Separation of 5H-benzo[b]carbazole from chrysene. A mixture of 50 g. of commercial chrysene purified as described above, 500 ml. of acetic anhydride, 2 g. of finely powdered anhydrous zinc chloride, and 2500 ml. of acetic acid was gently refluxed for 1 hr. After cooling, the precipitate of pure chrysene (42 g.) was filtered, washed with acetic acid, and recrystallized from toluene. A sample of this hydrocarbon gave no coloration in sulfuric acid. Dilution of the filtrate with water to a volume of 6000 ml. produced a precipitation of 4 g. of less pure chrysene. Dilution of the second filtrate to a volume of 10 l. yielded 4 g. of 5-acetyl-5H-benzo[b]carbazole, from which the nonacetylated heterocycle could be recovered by treatment with potassium hydroxide in ethanol. 5H-benzo[b]carbazole gave a brown-yellow halochromism in sulfuric acid.

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PARIS (V^e^), FRANCE

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Pyridylethylation of Skatole, Benzotriazole, and Benzimidazole

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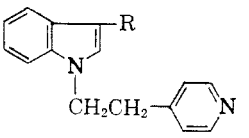
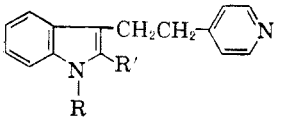
Skatole, 2-methylindole, benzimidazole, and benzotriazole have been pyridylethylated. Under alkaline conditions skatole yielded the 1-substituted derivative, 4-(3-methyl-1-indolylethyl)pyridine. The same product was obtained, in poor yield, when the reaction was carried out in boiling glacial acetic acid. Base catalyzed pyridylethylations of benzotriazole afforded mixtures of two, separable products. Ultraviolet spectral evidence indicates these to be the corresponding 1- and 2-substituted benzotriazole derivatives.

An earlier report[1] from these laboratories was concerned with the pyridylethylation of indole, *N* substitued indoles, and indene. The finding that certain of the derived indolylethylpyridines displayed an interestingly selective spectrum of central depressant effects[2] has stimulated further work in this area. The present paper deals with some aspects of this work, and in particular examines the course of the pyridylethylation reaction with related ring systems.

It is well known that indoles undergo substitution by electrophilic reagents preferentially at the 3-position—no doubt owing to the necessary participation of quinoid forms in the α-substitution process—but the orientation of further substituents is not so clear. Thus, apparently rate control in the Mannich reaction under either acidic or basic conditions results in the order of substitution, 3, *N*, 2[3]—except when stability of the product (as in the intramolecular Mannich-type cyclizations of tryptamines to tetrahydro-β-carbolines) overridingly directs reaction to the 2-position. On the other hand, presumably equilibrium control in Erlich-like reactions with aldehydes under more strongly acid conditions causes substitution to occur at the 3- and then the 2-position, the nitrogen being apparently unaffected.[4] Perhaps more pertinent is the report that skatole reacted with methyl vinyl ketone in a mixture of acetic acid and acetic anhydride to give (in poor yield) the more stable 2-substituted adduct.[5] It was, therefore, of interest to examine the pyridylethylation of skatole. Under alkaline conditions (sodium ethoxide in ethanol) skatole reacted with 4-vinylpyridine to yield 4-(3-methyl-1-indolylethyl)pyridine (I). The structural assignment is unequivocal in view of the reaction of indole under the same conditions to give I(R=H)[1] and of analogous experience with base catalyzed cyanoethylation (see references cited[1]). It would appear that the indole anion is involved in the rate determining step of these base catalyzed reactions. More interesting was the finding that the acid, boiling glacial acetic acid, catalyzed reaction of skatole with 4-vinylpyridine also afforded I, although in poor yield and accompanied by large



I. R = CH_3



II. R = H, R′ = CH_3
III. R = C_2H_5, R′ = H

(1) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).

(2) J. H. Mirsky, H. D. White, and T. B. O'Dell, *J. Pharmacol. Exptl. Therap.*, **125**, 122 (1959).

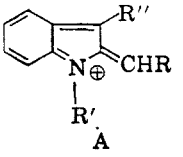
(3) (a) S. Swaminathan and S. Ranganathan, *J. Org. Chem.*, **22**, 70 (1957); *J. Org. Chem.*, **23**, 707 (1958); (b) J. Thesing and P. Binger, *Chem. Ber.*, **90**, 1419 (1957); (c) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1706 (1957).

(4)(a) H. v. Dobeneck and G. Maresch, *Hoppe-Seyler's Z. physiol. Chem.*, **289**, 271 (1952) [*Chem. Abstr.*, **49**, 5432 (1955)]; (b) H. v. Dobeneck and J. Maas, *Chem. Ber.*, **87**, 455 (1954); (c) A. Treibs and E. Hermann, *Hoppe-Seyler's Z. physiol. Chem.*, **299**, 168 (1955) [*Chem. Abstr.*, **50**, 943 (1956)]; (d) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(5) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957).

quantities of tarry, polymeric materials. The fact that the 1-substituted product is obtained under acidic or basic conditions suggests that pyridylethylation, like the Mannich reaction, is rate controlled. It was not ascertained whether or not more strongly acidic conditions (*e.g.* an acetic acid–acetic anhydride mixture) could alter the course of the reaction.

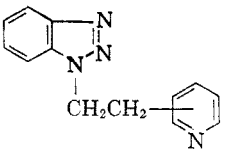
It should be mentioned that I gave an immediate, deep purple color in the Erlich test with *p*-dimethylaminobenzaldehyde, thus demonstrating that the 2-position was indeed unsubstituted.[6] 4-(1-Methyl-3-indolylethyl)pyridine (III. R=CH_3)[1] also gave a strong positive Erlich test whereas the 2,3-disubstituted analog, II, obtained by the pyridylethylation of 2-methylindole in boiling acetic acid, gave a negative test. On this basis, recent reports that 1,3-disubstituted indoles do not give the Erlich test[3a,7] require re-evaluation. Certainly, there would seem to be no *a priori* reason why a 1,3-disubstituted indole should not form an Erlich dye having the structure A. Inasmuch as there also seems to be no reason to doubt the structures assigned by the earlier workers to the compounds tested (ind-*N*-methyltryptophan[7] and its 1,3-reversed isomer[3a]), the negative tests may be ascribable to features peculiar to the substituents themselves. That, for example, cationic groups close to the indole nucleus are capable of inhibiting the reaction is suggested by the observation that gramine gives a negative test.



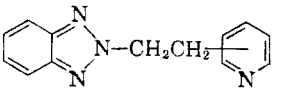
A

Benzotriazole offers an intriguing and closely related problem pertaining to the direction of substitution. It has been shown that alkylation of benzotriazole under alkaline conditions in alcohol solution yields both the 1- and 2-substituted benzotriazole derivatives.[8] The isomeric products have been found to be readily distinguishable on the basis of their ultraviolet absorption spectra in alcohol solution.[8b,c] The 1-substituted derivative is generally formed in somewhat larger amounts.[8a,b] Although one cannot base too much on simple yield data, the ratio of 1- to 2-isomer appears to vary directly with the reactivity of the alkylating agent; *e.g.*, based on the *per cent* yields reported by Krollpfeiffer, *et al.*, pertinent ratios are as follows: for benzyl chloride, 2.8; for methyl iodide, 1.7; for ethyl bromide, 1.1. Wiley and co-workers[9] have extensively studied the base catalyzed addition of benzotriazole and benz-substituted benzotriazoles to α,β-unsaturated carbonyl systems (acrylic acid, acrylonitrile, benzalacetophenone, *etc.*). In the absence of solvent, these conjugated systems were reported to react exclusively at the 1-position of benzotriazole itself,[9a] although presumably for steric reasons, just as exclusively at the 2-position of 4,7-disubstituted (chlorine, bromine) benzotriazoles.[9b,c]

In light of the foregoing it is particularly striking that pyridylethylation of the (unsubstituted) benzotriazole in alcohol solution with a few drops of a quaternary ammonium methoxide as base catalyst provided a mixture of both the 1- and 2-substituted products in which, on the basis of isolated *per cent* yields, the 2-isomer predominated. Thus, with 4-vinylpyridine the ratio of the amounts of 1-substituted (IV) to 2-substituted (V) benzotriazole derivative isolated was 0.65; with 2-vinylpyridine the corresponding ratio of VI to VII was 0.55. The isomeric products were conveniently separated by taking advantage of the circumstance that the 2-substituted benzotriazoles were quite soluble and the 1-substituted practically insoluble in petroleum ether (b.p. 60–70°). This accords with the reported greater solubility of the 2-isomers in nonpolar solvents.[8] An examination of the ultraviolet absorption spectra provided a firm basis for the structural assignments, IV and VI, showing the two maxima at *ca.* 255 and 280 mμ which are diagnostic for 1-substitution and V and VII the broad, single maximum at *ca.* 275 mμ characteristic of 2-substituted benzotriazoles[8b,c] (*cf.* Table I). It is apparent from Table I that absorption by the pyridine nucleus does not prevent identification of the isomers.



IV. 4-Pyridyl
VI. 2-Pyridyl



V. 4-Pyridyl
VII. 2-Pyridyl

Since both the alkylation and conjugate addition reactions are effected under alkaline conditions, it seems reasonable to implicate the benzotriazole anion in the rate determining step. If this be so, note should be taken of the fact that in the anion the nitrogen atoms in the 1- and 3-positions are indistinguishable. Therefore, on a purely statistical

(6) See F. Feigl, *Spot Tests*, Vol. II, 4th English Edition, Elsevier, Amsterdam, 1954, pp. 198–199; M. Strell, A. Zocher, and E. Kopp, *Chem. Ber.*, **90**, 1798 (1957) and references cited therein.

(7) J. Giral and J. Laguna, *Ciencia (Mex.)*, **10**, 83 (1950) [*Chem. Abstr.*, **44**, 10605 (1950)].

(8)(a) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Ann.*, **515**, 124 (1935); (b) F. Krollpfeiffer, H. Pötz, and A. Rosenberg, *Ber.*, **71**, 596 (1938); (c) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

(9)(a) R. H. Wiley, N. R. Smith, D. M. Johnson, and J. Moffat, *J. Am. Chem. Soc.*, **76**, 4933 (1954); (b) R. H. Wiley, K. F. Hussung, and J. Moffat, *J. Am. Chem. Soc.*, **77**, 5105 (1955); (c) R. H. Wiley and K. F. Hussung, *J. Am. Chem. Soc.*, **79**, 4395 (1957).

TABLE I

ULTRAVIOLET ABSORPTION OF BENZOTRIAZOLE DERIVATIVES[a]

Compound	λ_{max}, mμ	log ε
IV.HCl	257	3.93
	280	3.65
V.HCl	278	4.04
VI.HCl	260	4.00
	280 (shoulder)	3.68
VII.HCl	278	4.09
1-Methylbenzotriazole[b]	255	3.81
	283	3.68
2-Methylbenzotriazole[b]	275	3.90
Pyridine.HCl	255	3.72

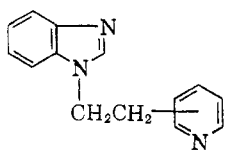
[a] Spectra determined on the hydrochloride salts in 95% ethanol using a Beckman Model DU spectrophotometer. [b] This data from Specker and Gawrosch[8c]; solvent: methanol.

basis one would expect the ratio of 1- to 2-substituted product to be 2. This suggests that alkylation with methyl iodide and ethyl bromide (but not benzyl chloride) as well as pyridylethylation occurs more readily at the 2- than at the 1-position.

In attempting to analyse these results it should be noted that the ultraviolet absorption spectrum of benzotriazole closely resembles that of a 1-substituted derivative whereas the spectrum of the benzotriazole anion just as closely resembles that of a 2-substituted isomer.[8b,c] It might then be inferred that the 1-substituted products are more stable than the 2, but that the electronic charge in the benzotriazole anion resides largely on the 2-nitrogen. On this basis the relative yields obtained in the irreversible (under the conditions) alkylation reactions[8a,b] seem at variance with the illuminating studies made by Kornblum, *et al.*[10] pertaining to the alkylation of ambident anions since these studies would lead to the prediction that the more an alkyl halide tended to react by an S_N1-like process the more it should effect 2-substitution. On the other hand, the reversible conjugate additions studied here and by Wiley and associates[9] have given results which at least are in accord with theory in that certainly under alkaline conditions the systems studied by the earlier workers would be more reactive than the vinylpyridines and would therefore be expected to yield a greater proportion of the more stable, 1-substituted product.[11] It is apparent, in any case, that the energetics of 1- *vs.* 2-substitution are closely balanced and that only slight changes in the nature of the reagents and, no doubt, conditions can markedly alter the course of the reaction.

The structure of the quite remarkably stable 2-substituted benzotriazoles has been the object of much study.[8,12] Their properties (ultraviolet and infrared[13] spectra, weak basicity, high solubility in nonpolar solvents and low melting point) can best be described in terms of a resonance hybrid, of which, in the absence of evidence to the contrary, the conventional quinoid canonical form (*cf.* V) is adopted here.

Reaction of benzimidazole with 2- or 4-vinylpyridine in the presence of base afforded in each case a single isolable product. Inasmuch as the alkylation and base catalyzed cyanoethylation of benzimidazole straightforwardly yield *N*-substituted derivatives,[14] there seems no reason to question formulation of the pyridylethylated products as VIII and IX. It is worth noting that although the anions



VIII. 4-Pyridyl
IX. 2-Pyridyl

of benzotriazole and of indazole[15] can be alkylated at the 2- as well as the 1-position, the anions of indole and of benzimidazole give no evidence of 2-substitution. Without doubt this is a reflection of the relative abilities of carbon and nitrogen to bear a negative charge and/or to act as nucleophilic reagents.

Structure-activity relationships. Many of these compounds display central depressant properties. The most striking, semiquantitatively measurable, pharmacological finding with the 4-(3-indolylethyl)pyridines is that these compounds, tested in mice, strongly inhibit amphetamine-stimulated motor activity at doses which have little or no effect on normal motor activity.[2] Comparison of the efficacies of close relatives has revealed some intriguingly specific structural requirements for this selectivity of biological action. This discussion will, therefore, be confined to a comparison of results obtained in these mouse tests.

The 4-(1-substituted 3-indolylethyl)pyridines (III, R = CH_3,[1] C_2H_5, $C_6H_5CH_2$[1]; R′ = H) are all about equally effective on stimulated and ineffective on normal activity. It would therefore appear that lipophilic balance, at least within this range, is not a determining factor. On the other

(10) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955) and preceding papers.

(11) The conditions (no solvent) used by Wiley, *et al.* would also favor product control.

(12)(a) K. v. Auwers, *Ber.*, **71**, 604 (1938); (b) see also D. D. M. Casoni, A. Mangini, R. Passerini, and C. Zauli, *Gazz. chim. ital.*, **88**, 977 (1958) [*Chem. Abstr.*, **53**, 18945 (1959)].

(13) Sadtler Laboratories, Philadelphia, Pa.

(14)(a) I. G. Farbenind. A. G., British Patent **457,621** (1936) [*Chem. Abstr.*, **31**, 3068 (1937)]; (b) see E. S. Schipper and A. R. Day in Elderfield, *Heterocyclic Compounds*, Vol. V, John Wiley and Sons, Inc., New York, 1957, p. 269.

(15) For references see R. C. Elderfield, *Heterocyclic Compounds*, Vol. V, John Wiley and Sons, Inc., New York, 1957, pp. 187–9.

hand, molecular geometry has a marked influence in that rearrangement of the indole substituents as in I and II sharply reduces the selectivity of the depressant action. 4-Skatylpyridine (X) is essentially without effect. In the indole series then, the biological properties under discussion seem to be distinctively provided by a III-type structure.

The considerably more polar benzimidazole derivatives (VIII, IX) are only weakly depressant on motor activity. The benzotriazole derivatives, of intermediate polarity, show intermediate inhibitory abilities. In direct contrast to the indole series, however, in the benzotriazole group it is the 2-pyridyl isomers (VI, VII) that display the selective antagonism to stimulated activity, the 4-pyridyl isomers (IV, V) being weaker and less discriminating in action. It apparently makes no difference, insofar as these biological properties are concerned, whether the benzotriazole nucleus is substituted at the 1- or 2-position. Of all the close analogs of III, the most potent depressants are 2- and 4-(3-indenylethyl)pyridine.[1] Both indene derivatives, however, are more general in their action, being almost as effective against normal as against stimulated activity. The inertness of 2-(1-naphthylethyl)pyridine[16] taken with the earlier indicated specificity of the 1,3-substituted indole structure makes it tempting to speculate as to the possible involvement of the unsaturated 5-membered ring in eliciting the depressant effects. In particular, the indolyl and indenyl derivatives could enter into reaction with oxidative enzyme systems.

EXPERIMENTAL[17]

The pyridylethylation of indoles. These were effected essentially as previously described for the preparation of corresponding derivatives.[1]

A. *4-(2-Methyl-3-indolylethyl)pyridine* (II). 2-Methylindole was treated with 4-vinylpyridine in boiling glacial acetic acid to give a 54% yield of II, m.p. 153–154° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{16}H_{16}N_2$:N (basic), 5.92. Found: N (basic), 5.77.

The *hydrochloride salt* showed m.p. 242–243° after recrystallization from ethanol-methanol.

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.46; H, 6.28; Cl, 13.00. Found: C, 69.90; H, 6.27; Cl (ionic), 12.97.

B. *4-(1-Ethyl-3-indolylethyl)pyridine* (III). The reaction of 1-ethylindole [b.p. 82–85° (0.7 mm.), n_D^{26} 1.5889][18] with 4-vinylpyridine in boiling glacial acetic acid afforded III, m.p. 47–50° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{17}H_{18}N_2$: N (basic), 5.59. Found: N (basic), 5.66.

The *hydrochloride salt* formed pale yellow crystals, m.p. 167–169°, from isopropyl alcohol–ether.

Anal. Calcd. for $C_{17}H_{19}ClN_2$: C, 71.18; H, 6.67; Cl, 12.36. Found: C, 71.26; H, 6.36; Cl (ionic), 11.99.

C. *4-(3-Methyl-1-indolylethyl)pyridine* (I). 1. *With base catalysis.* A mixture of 13.1 g. (0.1 mole) of skatole, 22.0 g. (0.21 mole) of freshly distilled 4-vinylpyridine, 0.5 g. of copper sulfate, and 50 ml. of ethanol containing 0.5 g. of sodium was heated in a sealed tube at 150° (oil-bath) for 10 hr. The cooled reaction mixture, diluted with toluene and filtered, was extracted with dilute hydrochloric acid. The acid solution was made basic and extracted with ether. Treatment of the ice-cold, dried ether solution with ethereal hydrogen chloride afforded a yellow precipitate which was recrystallized three times from isopropyl alcohol and once from ethanol to yield 9.0 g. (38%) of the *hydrochloride salt* of I in the form of yellow plates, m.p. 211–212°.

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.46; H, 6.28; Cl, 13.00. Found: C, 70.57; H, 6.18; Cl (ionic), 13.04.

Decomposition of the hydrochloride salt of I gave the base as an oil which could not be crystallized.

The salt gave a positive color test with an acid solution of *p*-dimethylaminobenzaldehyde, indicating that the indole nucleus was not substituted at the α position. 4-(1-Methyl-3-indolylethyl)pyridine[1] also gave a strong positive test. In comparison II gave a negative test.

2. *In acetic acid.* To a solution of 12.0 g. (0.09 mole) of skatole in 100 ml. of boiling glacial acetic acid was added, dropwise with stirring, 11.5 g. (0.11 mole) of freshly distilled 4-vinylpyridine containing 0.5 g. of hydroquinone. Heating under reflux was continued for 32 hr. Removal of the solvent *in vacuo* left a dark, tarry residue which was extracted with dilute hydrochloric acid. The acid solution was made alkaline and the precipitate exhaustively extracted with ether (considerable ether- and chloroform-insoluble, polymeric material remained). After a repetition of the acid-base extraction process, the dried ether solution was treated with ethereal hydrogen chloride in the cold. The resultant precipitate was repeatedly recrystallized from isopropyl alcohol to give 2.3 g. of material melting at 200–205°. Further recrystallization afforded I *hydrochloride*, m.p. 206–209°; a mixture with the product obtained under basic conditions showed m.p. 208–210°. The mother liquors from these recrystallizations afforded material which melted over a wide range and apparently was contaminated by vinylpyridine polymer which could not be removed.

Anal. Found: Cl (ionic), 13.04.

The pyridylethylation of benzotriazole. A. *With 4-vinylpyridine.* To a boiling solution of 40.0 g. (0.33 mole) of benzotriazole in 100 ml. of isopropyl alcohol containing 10 drops of a 40% methanolic solution of benzyltrimethylammonium methoxide was added, dropwise, 31.5 g. (0.3 mole) of undistilled 4-vinylpyridine. After being heated for 30 hr. at reflux the reaction solution was diluted with water and the precipitated oil was dissolved in ether. The ether extract was extracted with 5% hydrochloric acid, the acid extract made alkaline and extracted with ether. Drying and removal of the ether provided a residue which was extracted with hot petroleum ether (b.p. 60–70°). Upon cooling the solution deposited crystals which were twice recrystallized (with charcoal) from petroleum ether to yield 17.0 g. (25%) of colorless flakes, m.p. 92–95°. This is presumed to be *4-(2-benzotriazolylethyl)pyridine* (V).

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.68.

V *hydrochloride* formed colorless needles from isopropyl alcohol, m.p. 197–200°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 60.13; H, 4.74; Cl (ionic), 13.56.

The residual material which had not dissolved in petroleum ether was crystallized from benzene–petroleum ether (with charcoal) to give 11.0 g. (16% yield) of colorless crystals,

(16) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3805 (1957).

(17) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected for stem exposure. Basic nitrogens were determined by acetous-perchloric titration; ionic halogens by potentiometric titration with silver nitrate.

(18) Prepared by the alkylation of indole with ethyl iodide using sodamide in liquid ammonia (*cf.* ref.[1]). K. Kawasaki, *Ann. Rept. Shionogi Research Lab.*, **5**, 57 (1955), *Chem. Abstr.*, **50**, 16748 (1956), gives b.p. 107–108° (7 mm.).

m.p. 100–102°. This is considered to be *4-(1-benzotriazolylethyl)pyridine* (IV). A mixture of IV and V melted at 85–93°.

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.16.

IV *hydrochloride*, recrystallized from isopropyl alcohol, formed colorless needles, m.p. 200–202°. A mixture melting point of the hydrochloride salts of IV and V was depressed to 190–197°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 59.91; H, 5.01; Cl (ionic), 13.50.

B. *With 2-vinylpyridine.* Under essentially the same conditions 40.0 g. of benzotriazole was allowed to react with 31.5 g. of 2-vinylpyridine. As before the initial work-up afforded an oil residue which was extracted with hot petroleum ether. Removal of the solvent *in vacuo* and distillation of the residue gave 18.1 g. (27%) of a colorless oil, b.p. 150–155° (0.6 mm.), crystallized on standing. Recrystallization from petroleum ether yielded 15.4 g., m.p. 59–62°, apparently *2-(2-benzotriazolylethyl)pyridine* (VII).

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.27.

VII *hydrochloride*, recrystallized from isopropyl alcohol–ether, formed colorless plates, m.p. 183–185°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 60.20; H, 5.00; Cl (ionic), 13.59.

Distillation of the residual, insoluble oil yielded 10.2 g. (15%) of (presumably) *2-(1-benzotriazoylethyl)pyridine* (VI) as a thick, colorless oil, b.p. 150–158° (0.4 mm.), which could not be crystallized.

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.30.

VI *hydrochloride* formed colorless crystals, m.p. 161–163°, from isopropyl alcohol–ether. A mixture melting point of the hydrochloride salts of VI and VII was depressed to 148–153°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 59.90; H, 5.00; Cl (ionic), 13.67.

The pyridylethylation of benzimidazole. A. *4-(1-Benzimidazolylethyl)pyridine* (VIII). To 23.6 g. (0.23 mole) of freshly distilled 4-vinylpyridine and 23.6 g. (0.2 mole) of benzimidazole dissolved in 200 ml. of isopropyl alcohol was added 5 ml. of Triton A-20. The solution was heated at reflux for 20 hr. and evaporated to dryness *in vacuo*. Hydrogen chloride gas was bubbled into a solution of the residue in ethanol-ether and the resultant white precipitate was recrystallized from ethanol-ether to yield 19.7 g. (33%) of VIII *dihydrochloride*, m.p. 208–211°.

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.76; H, 5.10; Cl, 23.94. Found: C, 56.84; H, 5.05; Cl (ionic), 23.56.

An aqueous solution of the dihydrochloride salt was made weakly basic and exhaustively extracted with chloroform. Drying and removal of the chloroform gave VIII as a green oil residue which crystallized on standing, m.p. 97–98°.

Anal. Calcd. for $C_{14}H_{13}N_3$: N (basic), 12.56. Found: N (basic), 12.25.

B. *2-(1-Benzimidazolylethyl)pyridine* (IX). A mixture of 17.7 g. (0.15 mole) of benzimidazole, 17.9 g. (0.17 mole) of 2-vinylpyridine and a few drops of a 40% methanol solution of benzyltrimethylammonium methoxide was heated in an oil-bath. After being gradually raised, the temperature of the bath was maintained at 180° for a period of 3 hr. The reaction mixture was allowed to cool and the resultant thick oil dissolved in hot benzene. The cooled benzene solution deposited 5.6 g. (32%) of recovered benzimidazole, m.p. and mixture m.p. 168–170°. Concentration of the mother liquor left a residue which was extracted with anhydrous ether. Acidification of the ether solution with ethereal hydrogen chloride and recrystallization of the precipitate from ethanol–ethyl acetate (with charcoal) afforded 10.1 g. (23% yield) of IX *dihydrochloride*, m.p. 205–207°.

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.76; H, 5.10; Cl, 23.94. Found: C, 56.85; H, 5.12; Cl (ionic), 23.30.

4-Skatylpyridine (X). A previous paper described the reductive alkylation of indole with pyridinecarboxaldehydes in glacial acetic acid to give the corresponding skatylpiperidines.[19] 4-Skatylpyridine was prepared by the same process except that a palladium instead of a platinum catalyst was used to make it possible to stop the reduction before hydrogenation of the pyridine ring occurred.[20]

To an ice-cold solution of 23.5 g. (0.22 mole) of 4-pyridinecarboxaldehyde in 200 ml. of glacial acetic acid was added 23.4 g. (0.2 mole) of indole. The resultant orange solution was hydrogenated over 5 g. of 10% palladium on charcoal in an Adams-Parr apparatus at 50 p.s.i. and room temperature. One equivalent of hydrogen was absorbed in 5 hr., by which time the rate of uptake had become very slow. The filtered solution was diluted with about 1 l. of water and extracted with ether. Drying and removal of the ether and recrystallization of the residue (with charcoal) from aqueous methanol yielded 14.8 g. (46% based on indole) of 4-(3,3′-diindolylmethyl)pyridine as light yellow crystals, m.p. 152–155°.[1,19]

The aqueous layer was made alkaline with solid potassium carbonate and extracted with chloroform. Drying and removal of the solvent left a dark residue which was taken up in hot benzene. The cooled benzene solution was decanted from a thick, black oil which had separated, and evaporated to dryness *in vacuo*. The residue was crystallized from aqueous methanol to give, after the removal of initial dark, oily precipitates and treatment with charcoal, 1.7 g. of X, m.p. 108–110°.

Anal. Calcd. for $C_{14}H_{12}N_2$: N (basic), 6.73. Found: N (basic), 6.81.

The *hydrochloride salt* of X, recrystallized from isopropyl alcohol–ether, melted at 194–196°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; Cl, 14.49. Found: C, 68.83, H, 5.46; Cl (ionic), 14.36.

4-Skatylpyridine hydrochloride (in 95% ethanol) showed absorption in the ultraviolet typical of an additive combination of the indole and pyridine chromophores: λ_{max} 223 mμ (log ε 4.34); λ_{max} 259 mμ (log ε 3.79); λ_{max} 280 mμ (log ε 3.81).

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(19) A. P. Gray, *J. Org. Chem.*, **23**, 1453 (1958).

(20) This constitutes a one step synthesis of 4-skatylpyridine, albeit in low yield. Although this compound has apparently not been previously reported, 2-skatylpyridine has been obtained from a multi-step synthesis by G. R. Clemo and J. C. Seaton, *J. Chem. Soc.*, 2582 (1954).