Preparation of 3-Nitro-4-azidopyridine.—A solution of 3.2 g. (0.02 mole) of 3-nitro-4-chloropyridine and 2.6 g. (0.04 mole) of sodium azide in 23 ml. of methanol and 2 ml. of water was warmed to 35–40° for 10 minutes. The solution was filtered and concentrated to half its volume. Upon cooling, the azide separated as pale yellow crystalline rods, 2.55 g. (76.5%), m.p. 89° dec.

Anal. Calcd. for $C_5H_3N_5O_2$: C, 36.36; H, 1.83; N, 42.42. Found: C, 36.28; H, 2.03; N, 41.94.

Upon warming slightly above 90° for a few seconds decomposition occurred with a violent evolution of gas and formation of a yellow oil which changed rapidly into a dark-colored insoluble solid residue which neither melted nor decomposed under 300°.

Aminomethylpyridones.—Nitration of 2-amino-5-methylpyridine[14] followed by diazotization and hydrolysis afforded 2-hydroxy-3-nitro-5-methylpyridine, m.p. 253–255°, in 38% yield. To a suspension of 30.8 g. (0.2 mole) of this nitro compound in 400 ml. of 2% acetic acid, an excess of iron filings was added. The mixture was warmed on the water-bath with occasional stirring until the yellow color of the nitro compound had disappeared. The mixture was then neutralized with calcium carbonate, filtered while hot and the precipitate was washed several times with hot water. An excess of acetic anhydride was added with stirring to the filtrate, externally cooled in an ice-bath. The isolated precipitate was recrystallized from ethanol from which 2-hydroxy-3-acetamido-5-methylpyridine separated as rhombic leaflets, m.p. 253° (with slight sublimation), 22.2 g. (67%). A change in crystalline form from rhombic leaflets into needles occurred around 220°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.89; H, 6.05; N, 17.14.

Nitration of 2-amino-3-methylpyridine[14] followed by diazotization and hydrolysis brought about the formation of 2-hydroxy-3-methyl-5-nitropyridine in 71% yield.[15] According to the above directions it was reduced and acetylated in 69% yield. Upon recrystallization from ethanol, 2-hydroxy-3-methyl-5-acetamidopyridine separated as colorless needles, m.p. 247°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.44; H, 6.36; N, 16.45.

Oxidation of 2-Hydroxy-3-acetamido-5-methylpyridine.—A suspension of 3.0 g. (0.018 mole) of 2-hydroxy-3-acetamido-5-methylpyridine in 50 ml. of 16% (by volume) sulfuric acid was heated at 95–100° for 5 minutes. Longer heating at this stage diminished the final yield. The pale yellow solution was cooled to 25°, and 1.0 g. (0.006 mole) of potassium bromate in 25 ml. of water was added in one portion. The solution turned purple immediately and was cooled externally so that the temperature was held under 40°. A marked decrease in yield was observed if the temperature at this stage was allowed to reach 50–55°. A violet-brown precipitate separated from a blue solution upon standing at room temperature for 2 hr. and in the refrigerator for 24 hr. The crude product, 0.7 to 1.0 g. (29 to 42%), was washed with cold water and dried. An increase in the molar ratio of bromate resulted in nearly complete destruction of this product. Recrystallization from methanol allowed the separation of thin birefringent green-gray leaflets of impure quinhydrone, V·VII (R = CH_3), indefinite decomposition above 300°, from a deep purple supernatant liquid.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 54.56; H, 4.94; N, 14.99; O, 25.49.

The product dissolved in alkali with the formation of an intense blue color which faded after a few hours and changed to a yellow-red. During the course of this alkaline decomposition a green-blue fluorescence under ultraviolet light was noted.

A suspension of 2.0 g. (0.008 mole) of the quinhydrone, V·VII (R = CH_3), in a solution of 5.0 ml. (0.05 mole) of phenylhydrazine in the minimum amount of 10% acetic acid was heated on the water-bath for 6 hr. as the color of the suspended solid slowly changed from purple to brown. From the cooled mixture a monophenylhydrazone of VII ⇌ VIII (R = CH_3) separated, 1.2 g. (67%), and recrystallized from methanol (less soluble) or ethanol as brown-red needles, m.p. 254° dec., whose color changed to yellow-red upon heating to 210°; lit.[7] reports yellow-red needles, m.p. 240° dec. It dissolved in dilute alkali with the formation of a yellow color.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.85; N, 18.38; O, 13.89. Found: C, 62.69; H, 4.90; N, 18.11; O, 14.15.

Oxidation of 2-Hydroxy-3-methyl-5-acetamidopyridine.—The conditions used above for the oxidation of isomeric 2-hydroxy-3-acetamido-5-methylpyridine were used. The final oxidation product, quinhydrone VI·VIII (R = CH_3), recrystallized from dioxane as green-gray platelets and decomposed above 300°. The deep purple dioxane solutions of this product were stable for short times only and soon became red-yellow in color with the simultaneous formation of a green-blue fluorescence to ultraviolet light. It was also soluble in alkali with decomposition and with the development of a green-blue fluorescence.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 55.02; H, 4.88; N, 15.07; O, 24.63.

NEW ORLEANS, LOUISIANA

(14) Obtained from Reilly Tar and Chemical Co., Indianapolis, Ind.

(15) G. F. Hawkins and A. Roe, *J. Org. Chem.*, **14**, 328 (1949).

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

The Pyridylethylation of Indole and Related Reactions

BY ALLAN P. GRAY AND WESLEY L. ARCHER

RECEIVED JANUARY 19, 1957

Pyridylethylation of indole and 1-substituted indoles in refluxing glacial acetic acid smoothly yielded 3-indolylethylpyridine derivatives. In ethanol containing a catalytic amount of sodium ethoxide, indole added to 4-vinylpyridine to provide 4-(1-indolylethyl)-pyridine. Under alkaline conditions indene yielded monopyridylethylated products which are tentatively formulated as 3-indenyl derivatives. Indole and 1-methylindole readily condensed with pyridinecarboxaldehydes in glacial acetic acid at room temperature to give relatively unstable di-indolylmethylpyridine products. Fischer cyclization in polyphosphoric acid of the phenylhydrazones of 3- and 4-acetylpyridine afforded the corresponding 2-indolylpyridines. The methobromide of 4-(2-indolyl)-pyridine gave no evidence of anhydronium base formation. Catalytic hydrogenation of the methobromides of many of the indolyl-substituted pyridines yielded the 1-methylpiperidine derivatives.

A general interest in pyridine derivatives with relatively large substituents[1] prompted this investigation. Although primary concern in the present paper is with a study of the reactions of indole and its 1-substituted derivatives with vinylpyridines and pyridinecarboxaldehydes, preparations of some related bases also are discussed.

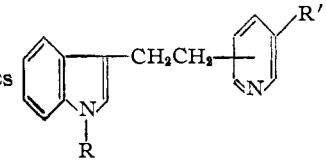
Pyridylethylation.—The experiments of Doering and Weil[2] established 2- and 4-vinylpyridine as

(1) *E.g.*, A. P. Gray, W. L. Archer, E. E. Spinner and C. J. Cavallito THIS JOURNAL, **79**, July 20 (1957).

(2) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

TABLE I

INDOLYLETHYLPYRIDINES



	Vinyl-pyridine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Nitrogen, %[c] Calcd.	Nitrogen, %[c] Found
I	4-Vinyl-	H	..	149–151	$C_{15}H_{14}N_2$							6.30	6.32
	4-Vinyl-	H	HCl	260–262	$C_{15}H_{15}ClN_2$	69.62	69.78	5.84	5.78	13.70	13.71		
	4-Vinyl-	H	CH_3Br	211–213	$C_{16}H_{17}BrN_2$	60.57	60.64	5.40	5.36	25.19	25.11		
II	4-Vinyl-	CH_3	..	96–98	$C_{16}H_{16}N_2$							5.93	5.99
	4-Vinyl-	CH_3	HCl	152–153	$C_{16}H_{17}ClN_2$	70.45	70.85	6.28	5.87	13.00	13.09		
III	4-Vinyl-	$C_6H_5CH_2$	..		$C_{22}H_{20}N_2$							4.48	4.51
	4-Vinyl	$C_6H_5CH_2$	HCl	199–200	$C_{22}H_{21}ClN_2$	75.74	75.47	6.07	5.96	10.16	9.95		
IV	2-Vinyl-	H	..	118–120	$C_{15}H_{14}N_2$							6.30	6.41
	2-Vinyl-	H	HCl	157–159	$C_{15}H_{15}ClN_2$	69.62	69.65	5.84	6.07	13.70	13.58		
	2-Vinyl-	H	CH_3Br	226–227	$C_{16}H_{17}BrN_2$	60.57	60.67	5.40	5.45	25.19	25.17		
V	2-Vinyl-	CH_3	..	[f]	$C_{16}H_{16}N_2$							5.93	6.12
VI	2-Vinyl-5-ethyl	H	..	112–113	$C_{17}H_{18}N_2$							5.60	5.61
	2-Vinyl-5-ethyl	H	HCl	164.5–165.5	$C_{17}H_{19}ClN_2$	71.19	70.96	6.68	6.54	12.36	11.94		
VII	2-Vinyl-5-ethyl	CH_3	..	[g]	$C_{18}H_{20}N_2$							5.30	5.57
VIII	4-Vinyl-	[d]	..	41–45	$C_{15}H_{14}N_2$							6.30	6.31
	4-Vinyl-	[d]	HCl	206–208	$C_{15}H_{15}ClN_2$	69.62	69.46	5.84	5.45	13.70	13.83		

[a] Most of the salts melt with decomposition. [b] Ionic halogen determinations. [c] Basic nitrogens by acetous-perchloric titration. [d] The 1-indolyl isomer of I; (*i.e.*, R = H; R and the 4-pyridylethyl moiety are interchanged). [e] Thick oil, b.p. 220–230° (0.3 mm). [f] Yellow oil, b.p. 170–185° (0.5 mm.), $n^{25}D$ 1.6140. [g] Yellow oil, b.p. 175–185° (0.4 mm.), $n^{25}D$ 1.5957.

electrophilic reagents comparable to other conjugated α,β-unsaturated systems, and this reactivity has been much exploited in recent years.[3] Reports have also appeared on the addition of indole and its derivatives to conjugated olefins such as acrylonitrile,[4] nitroethylene[5] and to substituted acrylic acids.[6] Under controlled alkaline conditions, N-substituted indoles are formed, whereas acid catalysis, high temperatures or use of a Grignard reagent directs reaction to the 3-position. Although Reich and Levine[3] have 2-pyridylethylated pyrrole at the 1-position under alkaline conditions, no report of the pyridylethylation of indole has come to our attention.

In the present work main interest centered on the preparation of 3-substituted indole derivatives. Acetic acid was found to provide an excellent solvent-catalyst for this purpose. Thus, refluxing a glacial acetic acid solution of indole and 4-vinylpyridine smoothly afforded 4-(3-indolylethyl)-pyridine (I) in approximately 70% yield. The 3-indolylethylpyridines II through VII, listed in Table I, were prepared in similar fashion. On the other hand, when indole was 4-pyridylethylated in an ethanol solution containing small amounts of sodium ethoxide and copper sulfate (polymer inhibitor), 4-(1-indolylethyl)-pyridine (VIII) was obtained in 57% yield.

Although an ample basis already exists for the structural assignments, a few points may be worthy of mention. In this connection may be noted the infrared spectrum[7] of I which exhibits an intense absorption band in the N–H stretching region. The spectrum of VIII, however, possessed a very weak band in the same region, suggesting the contamination of this compound by a small amount of I. (This is not too surprising in view of the long appreciated difficulties in obtaining *pure* 1-alkylated indole derivatives.) Catalytic hydrogenation of the methobromide of 2-(3-indolylethyl)-pyridine (IV) readily provided 2-(3-indolylethyl)-1-methylpiperidine (XI), the melting point of which agreed with that of the compound obtained by the catalytic hydrogenation of the condensation product from 3-indolecarboxaldehyde and 2-picoline methohalide (see footnote *d*, Table II). Finally, as is apparent from Table I, 1-methyl- and 1-benzylindole also smoothly afforded pyridylethylated derivatives in hot glacial acetic acid.

The 1-substituted indoles, as anticipated,[8] were more sluggish than indole in the acetic acid catalyzed reaction, albeit comparable yields of the products were obtained after more prolonged refluxing. It is interesting to note that acetic acid solutions of 1-methylindole (but not indole) developed an emerald green color on warming. Although this is suggestive of the formation of the indolenine salt, it probably has no mechanistic bearing on the reaction. Indeed, the only logical path for acid catalysis would seem to be *via* protonation of the vinylpyridine, thus polarizing the molecule and lowering the transition state energy.[9] Yields obtained from 4-vinylpyridine were somewhat better than from the 2-isomer and markedly

(3) See (among others): V. Boekelheide and J. H. Mason, *ibid.*, **73**, 2356 (1951); H. E. Reich and R. Levine, *ibid.*, **77**, 4913 (1955); G. Magnus and R. Levine, *ibid.*, **78**, 4127 (1956); A. P. Phillips, *ibid.*, **78**, 4441 (1956).

(4) I. G. Farbenind. A. G., British Patent 457,621 (1936) [*C.A.*, **31**, 3068 (1937)]; A. P. Terent'ev, A. N. Kost, and V. A. Smit, *Zhur. Obshchei Khim.*, **26**, 557 (1956)[*C. A.*, **50**, 13871*h* (1956)]; H. Erdtman and Å. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954)[*C. A.*, **49**, 13963*a* (1955)].

(5) W. E. Noland and P. J. Hartman, THIS JOURNAL, **76**, 3227 (1954).

(6) H. R. Snyder and J. A. MacDonald, *ibid.*, **77**, 1257 (1955).

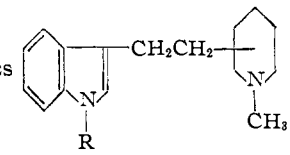
(7) Infrared spectra were determined by the Sadtler Research Laboratories, Philadelphia, Pa.

(8) *Cf.* H. R. Snyder and E. L. Eliel, THIS JOURNAL, **70**, 1703 (1948); A. P. Gray, *ibid.*, **75**, 1252 (1953).

(9) *Cf.* Phillips, and Reich and Levine (ref. 3). These authors, whose papers on the acetic acid catalyzed additions of amines to vinylpyridines appeared after the present work was completed, seem to envision the acid as taking part in ways which should not affect the rate of reaction.

TABLE II

INDOLYLETHYLPIPERIDINES

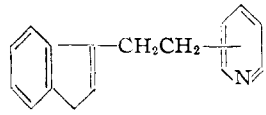


	Position of attachment to piperidine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, %[b] Calcd.	Chlorine, %[b] Found	Nitrogen, %[b] Calcd.	Nitrogen, %[b] Found
IX	4	H	..	171–173	$C_{16}N_{22}N_2$							5.78	5.70
	4	H	HCl	206–208	$C_{16}H_{23}ClN_2$	68.92	69.23	8.31	8.06	12.72	12.37		
X	4	CH_3	..	158–160	$C_{17}H_{24}N_2$							5.46	5.73
	4	CH_3	HCl	143–145	$C_{17}H_{25}ClN_2$	69.72	68.99	8.61	8.66	12.11	11.56		
XI	2	H	..	137–138[d]	$C_{16}H_{22}N_2$							5.78	5.64
	2	H	HCl	170–173	$C_{16}H_{23}ClN_2$	68.92	69.19	8.31	7.85	12.72	12.51		
							68.90		8.05		12.62		
XII	2	CH_3	..	[e]	$C_{17}H_{24}N_2$							5.46	5.59
	2	CH_3	HCl	187–188	$C_{17}H_{25}ClN_2$	69.72	69.72	8.61	8.53	12.11	11.87		

[a,b,c] See corresponding footnotes of Table I. [d] J. Finkelstein and J. Lee, U. S. 2,695,290 (1954), reported m.p. 138–140°; A. M. Ackerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954), gave m.p. 141° for this compound prepared by a different method. [e] Low melting solid, b.p. 165–167° (0.5 mm.).

better than from 2-vinyl-5-ethylpyridine (see Experimental part); this, however, could have been a result of differences in ease of isolation of the products.

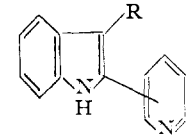
In connection with this program, indene was added, under alkaline conditions, to both 2- and 4-vinylpyridine. Catalysis with either sodium ethoxide or sodamide furnished rather modest yields of monopyridylethylated indene products accompanied by considerable tar. Optimum yields were obtained when excess indene was used. Increasing the proportion of vinylpyridine lowered the yield of mono-derivative, although no pure poly-pyridylethylated materials were isolated. In comparison, cyanoethylation using Triton B affords tris-(cyanoethyl)-indene.[10] Although no experimental evidence as to structure was obtained, these products are tentatively formulated as 3-indenylethylpyridines in view of the facile isomerization of 1-substituted into the presumably more stable 3-substituted indenes under very mild alkaline conditions.[11]



XVII, 2-isomer
XVIII, 4-isomer

Pyridinecarboxaldehyde Reactions.—Indole has long been known to condense readily with carbonyl compounds, *e.g.*, under acid or Grignard conditions. This nucleophilic reactivity has been fruitfully exploited in the Mannich reaction and in the preparation of arylidene and diindolylmethyl derivatives.[12] The corresponding reactions of indole and of 1-methylindole with the pyridinecarboxaldehydes proceeded exothermically in glacial acetic acid at room temperature to provide fair yields (50–75%) of the diindolylmethylpyridine derivatives described in Table III. As has been previously noted for diindolylmethyl derivatives,[12] these products were relatively unstable and underwent disproportionation and air oxidation to highly colored materials.

XIX, 3-isomer, R = H
XX, 4-isomer, R = H



Related Derivatives.—3- and 4-(2-indolyl)-pyridine were prepared by the Fischer indole synthesis from the phenylhydrazone of the corresponding acetylpyridine. Although a few (3-alkyl-2-indolyl)-pyridines have been prepared[13] by Fischer cyclization from the appropriate pyridyl ketone, apparently none of the *unsubstituted* 2-indolylpyridines have been obtained previously. In this context it is noteworthy that attempted cyclization of the phenylhydrazone of 4-acetylpyridine under the conditions successfully employed[13] for the preparation of the 2- and 3-isomers of XIX in which R = methyl or ethyl (*i.e.*, hydrogen chloride in refluxing ethanol) resulted in almost quantitative recovery of the starting phenylhydrazone. Even hydrogen chloride in refluxing glacial acetic acid gave back only starting material (80% recovery). XIX and XX were satisfactorily (55–65% yield) obtained, however, by somewhat harsher treatment with polyphosphoric acid.[14] The markedly

(10) H. A. Bruson, THIS JOURNAL, **64**, 2457 (1942).

(11) See E. H. Rodd, "The Chemistry of Carbon Compounds," Vol. IIIB, Elsevier Publishing Co., 1956, pp. 1257–1259, for an authoritative account.

(12) See P. L. Julian, E. W. Meyer and H. C. Printz in Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., pp. 93–95.

Also see H. v. Dobeneck and J. Maas, *Chem. Ber.*, **87**, 455 (1954); A. Treibs and E. Herrmann, *Hoppe-Seyler's Z. physiol. Chem.*, **299**, 168 (1955) [*C. A.*, **50**, 943i (1956)]; R. Dahlbom and A. Misiorny, *Acta Chem. Scand.*, **9**, 1074 (1955) [*C. A.*, **50**, 13869*i* (1956)].

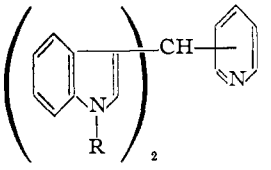
It might be noted in passing that in attempted Mannich reactions of indole with *substituted* aldehydes in place of formaldehyde (benzaldehyde, *p*-dimethylaminobenzaldehyde) and dimethylamine in aqueous acetic acid at room temperature, good yields of phenyldiindolylmethane and *p*-dimethylaminophenyldiindolylmethane (respectively) were obtained as the only products (unpublished results from this Laboratory).

(13) F. B. LaForge, THIS JOURNAL, **50**, 2477 (1928); R. M. Anderson, G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 2962 (1954); Yee-Sheng Kao and R. Robinson, *ibid.*, 2865 (1955).

(14) H. M. Kissman, D. W. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952).

TABLE III

DIINDOLYLMETHYLPYRIDINES

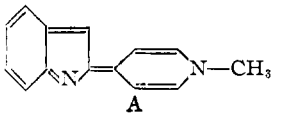


	Position of attachment to pyridine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Nitrogen, %[c] Calcd.	Nitrogen, %[c] Found
XIII	4	H	..	152–155	$C_{22}H_{17}N_3$							4.33	4.09
	4	H	HCl	204–205	$C_{22}H_{18}ClN_3$	73.43	73.70	5.04	5.45	9.85	9.30		
	4	H	CH_3Br	239–240	$C_{23}H_{20}BrN_3$	66.03	66.32	4.82	5.01	19.10	18.83		
XIV	4	CH_3	..	186–188	$C_{24}H_{21}N_3$	82.02	82.25	6.02	5.94				
	4	CH_3	HCl	224–225	$C_{24}H_{22}ClN_3$	74.31	74.59	5.72	5.47	9.14	8.74		
XV	3	H	..	162–163	$C_{22}H_{17}N_3$							4.33	3.96
	3	H	HCl	214–215	$C_{22}H_{18}ClN_3$	73.43	73.29	5.04	5.15	9.85	9.04		
XVI	2	H	..	208–210	$C_{22}H_{17}N_3$							4.33	4.23
	2	H	HCl	218–220	$C_{22}H_{18}ClN_3$	73.43	73.31	5.04	4.91	9.85	9.68		

[a] These compounds melt with decomposition. [b,c] See corresponding footnotes of Table I.

greater stability of the phenylhydrazones of methyl *vs.* methylene ketones to acid is well known and presumably can be ascribed to the relative stabilities of the respective carbonium ions (prim. *vs.* sec.). Reaction of the phenylhydrazone of 3-acetylpyridine in polyphosphoric acid was decidedly less violent than that of the 4-isomer, the product was obtained in poorer yield and accompanied by more tar.

Of incidental interest is the fact that the methobromide of XX (or XIX) gave no indication of anhydronium base formation in aqueous alcohol by titration with 0.1 *N* NaOH.[15] In contrast to the carboline anhydronium bases, the properties of which seemed to correspond more closely to the charge-separated structures,[15] the present information points up the importance of resonance contributions to stability from quinoid forms; *i.e.*, A



A

should contribute very little to over-all stabilization.[16]

Catalytic hydrogenation of the methobromides of a number of the indolyl-substituted pyridines readily yielded the corresponding 1-methylpiperidines; most of these are listed in Table II.

NOTES ADDED IN PROOF.—After this paper had been accepted for publication, the abstract of an article [S. Sugasawa, M. Terashima and Y. Kanaoka, *Pharm. Bull.* (Japan), **4**, 16 (1956) [*C. A.*, **51**, 3593*d* (1957)]] appeared describing the preparation of 2-, 3-, and 4-(2-indolyl)-pyridine by essentially the same procedure (polyphosphoric acid cyclization) employed here. Physical properties of the products and derivatives are in good agreement.

It is recognized, as mentioned in a private conversation with Dr. W. E. Noland at the Miami meeting, that pure 3,3'-diindolylmethylpyridines should be colorless. The analytical data and the fact that the compounds are all monoacidic bases argue against formulation of the materials as the rosindole oxidation products. This question is being further investigated.

Acknowledgment.—The authors are grateful to Dr. C. J. Cavallito for continued interest and encouragement. Ionic halogens and basic nitrogens were determined by Mr. Dean F. Cortright.

Experimental[17]

Intermediates.—1-Methylindole, b.p. 114–115° (14 mm.), $n^{25}D$ 1.6038, was obtained in 80–85% yield by the reaction of indole with sodamide and dimethyl sulfate in dry toluene[18] at steam-bath temperatures. 1-Benzylindole, b.p. 145–147° (0.3 mm.), m.p. 43°, was prepared essentially as described by Plieninger.[18] The vinylpyridines were obtained from the Reilly Tar and Chemical Corp. and the pyridinecarboxaldehydes from the Aldrich Chemical Co. Dr. F. Cislak of Reilly kindly supplied samples of 3- and 4-acetylpyridine.

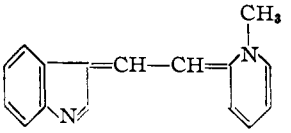
Pyridylethation at the 3-Position of the Indole Nucleus.—These reactions were run in hot glacial acetic acid, usually with approximately equimolar proportions of the reactants. Frequently the vinylpyridine was freshly distilled prior to use, although the commercial product (containing inhibitor) gave perfectly satisfactory results. The products were purified either by recrystallization (I, IV, VI), *via* the hydrochloride (II), or by distillation (III, V, VII). Yields averaged 65–75% with 4-vinylpyridine, 50–65% with 2-vinylpyridine and only 25–30% with 2-vinyl-5-ethylpyridine.

A. 4-(3-Indolylethyl)-pyridine (I).—A solution of 26.0 g. (0.25 mole) of 4-vinylpyridine (undistilled) and 23.4 g. (0.2 mole) of indole in 100 ml. of glacial acetic acid was refluxed (oil-bath) for 3 hr. The solution was concentrated *in vacuo* and the residue made weakly basic with dilute alkali. The resultant crystalline precipitate was recrystallized from aqueous isopropyl alcohol to yield 30.6 g. (69%) of I, m.p. 149–151°.

B. 4-(1-Methyl-3-indolylethyl)-pyridine (II).—To a refluxing (emerald green) solution of 1965 g. (15 moles) of 1-methylindole in 4.5 liters of glacial acetic acid was added, dropwise with stirring, 1590 g. (15 moles) of 4-vinylpyridine. After 22 hr. refluxing the solution was concentrated under reduced pressure. The residue was dissolved in dilute hydrochloric acid, the solution was filtered and then treated with concentrated hydrochloric acid in order to precipitate the hydrochloride salt of the product. (This step removed tarry, polymeric basic materials which were otherwise diffi-

(15) *Cf.* A. P. Gray, THIS JOURNAL, **77**, 5930 (1955).

(16) *Cf.* Ackerman and Veldstra, footnote *d*, Table II, who report the facile formation of an anhydronium base from the methiodide of 2-(3-indolylethenyl)-pyridine. The relevant canonical form is



(17) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. Melting points are corrected for stem exposure.

(18) *Cf.* H. Plieninger, *Chem. Ber.*, **87**, 127 (1954). Toluene was found to be a more convenient solvent for the methylation reaction than liquid ammonia and ether.

cult to separate.) The collected salt was dissolved in water and the solution was made alkaline with ammonia to precipitate 2580 g. (73% yield) of II, m.p. 91–93°. Recrystallization from aqueous acetone raised the melting point to 96–98°.

C. 2-(1-Methyl-3-indolylethyl)-pyridine (V).—A solution of 30 g. (0.23 mole) of 1-methylindole and 25 g. (0.24 mole) of 2-vinylpyridine in 100 ml. of glacial acetic acid was refluxed for 18 hr. After removal of the solvent under reduced pressure, the residue was dissolved in dilute hydrochloric acid, the aqueous solution was washed with ether, made alkaline and extracted with ether. Concentration of the dried extract left an oil which was distilled to yield 26.3 g. (49%) of V, b.p. 170–185° (0.5 mm.), $n^{25}D$ 1.6140.

4-(1-Indolylethyl)-pyridine (VIII).—To 50 ml. of ethanol containing 0.5 g. of sodium and 0.5 g. of cupric sulfate was added 29.2 g. (0.25 mole) of indole and 52.4 g. (0.5 mole) of 4-vinylpyridine. The reaction mixture was heated in a sealed tube for 4 hr. at 140–150° (oil-bath temperature), allowed to cool to room temperature, filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in ether, extracted with acid, the acid solution was made alkaline and extracted with ether. Drying and removal of the ether left a red oil which was distilled *in vacuo*. Redistillation afforded 31.7 g. (57% yield) of VIII as an oil which crystallized on standing, b.p. 160–165° (0.1 mm.), m.p. 41–45°. A weak absorption band in the N–H stretching region of the infrared indicated that this product was contaminated by a little of the 3-isomer.

4-(3(?)-Indenylethyl)-pyridine (XVII).—A mixture of 50.0 g. (0.43 mole) of freshly distilled indene and 1 g. of metallic sodium dissolved in 5 ml. of ethanol was heated to 80°, and 23.0 g. (0.22 mole) of 4-vinylpyridine (undistilled) was added dropwise with stirring. Stirring was continued and the reaction mixture was heated for 5 hr. at 80°. The ethylene dichloride extract of the cooled mixture was washed with water, dried over sodium sulfate and distilled. A fraction which immediately crystallized, b.p. 145–170° (0.3 mm.), was charcoaled and recrystallized from Skellysolve B to give 16.6 g. (34% yield) of XVII, m.p. 96–97°. The picrate melted at 176° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N (basic), 6.52.

The methobromide of XVII, recrystallized from ethanol, melted at 210–212° dec.

Anal. Calcd. for $C_{17}H_{18}BrN$: C, 64.56; H, 5.74; Br, 25.27. Found: C, 64.66; H, 5.50; Br (ionic), 25.27.

2-(3(?)-Indenylethyl)-pyridine (XVIII).—To 116 g. (1.0 mole) of indene and 2.0 g. of powdered sodamide in 300 ml. of dry toluene, stirred and brought to reflux in an oil-bath, was added, dropwise, 52.5 g. (0.5 mole) of 2-vinylpyridine in 50 ml. of toluene. Stirring was continued and the reaction mixture was refluxed for 5 hr. The solution was separated from considerable tarry material and distilled *in vacuo*. Redistillation afforded 33.0 g. (30% yield) of XVIII, b.p. 145–155° (0.4 mm.), $n^{25}D$ 1.5987.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N (basic), 6.39.

The hydrochloride formed colorless crystals from isopropyl alcohol–ether, m.p. 148–150° dec.

Anal. Calcd. for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; Cl, 13.76. Found: C, 74.25; H, 6.19; Cl (ionic), 13.58.

3-(2-Indolyl)-pyridine (XIX).—To the polyphosphoric acid prepared from 36 g. of phosphorus pentoxide and 20 g. of 85% phosphoric acid was added 30.8 g. of the crude, powdered phenylhydrazone of 3-acetylpyridine (m.p. 139–141°[19]). The mixture was stirred by hand with a thermometer and gradually heated in an oil-bath until the internal temperature reached 125–130°. At this point a vigorous reaction ensued. The reaction flask was immediately removed from the oil-bath as the temperature shot rapidly to >230°. After the reaction had subsided (in 3–4 minutes), the flask was cooled under a cold water tap to an internal temperature of about 90° and diluted with water. The tarry, aqueous mixture was washed with ethyl acetate, made alkaline with a saturated solution of sodium carbonate and exhaustively extracted with chloroform. The chloroform extract was dried over a mixture of anhydrous sodium sulfate and sodium carbonate and concentrated to dryness. The crystalline residue was charcoaled in ethanol, the solution was diluted with water, decanted from the initial tarry precipitate and diluted with more water to yield, after refrigeration, 15.6 g. (55%) of crude product, m.p. 166–173°. Further recrystallization (with charcoaling) from ethanol–water afforded XIX as almost colorless platelets, m.p. 173–175°.

Anal. Calcd. for $C_{13}H_{10}N_2$: N (basic), 7.21. Found: N (basic), 6.86.

The hydrochloride salt of XIX formed pale yellow crystals from methanol–ether, m.p. 259–261° dec.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; Cl, 15.37. Found: C, 68.02; H, 4.96; Cl (ionic), 15.03.

The methiodide crystallized from methanol–ethyl acetate in clusters of small, yellow, prismatic needles, m.p. 248–250° dec.

Anal. Calcd. for $C_{14}H_{13}IN_2$: C, 50.02; H, 3.90. Found: C, 50.18; H, 3.79.

The methobromide, recrystallized from methanol–ether, melted at 266–268° dec.

Anal. Calcd. for $C_{14}H_{13}BrN_2$: C, 58.14; H, 4.53; Br, 27.64. Found: C, 57.94; H, 4.65; Br (ionic), 27.43.

4-(2-Indolyl)-pyridine (XX).—This compound was prepared similarly to the 3-isomer. The reaction was considerably more vigorous, however, and afforded a cleaner product in better yield. An intimate mixture of polyphosphoric acid (60 g. of phosphorus pentoxide and 32 g. of 85% phosphoric acid) and 51.2 g. of the crude, powdered phenylhydrazone of 4-acetylpyridine (m.p. 143–146°[20]) was stirred with a thermometer and gradually heated until the internal temperature reached 115–120°. The flask was removed from the bath as a violent reaction accompanied by considerable fuming took place. The temperature rose to 280–285° in less than five minutes. When the reaction had subsided (in an additional 2–3 minutes), the mixture was cooled under a cold water tap, taken up in water and washed with ethyl acetate. The mixture of water and solid was made alkaline with excess saturated sodium carbonate and triturated until all of the insoluble salts had been converted to base. The solid precipitate was collected, exhaustively extracted with hot ethanol and the solution charcoaled. XX crystallized from the refrigerated ethanol solution in cream-colored plates, m.p. 208–209°; the yield was 30.6 g. (65%).

Anal. Calcd. for $C_{13}H_{10}N_2$: N (basic), 7.21. Found: N (basic), 7.21.

The hydrochloride salt of XX crystallized from methanol–ether in pale yellow crystals, melting above 285°.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; Cl, 15.37. Found: C, 67.62; H, 4.77; Cl (ionic), 15.25.

The methiodide formed tiny, orange cubes from methanol–ethyl acetate, melting with decomposition at 260°.

Anal. Calcd. for $C_{14}H_{13}IN_2$: C, 50.02; H, 3.90. Found: C, 49.99; H, 3.71.

The methobromide, crystallized from methanol–ether, showed m.p. 272–274° dec.

Anal. Calcd. for $C_{14}H_{13}BrN_2$: C, 58.14; H, 4.53; Br, 27.64. Found: C, 58.76; H, 4.60; Br (ionic), 27.37.

Catalytic Hydrogenation of Indolyl-pyridine Methobromides.—The following are representative examples. Crude salts were used in those cases in which no methobromide is listed in Table I.

A. 4-(3-Indolylethyl)-1-methylpiperidine (IX).—A solution of 8.0 g. (0.025 mole) of the methobromide of I dissolved in 100 ml. of analytical grade methanol containing 0.5 g. of platinum oxide (Adams catalyst; added under nitrogen) was hydrogenated in an Adams–Parr apparatus at 40 p.s.i. and room temperature. Hydrogen absorption ceased in 20 minutes. The filtered solution was evaporated to dryness, the residue was dissolved in warm water, the solution made alkaline and the resultant precipitate was recrystallized from aqueous ethanol to yield 4.3 g. (69%) of IX as fine, colorless needles, m.p. 171–173°.

B. 3-(2-Indolyl)-1-methylpiperidine (XXI).—A solution of 6.1 g. (0.021 mole) of the methobromide salt of XIX in 200 ml. of 75% methanol was hydrogenated over 0.5 g. of Adams catalyst at 45 p.s.i. and room temperature. Hy-

(19) C. Engler and W. Kiby, *Ber.*, **22**, 598 (1889).

(20) A. Pinner, *ibid.*, **34**, 4250 (1901).

drogenation was complete in less than 1 hr. The filtered solution was evaporated to a thick resin which was taken up in water, treated with alkali and extracted into ether. The dried ether extract was concentrated to a crystalline residue. Recrystallization from aqueous ethanol and then from benzene–Skellysolve B afforded 2.55 g. (56% yield) of XXI, m.p. 118–120°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.24.

XXI hydrochloride showed m.p. 204–206° dec. after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64. Found: C, 66.89; H, 7.27.

C. 4-(2-Indolyl)-1-methylpiperidine (XXII).—Similarly, 18.8 g. of XX methobromide was hydrogenated to yield, after recrystallization from ethanol, 9.2 g. (67%) of XXII in the form of colorless prisms, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.57.

XII hydrochloride formed glistening plates from aqueous methanol–acetone, m.p. 259–260° dec.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14. Found: C, 66.85; H, 7.73; Cl (ionic), 13.89.

Condensation of Indoles with Pyridinecarboxaldehydes.—These reactions were carried out in acetic acid at room temperature. The products were relatively unstable, rapidly oxidizing in air to highly colored materials and were stored under nitrogen.

A. 4-(3,3′-Diindolylmethyl)-pyridine (XIII).—To a solution of 32.1 g. (0.3 mole) of 4-pyridinecarboxaldehyde in 150 ml. of glacial acetic acid, cooled in an ice-bath, was added 70.2 g. (0.6 mole) of indole. The mixture was allowed to warm to room temperature. As the indole dissolved, a moderately exothermic reaction took place, and the resultant solution developed a deep purple color. After standing for 18 hr., the solution was diluted with aqueous hydrochloric acid to precipitate a purple hydrochloride salt which was recrystallized from ethanol–ether. Addition of aqueous alkali to an ethanol solution of the hydrochloride precipitated the base. This was crystallized from benzene–ethanol with the addition of Skellysolve B to provide 73 g. (75% yield) of yellow-orange crystals of XIII, m.p. 152–155° dec.

B. 4-[Bis-(1-methyl-3-indolyl)-methyl]-pyridine (XIV).—Some heat was evolved on dissolving 5.0 g. (0.047 mole) of 4-pyridinecarboxaldehyde and 12.2 g. (0.094 mole) of 1-methylindole in 50 ml. of glacial acetic acid at room temperature. After standing for 21 hr. the deep purple solution was worked up as described above. The isolated base was recrystallized from benzene–Skellysolve B, affording 8.9 g. (54% yield) of flesh-colored crystals of XIV, m.p. 186–188° dec.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Chlorinated 4-Indanols: Preparation and Proof of Structures[1]

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Chlorination of 4-indanol with sulfuryl chloride yields 5-chloro-4-indanol and 7-chloro-4-indanol. The structure assignment has been carried out by analysis of the infrared spectra as well as by unambiguous synthesis. It is shown that the OH stretching frequencies of the two isomeric chloro-4-indanols coincide with the corresponding frequencies of *o*-chloro- and *p*-chlorophenol. Chemical structure proof starts with *p*-chlorophenyl β-chloropropionate which rearranges with $AlCl_3$ to 5,β-dichloro-2-hydroxypropiophenone which in turn cyclizes to form 4-chloro-7-hydroxy-1-hydrindone. The latter compound is reduced with Zn in HCl to the corresponding 7-chloro-4-indanol.

The recent availability of 4-indanol[3] (I) from the coal hydrogenation process prompted us to investigate some of its chlorinated derivatives as potential antiseptic agents. The reaction of one equivalent of sulfuryl chloride on 4-indanol yielded a mixture from which two white crystalline products were isolated. The more abundant of the two melted at 91.0–93.7° and was assumed to be 7-chloro-4-indanol (III). This assumption was later proved correct by infrared studies and by synthesis by another route as outlined below (V → VI → VII → III). From the filtrates of the chlorination mixture there was obtained a smaller amount of a substance melting at 70.4–73.1° which appeared to be 5-chloro-4-indanol (II). Actual proof of this structure was supplied by infrared spectral analyses.

The reaction of 4-indanol (I) with two equivalents of sulfuryl chloride yielded a mixture from which a solid was isolated melting at 54.5–56.8°. That this product was indeed 5,7-dichloro-4-indanol (IV) was proved by showing that treatment of either 5-chloro- (II) or 7-chloro-4-indanol (III) with sulfuryl chloride yielded this same material.

(1) Presented before the Division of Organic Chemistry at the 131st meeting of the American Chemical Society, Miami, Fla., April, 1957.

(2) Deceased.

(3) Samples of 4-indanol were kindly supplied by Carbide and Carbon Chemicals Co.

Physicochemical Data.—The spectra of the two isomeric chloroindanols (II and III) and the unchlorinated starting material I in CS_2 solution are sufficiently different to permit differential assays. The 7-chloro-4-indanol (III) has a strong band at 12.35 μ while the 5-chloro analog II does not absorb in this region, which is used to estimate the former compound. In the 9.5 to 10.5 μ region both compounds show doublets, the 7-chloro-4-indanol absorbing at 9.98 and 10.11 μ and the 5-chloro-4-indanol at 9.98 and 10.05 μ. The intensity of the first and second maximum are reversed with respect to the pair. Distortion (in the case of 0.4 to 0.6 mole fraction of the 7-chloro compound) or peak ratio assays (in the case of 0.8 to 1.0 mole fraction of the 7-chloro compound) establish their relative concentration. Unchlorinated starting material shows a doublet at 12.97 and 13.12 μ where neither of the monochloro derivatives absorbs.

Structure Assignment of 5- and 7-Chloro-4-indanol *via* Infrared Spectra.—The two isomeric indanols can be compared with *o*- and *p*-chlorophenol with respect to the geometry of their substituents. The trimethylene bridge of the indanol should not influence the position of the OH stretching frequency to any extent just as it would not exert any marked effect upon the dipole moment of the molecules. Dipole–dipole interaction, *viz.*,