was added successively acetic acid (17 ml.) and formalin (10 ml., 36%, 0.12 mole) maintaining the temperature below 5°. 3-Cyanoindole (10.7 g., 0.075 mole) was then added and the mixture heated on a water bath with stirring in an atmosphere of nitrogen for 8 hr. The mixture was made alkaline with 20% sodium hydroxide solution, cooled, and filtered. The solid thus obtained was dissolved in ether and the solution filtered from some undissolved matter and extracted twice with excess *N* hydrochloric acid. The combined acid extracts when made alkaline furnished the base; m.p. 85–87°; yield, 7.2 g. (49%). After a crystallization from petroleum ether (60–80°) the product had m.p. 88–90°.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.4; H, 6.6. Found: C, 72.8; H, 6.6.

The infrared spectrum of the base in chloroform showed strong absorption at 4.5μ (CN) but no absorption around 3μ (NH).

1-Dimethylaminomethyl-3-cyanoindole methiodide (IV). A solution of methyl iodide (13.6 g., 0.096 mole) in dry ether (50 ml.) was added in one portion to a solution of III (5.6 g., 0.028 mole) in dry ether (100 ml.) cooled in ice. The methiodide crystallized out slowly on leaving aside for a few days at room temperature; m.p. 190–192°, yield 5.6 g. (59%). In some runs the product that separated was found to be a mixture of the free base and the methiodide requiring further treatment with methyl iodide. Also addition of some ethanol appeared to hasten the formation of the methiodide. The analytical sample obtained by recrystallization from hot water had m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{16}N_3I$: C, 45.8; H, 4.7. Found: C, 45.7; H, 4.9.

1-Dimethylaminomethyl-2,3-dimethylindole. To an ice cold solution of dimethylamine hydrochloride (2.5 g., 0.03 mole) in sodium hydroxide solution (12 ml., 10%, 0.03 mole) was added glacial acetic acid (4.5 ml.) and formalin (3 ml., 36%, 0.036 mole) as usual and the solution was then mixed with 2,3-dimethylindole[26] (4.35 g., 0.03 mole). The mixture was stirred for 4 hr. at room temperature and then on a water bath for 4 hr. On working up the reaction mixture as described for the preparation of 1-dimethylaminomethyl-3-ethylindole, crude base (*ca.* 2 g.) was obtained which was distilled *in vacuo;* b.p. 154–156°/4 mm. The distillate solidified when cooled and was crystallized from petroleum ether (60–80°); m.p. 82°; yield 0.7 g. (12%).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0. Found: C, 76.7; H, 8.7.

1-Dimethylaminomethyl-2-methyl-3-ethylindole. Employing a solution of dimethylamine hydrochloride (1.7 g., 0.02 mole) in 10% sodium hydroxide solution (8 ml., 0.02 mole), glacial acetic acid (4 ml.), 36% formalin (2 ml., 0.024 mole), and 2-methyl-3-ethylindole[26] (3.2 g., 0.02 mole) and carrying out the reaction as described above, the base (1.2 g., 28%) was obtained; b.p. 154–158°/2 mm. The picrate was crystallized from ethanol; m.p. 186–187°.

Anal. Calcd. for $C_{20}H_{23}O_7N_5$: C, 53.9; H, 5.2; Found: C, 53.8, H, 5.5.

1-Dimethylaminomethyl-2,5-dimethylpyrrole. To dimethylamine hydrochloride (4.3 g., 0.053 mole) dissolved in water (3 ml.) was added successively 36% formalin (5 ml., 0.06 mole) and 2,5-dimethylpyrrole[27] (5 g., 0.053 mole). The mixture warmed up and was allowed to stand overnight. The homogeneous solution was poured into ice cold 20% sodium hydroxide solution (15 ml.) and extracted with ether. The ether extract after removal of solvent furnished a syrupy liquid which, when distilled *in vacuo* at 100°/2 mm., gave colorless crystalline product (4 g., 51%). A portion was crystallized from petroleum ether (60–80°); m.p. 93–96°.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.0; H, 10.6. Found: C, 70.7; H, 10.3.

3-Benzylindole. The preparation of this indole by the Fischer method is mentioned in a patent,[28] but details are not given. The following procedure proved satisfactory:

The crude phenylhydrazone obtained from phenylhydrazine (10.5 g., 0.097 mole) and hydrocinnamaldehyde (13 g., 0.097 mole) was mixed with anhydrous zinc chloride (1.5 g.) in a flask provided with a condenser and the mixture heated to and maintained at 240° for 0.5 hr. The mixture was cooled and extracted with petroleum ether (60–80°) repeatedly. The extracts when cooled furnished crude product which was recrystallized from the same solvent to give material (2.7 g.) m.p. 98–103°. This was mixed with the petroleum ether insoluble residue and the combined material crystallized from a mixture of benzene and petroleum ether (60–80°) to give product m.p. 107–109°; yield 7 g.

Reaction of 3-benzylindole with dimethylamine and formalin. The reaction was carried out as usual with a solution of dimethylamine hydrochloride (1.8 g., 0.022 mole), in 10% sodium hydroxide (10 ml., 0.025 mole), glacial acetic acid (15 ml.), 36% formalin (1.6 ml., 0.019 mole), and 3-benzylindole (4.15 g., 0.02 mole). On working up the reaction mixture as

(22) G. R. Clemo, *J. Chem. Soc.*, 1695 (1936).

(23) H. Schmid, A. Ebnother, and P. Karrer, *Helv. Chim. Acta*, **33**, 1486 (1950).

(24) R. Pschorr and G. Hoppe, *Ber.*, **43**, 2543 (1910).

(25) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1950).

(26) E. Fischer, *Ann.*, **236**, 126 (186).

(27) D. M. Young and C. F. H. Allen, *Org. Syntheses*, **Coll. Vol. II**, 219 (1943).

(28) German patent, **38,784**.

in previous experiments, the acid extract furnished little basic material. However the ether solution remaining after acid extraction furnished neutral material which was crystallized from a mixture of benzene and petroleum ether; m.p. 173–175°; yield 1.3 g. After two recrystallizations from benzene, the product had m.p. 174–175°.

Anal. Calcd. for $C_{31}H_{26}N_2$: C, 87.3; H, 6.1. Found: C, 87.2; H, 6.0.

The infrared spectrum of this product in chloroform did not show any absorption near 3μ, suggesting the absence of —NH-group. The product is considered to be bis(3-benzyl-1-indolyl)methane.

Reaction of 2-methyl-3-benzylindole with dimethylamine and formalin. Under the same conditions as in the previous experiment, 2-methyl-3-benzylindole[29] (5.5 g.) furnished neutral material (1.16 g., m.p. 162–166°) but no base. The analytical sample was prepared by crystallization from a mixture of benzene and alcohol; m.p. 167–168°.

Anal. Calcd. for $C_{33}H_{30}N_2$: C, 87.2; H, 6.7. Found: C, 86.7; H, 6.5.

The infrared spectrum ($CHCl_3$) showed no absorption near 3μ, suggesting the absence of —NH-group. The product is considered to be bis(3-benzyl-2-methyl-1-indolyl)methane.

Reaction of tetrahydrocarbazole with dimethylamine and formalin. Tetrahydrocarbazole[30] (6.9 g.), under the same conditions as before, gave neutral product (1.4 g.) m.p. 203–204° but no base. After two crystallizations from benzene, the compound had m.p. 205–207°.

Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.7; H, 7.4. Found: C, 84.5; H, 7.3.

The infrared spectrum ($CHCl_3$) indicated the absence of —NH-group. The product is considered to be 9,9′-bis(tetrahydrocarbazolyl)methane.

Reaction of 1-dimethylaminomethylskatole (I) with sodium cyanide. The base I (5 g., 0.027 mole) was refluxed with a solution of sodium cyanide (5 g., 0.102 mole) in water (50 ml.) for 6 hr. and cooled. The solid was collected and crystallized from petroleum ether (60–80°). Skatole (2.1 g.) melting point and mixed melting point with an authentic specimen 91–92.5° was obtained.

Skatole (2 g.) was again obtained when a mixture of I (2.9 g.) sodium cyanide (4.4 g.), acetic acid (6 ml.), and water (45 ml.) was refluxed for 4 hr.

Decomposition of 1-dimethylaminomethylskatole (I) *to skatole.* (*a*) In water: The base (0.5 g.) was refluxed with water (10 ml.) for 24 hr. The mixture was cooled when a semi-solid separated. Crystallization of the semi-solid from petroleum ether (60–80°) furnished skatole (150 mg.) m.p. 89–90° undepressed by authentic skatole.

(*b*) In 10% sodium hydroxide solution: When the base (1 g.) was refluxed with 10% sodium hydroxide solution (10 ml.) for 16 hr. and then cooled, skatole (0.6 g., m.p. 89–91°) was obtained.

β-(1-Skatyl)-α-carboxypropionic acid. To a stirred solution of sodium (0.46 g., 0.02 g. at.) in ethyl malonate (16 g., 0.1 mole) dissolved at 80–90° was added 1-dimethylaminomethylskatole methiodide (6.7 g., 0.02 mole). The temperature was raised to and maintained at 130–140° for 10 hr. with continued stirring. Trimethylamine evolved steadily during this period at the end of which the bath temperature was raised and kept at 140–150° for an additional 2 hr. The mixture was cooled and refluxed with a solution of potassium hydroxide (20 g., 0.36 mole) in 80% ethanol (200 ml.) for 4.5 hr. The mixture was diluted with water (70 ml.) and concentrated to remove excess alcohol. The residue was extracted with two 30-ml. portions of benzene and the aqueous layer acidified. After overnight cooling the crystalline material was collected and redissolved in saturated sodium bicarbonate solution. After treatment with animal charcoal, the bicarbonate solution was acidified and cooled when the product (1.8 g., 36%) crystallized; m.p. 119–120°. After two crystallizations from a mixture of ethyl acetate and petroleum ether (60–80°), the product had m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.2; H, 5.3. Found: C, 63.6; H, 5.5.

β-(1-Skatyl)propionic acid. A solution of the substituted malonic acid (0.9 g.) in pyridine (10 ml.) was refluxed for 20 min. The pyridine was removed *in vacuo*, the residue cooled and acidified with 20% hydrochloric acid (10 ml.). The semi-solid which separated, solidified when cooled and was purified by dissolution and reprecipitation from sodium bicarbonate solution. The crude acid (550 mg., 74%; m.p. 79–80°) was crystallized three times from petroleum ether (60–80°); m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.9; H, 6.5. Found: C, 70.7; H, 7.0.

Attempted alkylation of ethyl malonate with 1-dimethylaminomethylskatole. A mixture of 1-dimethylaminomethylskatole (3.8 g., 0.02 mole) and ethyl malonate (4 g., 0.025 mole) was heated at 150–160° for 3.5 hr. The reaction mixture was worked up as described under the preparation of β-(1-skatyl)-α-carboxy propionic acid. No alkylated product was isolated from the acidified layer; the benzene extract furnished skatole (0.9 g.) m.p. 89–90°.

1-Benzylskatole. A solution of phenylmagnesium bromide (0.1 mole) in dry *n*-butyl ether (80 ml.) was stirred with 1-dimethylaminomethylskatole methiodide (7.2 g., 0.022 mole) for 80 hr. on a steam bath in an atmosphere of nitrogen. The reaction mixture was then cooled and decomposed with 100 ml. of *N* hydrochloric acid. The butyl ether layer was separated and mixed with an additional ether extract of the aqueous solution. The combined ether extracts were washed successively with water, sodium hydroxide solution, sodium thiosulfate solution, and water. After drying over anhydrous magnesium sulfate, the solvent was removed and the residual liquid distilled *in vacuo;* biphenyl distilled at 69–74°/1 mm. (m.p. 67.5–68°) followed by a fraction (3 g., 63%) at 147–152°/1 mm. The latter solidified when chilled and was crystallized from petroleum ether (60–80°); m.p. 70–71.5°. Two further crystallizations yielded material, m.p. 72–73.5° (lit.[31] m.p. 74–75°).

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.9; H, 6.8. Found: C, 87.2; H, 6.8.

Amine exchange reactions of 1-dimethylaminomethylskatole methiodide (II) *with* (*a*) *piperidine,* (*b*) *morpholine.* Piperidine (10 ml.) was refluxed with II (1 g.) for 3 hr. The mixture was cooled and filtered from the precipitated salt. The filtrate was concentrated under reduced pressure, the residue taken up in benzene and repeatedly washed with water. The dry benzene extract after removal of solvent furnished 632 mg. (52%) of liquid which gave a picrate m.p. and mixed m.p. 163–167° with an authentic sample of the picrate of 1-piperidinomethyl skatole.

When morpholine was used instead of piperidine, 315 mg. (26%) of the morpholine base was obtained. The picrate had m.p. and mixed m.p. 192–194° with an authentic sample of the picrate of 1-morpholinomethylskatole.

Attempted alkylation of sodium cyanide with IV. The methiodide IV (1.5 g., 0.0044 mole) was refluxed with a solution of sodium cyanide (1.5 g., 0.031 mole) in water (15 ml.) for 9 hr. The reaction mixture when cooled and filtered furnished the starting methiodide (0.7 g.) having m.p. and mixed m.p. 198–200° with an authentic specimen. Acidification of the filtrate did not furnish any product.

In a modification of the above procedure, an aqueous solution of IV (3.2 g., 0.009 mole) and sodium cyanide (2.5 g., 0.051 mole) was concentrated on a water bath and the dry residue heated to and maintained for 0.5 hr. at 300°. There was a vigorous evolution of gas during this period. The reac-

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tion mixture was then sublimed *in vacuo* and product (200 mg., m.p. 160–172°) collected at 200°/2 mm. After one crystallization from benzene, the material had m.p. and mixed m.p. 174–176° with an authentic specimen of 3-cyanoindole.

Attempted alkylation of ethyl acetamidocyanoacetate with IV. *Procedure A:* To a solution of sodium (0.29 g., 0.013 g. at.) in absolute ethanol (60 ml.) was added successively ethyl acetamidocyanoacetate (2.1 g., 0.012 mole) and IV (4.2 g., 0.012 mole) and the mixture was refluxed for 40 hr. The mixture was freed of solvent *in vacuo* and the residue triturated with water and filtered. The dark residue (2.2 g., m.p. 174–176°) was crystallized from ethanol; yield 1.17 g., m.p. 180–182°. Ether extraction of the aqueous filtrate as such and also after acidification did not furnish any material. The crystalline product was identified as the starting methiodide after a further crystallization from alcohol.

Procedure B: To powdered sodium (120 mg., 0.005 g. at.) in *n*-butylether (9 ml.) was added ethyl acetamidocyanoacetate (1.1 g., 0.006 mole). The mixture was heated with stirring at 130° in an atmosphere of nitrogen for 8 hr. To the resulting semi-solid was added IV (1.5 g.) and the mixture heated for an additional 6 hr. The solution was filtered hot and the filtrate, when cooled, furnished material (1.1 g.) having m.p. and mixed m.p. 198–200° with an authentic sample of IV. No other product could be obtained by concentrating the filtrate.

Treatment of III *with sodium hydroxide.* A mixture of III (0.5 g.) and 10% ethanolic sodium hydroxide solution (3 ml.) was refluxed for 5 hr. and the alcohol was removed. The residue was diluted with water and cooled overnight. The product (m.p. 171–172°, 454 mg.) was collected and recrystallized from benzene; melting point and mixed melting point with authentic 3-cyanoindole 174–176°.

3-Carboxy-1-dimethylaminomethylindole methiodide. The methiodide IV (2.3 g., 0.007 mole) was refluxed for 1 hr. with 10% sodium hydroxide solution (15 ml.). The mixture was cooled, filtered, and made acidic with hydriodic acid. The crude product was collected and crystallized from alcohol; m.p. 185–190°; yield 1 g. Repeated crystallizations from alcohol raised the m.p. to 202–204°.

Anal. Calcd. for $C_{13}H_{17}O_2N_2I$: C, 43.4; H, 4.8. Found: C, 43.6; H, 5.4. Neut. equiv.: Calcd. 360. Found: 353.2.

Ethyl-α-piperidinomethyl-α-acetamido malonate. Piperidine (3.3 g., 0.039 mole) was added to ethyl acetamidomalonate (8.7 g., 0.04 mole). Formalin (4 ml., 36%, 0.048 moles) was then added and the mixture was warmed on a waterbath for 5 min. and refrigerated overnight. The crude base (12 g.) was collected and crystallized from petroleum ether (60–80°); m.p. 67–68°; yield 8 g. (64%).

Anal. Calcd. for $C_{15}H_{26}O_5N_2$: C, 57.3; H, 8.3. Found: C, 57.3; H, 8.5.

Attempted alkylation of 3-cyanoindole with ethyl α-piperidinomethyl-α-acetamidomalonate. Under dry conditions a mixture of ethyl α-piperidinomethyl-α-acetamidomalonate (3.14 g., 0.01 mole), 3-cyanoindole (1.5 g., 0.011 mole), powdered sodium hydroxide (catalytic amount), and xylene (10 ml.) was refluxed with stirring in an atmosphere of nitrogen for 6 hr. The mixture was filtered hot, diluted with benzene, and extracted with dilute hydrochloric acid. The benzene extract furnished unreacted 3-cyanoindole (587 mg.) which after recrystallization from benzene had melting point and mixed melting point with authentic specimen 174–176°. The acid extract was made alkaline and extracted with ether. The ether extract furnished a solid which was crystallized from petroleum ether (60–80°); yield 1.3 g., melting point and mixed melting point with an authentic sample of 1-piperidinomethyl-3-cyanoindole 88–90°.

1-Piperidinomethyl-3-cyanoindole. To piperidine (0.86 g., 0.01 mole) cooled in ice was added successively acetic acid (2 ml.) and 36% formalin (1 ml., 0.012 mole), maintaining the temperature below 5°. 3-Cyanoindole (1.3 g., 0.009 mole) was added and the mixture heated for 8 hr. on a water bath and then poured into sodium hydroxide solution. The liquid which separated solidified when left overnight in the refrigerator and was crystallized from petroleum ether; m.p. 88–90°; yield 1.3 g. (54%).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.3; H, 7.2. Found: C, 75.6; H, 7.1.

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MADRAS 25, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pyrroles. XII. The Reaction of Pyrrolealdehydes with Arylacetonitriles[1,2]

WERNER HERZ AND JAY BRASCH[3]

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Triton B is an excellent catalyst for the preparation of pyrrole-substituted acrylonitriles from 2-pyrrolealdehyde. Secondary cyclic amines like piperidine, morpholine, and pyrrolidine, although capable of functioning as catalysts, enter into reaction with 2-pyrrolealdehyde and form bimolecular pyrrole Mannich bases. The acrylonitriles could not be hydrolyzed satisfactorily. Other attempts to prepare pyrrole analogs of stilbene are described.

In continuation of earlier work on the synthesis of 2-vinylpyrroles,[4] we were interested in preparing pyrrole analogs of stilbene. The decarboxylation of substituted cinnamic acids is a convenient method for the preparation of certain styrenes and stilbenes.[5] However, condensation between 2-pyrrolealdehyde and 2-*N*-methylpyrrolealdehyde, on the one hand, and phenylacetic acid on the other, could not be effected under the usual conditions.[6]

(1) Paper XI, W. Herz, *J. Org. Chem.*, **22**, 1260 (1957).

(2) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-436.

(3) Abstracted from the M.S. Thesis of Jay Brasch, August 1957.

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(6) See ref. 5, pp. 55–56, for leading references.