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The Catalytic Hydrogenation of Indolylethylpyridines. 4-(Indolylethyl)-1-aralkylpiperidines as Potent Analgesics

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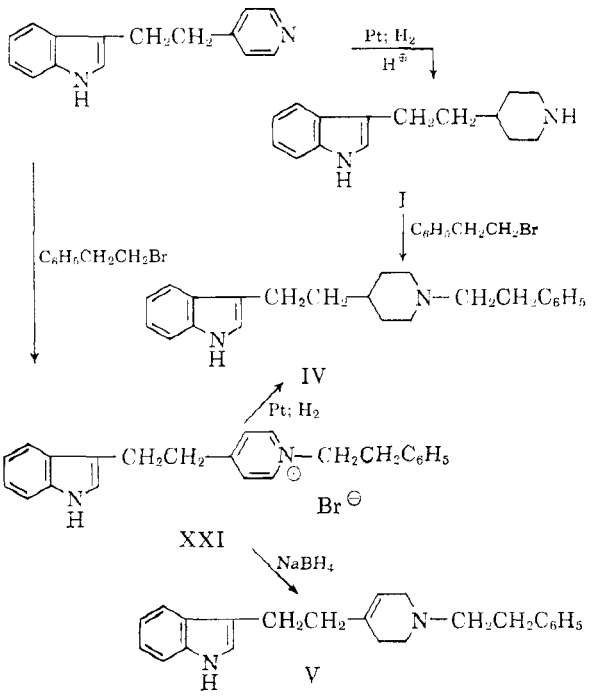
Catalytic hydrogenation of indolylethylpyridine bases in acidic solutions afforded the corresponding indolylethylpiperidines. These reacted with aryl substituted alkylating agents to give indolylethyl-1-aralkylpiperidine derivatives. The same products could be obtained by initial quaternization of the pyridine followed by hydrogenation under neutral conditions. Several of the derived compounds proved to be as effective as morphine in producing analgesia in animals.

A recent report[1] from these laboratories indicated that catalytic hydrogenation of indole-substituted pyridines under acid conditions leads first, when the two ring systems are not conjugated, to saturation of the pyridine ring. The present paper documents some of the evidence for this and, in particular, is concerned with the hydrogenation of indolylethylpyridine bases[2] to the corresponding piperidines. Certain of the derived products, *viz.* 4-(indolylethyl)-1-aralkylpiperidines, have been found to possess analgesic activity equivalent to morphine when tested in mice and rabbits.[3,4] These compounds display a profile of central nervous system depressant properties which distinctly differs from that of morphine.

Platinum-catalyzed hydrogenation of 4-(3-indolylethyl)pyridine, 4-(1-methyl-3-indolylethyl)-pyridine and 2-(indolylethyl)pyridine in either glacial acetic acid or aqueous alcohol containing hydrochloric acid provided the piperidine derivatives, I, XIV, and XVII, respectively, in yields of 60–80%. Uptake of hydrogen was more rapid in the stronger, mineral acid medium. That the indole nucleus was not reduced under these conditions is clearly evidenced by the ultraviolet absorption data given in Table III.[5] Further, alkylation of I with phenethyl bromide afforded an 80% yield of 4-(3-indolylethyl)-1-phenethylpiperidine (IV), identical with the product obtained by catalytic hydrogenation in a neutral medium of the quaternary salt 4-(3-indolylethyl)-1-phenethylpyridinium bromide (XXI). Sodium borohydride reduction of XXI yielded the piperideine derivative V, with the double bond presumed to be in the 3,4-position.[6]



The compounds listed in Tables I and II were for the most part prepared *via* one or the other of these routes—*i.e.*, alkylation of the appropriate piperidine or reduction of the corresponding pyridine quaternary salt (described in Table IV). The former process was more generally applicable; the latter was somewhat more satisfactory, since (as expected) platinum-catalyzed, low pressure hydrogenation of the quaternary salts in alcohol proceeded rapidly and cleanly to give 85–90% yields of the piperidine derivatives.

Generally speaking, these reactions were unexceptional. It might be mentioned that the cinnamyl derivative IX appeared to be somewhat labile to acid and was obtained only as the free base. The ultraviolet spectrum of IX (see Table III), compared with those of III and IV, demonstrates that the double bond is conjugated with the benzene ring[7] and rules out the remote possibility

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

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

(3) T. B. O'Dell *et al.*, to be published.

(4) One of these compounds, 4-(3-indolylethyl)-1-phenethylpiperidine, is undergoing further evaluation.

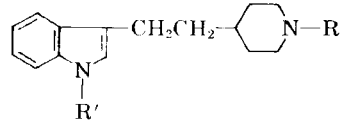
(5) The indole chromophore generally shows absorption maxima at *ca.* 225 mμ and 280 mμ. It is of incidental interest that an ind-*N*-alkyl substituent produces a consistent bathochromic shift of 5–8 mμ in the spectrum; compare the absorption of II with that of its ind-*N*-methyl derivative.

(6) See M. Ferles, *Chem. listy*, **51**, 474 (1957) [*Chem. Abstr.*, **51**, 10515 (1957)]. Physical (pK_a, spectral—Table III) data obtained on V and related compounds in these laboratories also accord with this structural assignment.

(7) The spectrum of IX is essentially equivalent to a composite of the spectra of an indole and styrene.

TABLE I

4-(3-INDOLYLETHYL)PIPERIDINES



	R	Salt	M.P.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, %[b] Calcd.	Chlorine, %[b] Found	Relative Analgesic Activity[c]
				A. R′ = H							
I	H	—	162–163	$C_{15}H_{20}N_2$					6.14	6.03	
		HCl	213–215	$C_{15}H_{21}ClN_2$	68.04	68.22	8.00	8.05	13.39	13.47	
II	Methyl[d]										0
III	Benzyl	—	91–92	$C_{22}H_{26}N_2$					4.40	4.38	
		HCl	192–193	$C_{22}H_{27}ClN_2$	74.44	73.91	7.67	7.69	9.99	9.84	3
IV	Phenethyl	—	130–132	$C_{23}H_{28}N_2$					4.21	4.22	
		HCl	225–226	$C_{23}H_{29}ClN_2$	74.87	75.00	7.92	8.17	9.61	9.66	4
V	Phenethyl[e]	—	132–133	$C_{23}H_{26}N_2$					4.24	4.18	
		HCl	179–180	$C_{23}H_{27}ClN_2$	75.28	75.33	7.42	7.55	9.66	9.61	4
VI	γ-Phenylpropyl	—	110–112	$C_{24}H_{30}N_2$					4.04	4.08	
		HCl	180–181	$C_{24}H_{31}ClN_2$	75.26	75.09	8.16	8.28	9.26	9.23	1
VII	β-Hydroxyphenethyl	—	133–135	$C_{23}H_{28}N_2O$					4.02	3.99	
		HCl	193–194	$C_{23}H_{29}ClN_2O$	71.76	71.65	7.59	7.88	9.21	9.22	3
VIII	Phenacyl	—	173–174	$C_{23}H_{26}N_2O$					4.04	4.05	
		HCl	233–234	$C_{23}H_{27}ClN_2O$	72.14	71.68	7.11	7.23	9.26	9.16	4
IX	Cinnamyl	—	129–131	$C_{24}H_{28}N_2$	83.67	83.46	8.19	8.21	4.07	3.99	[g]
X	Phenoxyethyl	—	102–103	$C_{23}H_{28}N_2O$					4.02	3.99	
		HCl	170	$C_{23}H_{29}ClN_2O$	71.76	72.13	7.59	7.75	9.21	9.20	2
XI	β-Hydroxy-γ-phenoxypropyl	—	96–97	$C_{24}H_{30}N_2O_2$					3.74	3.67	
		HCl	196–197	$C_{24}H_{31}ClN_2O_2$	69.46	69.00	7.53	7.65	8.55	8.37	2
XII	p-Nitrophenethyl	—	173–175	$C_{23}H_{27}N_3O_2$					3.71	3.70	
		HCl	254–255	$C_{23}H_{28}ClN_3O_2$	66.73	66.54	6.82	6.79	8.57	8.41	[g]
XIII	p-Aminophenethyl	di-HCl	203	$C_{23}H_{31}Cl_2N_3$	65.70	65.94	7.43	7.24	16.87	16.57	2.5
				B. R′ = Methyl							
XIV	H	—	65–66	$C_{21}H_{26}N_2$					5.78	5.78	
		HCl	200–201	$C_{21}H_{23}ClN_2$	68.92	68.70	8.32	8.25	12.72	12.70	0
XV	Phenethyl	HCl[f]	201–202	$C_{21}H_{31}ClN_2$	75.26	75.11	8.16	7.97	9.25	9.22	4
XVI	β-Hydroxyphenethyl	HCl[f]	193–195	$C_{21}H_{31}ClN_2O$	72.25	72.20	7.83	8.10	8.89	8.79	1

[a] Most of the salt melt with decomposition. [b] Ionic chlorine by potentiometric titration or (bases) basic nitrogen by acetous perchloric titration. [c] Relative analgesia produced by 10–20 mg./kg. of compound administered intraperitoneally to mice, as measured by reaction time to radiant heat stimulus applied to hind foot. [T. B. O'Dell, L. R. Wilson, M. D. Napoli, H. D. White, and J. H. Mirsky, *J. Pharmacol. Exptl. Therap.*, **128**, 65 (1960)]. A value of 4 indicates a potency equal to that of morphine; 0 indicates no analgesic action at these doses. [d] Prepared earlier.[2] [e] $\Delta^{3,4}$-Piperideine analog. [f] Free base was obtained as an oil that could not be crystallized. [g] The low solubility of these compounds prevented quantitative evaluation of potency; suffice to say that they appeared to be less active than IV.

TABLE II

INDOLYLETHYLPIPERIDINES

R′—CH_2CH_2—(piperidine)—N—R

	R	R′	Piperidine Position	Salt	M.P.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, %[b] Calcd.	Chlorine, %[b] Found	Relative Analgesic Activity[c]
XVII	H	3-Indolyl	2	—	139–141	$C_{15}H_{20}N_2$					6.14	6.10	
				HCl	218–219	$C_{15}H_{21}ClN_2$	68.03	67.52	7.99	7.86	13.39	13.49	
XVIII	β-Hydroxyphenethyl	3-Indolyl	2	HCl[d]	123–125	$C_{23}H_{29}ClN_2O$	71.76	71.83	7.59	7.70	9.21	9.29	0
XIX	Phenethyl	1-Indolyl	4	HCl[d]	161–166	$C_{23}H_{29}ClN_2$	74.87	74.76	7.92	7.85	9.61	9.55	2.5
XX	3-Indolylethyl	Phenyl	4	—	119–120[e]								
				HCl	233–235	$C_{21}H_{29}ClN_2$	74.87	74.64	7.92	8.01	9.61	9.66	±

[a] [c] *Refer to corresponding footnotes in Table I.* [d] *Free base was obtained as an oil that could not be crystallized.* [e] Lit.[8] m.p. 119°.

that the reaction with cinnamyl chloride involved allylic rearrangement. 1-(3-Indolylethyl)-4-phenethylpiperidine (XX),[8] isomeric with IV, was conveniently synthesized by the acylation of 4-phenethylpiperidine with 3-indoleglyoxylyl chloride followed by lithium aluminum hydride reduction of the product.

Biological properties.[3] Since the first announcements that replacement of an *N*-methyl substituent in a strong, morphine-like analgesic by an aralkyl group can increase potency,[9] a number of groups of workers have reported on the synthesis of more active agents by the attachment of a variety of moieties to the basic nitrogen of a known analgesic structure.[10] Structural requirements for activity, particularly in relation to the potent, new aralkyl derivatives, have been comprehensively reviewed.[11] The indolylethylpiperidine derivatives presently under discussion are exceptional in that they do not possess certain of the structural features presumed to be prerequisite[11] to analgesic potency of the order of morphine, nor do they seem (in animal tests) to resemble morphine in their extra-analgesic biological properties. From a structural point of view it is most notable that the active compounds described in Tables I and II do not have a "central" atom, two carbons removed from the basic nitrogen, to which is attached an aromatic ring but no hydrogen.[12] As to pharmacological properties, tests in animals[3] have not revealed the side effects (*e.g.*, mydriasis, cord stimulation) usually associated

(8) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957), have synthesized this compound by another method.

(9) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); J. Weijlard, P. D. Orahovats, A. P. Sullivan, Jr., G. Purdue, F. K. Heath, and K. Pfister, *3rd, J. Am. Chem. Soc.*, **78**, 2342 (1956); B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(10) *Inter al.*, B. Elpern, P. Carabateas, A. E. Soria, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **81**, 3784 (1959); E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959) and references cited therein; I. N. Nazarov, N. S. Prostakov, I. G. Zavel'skaya, and N. N. Mikheeva, *Izvest. Vysshykh Ucheb. Zavedenii, Khim. i. Khim. Tekhnol.*, No. 3, 69 (1958) [*Chem. Abstr.*, **53**, 4285 (1959)] and earlier references; P. M. Frearson, D. G. Hardy, and E. S. Stern, *J. Chem. Soc.*, 2103 (1960) and references cited therein; A. H. Beckett, A. F. Casey, and G. Kirk, *J. Med. Pharm. Chem.*, **1**, 37 (1959); P. A. J. Janssen *et al.*, *J. Med. Pharm. Chem.*, **2**, 271 (1960) and earlier references; B. G. Boggiano, V. Petrow, O. Stephenson, and A. M. Wild, *J. Chem. Soc.*, 1143 (1959).

(11) (a) N. B. Eddy, H. Besendorf, and B. Pellmont, *Bull. Narcotics, U.N., Dept. Social Affairs*, **10**, No. 4, 23 (1958); (b) N. B. Eddy, *Chem. & Ind.*, 1462 (1959); (c) P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960).

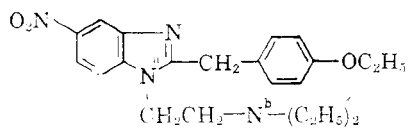
(12) The only strong analgesic type cited by Eddy[11b] as an exception to this rule, the benzimidazoles described by A. Hunger, J. Kebrle, A. Rossi and K. Hoffmann, *Experientia*, **13**, 400 (1957) [see also F. Gross and H. Turrian, *Experientia*, **13**, 401 (1957)], can be seen not to be exceptional; *i.e.*, in the exampled formula, if N^b is considered as the basic nitrogen (as it should be), then N^a represents the "central" atom meeting the requirements.

TABLE III

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compound	λ_{max} mμ	log E
I·HCl	222	4.24
	280	3.76
XVII·HCl	222	4.30
	280	3.78
II·HCl	222	4.15
	280	3.71
Ind-*N*-Methyl-II.HCl[b]	227	4.20
	288	3.74
III·HCl	223	4.48
	282	3.75
IV·HCl	223	4.48
	282	3.76
IX	223	4.52
	252	4.26
	280[c]	3.82
V·HCl	223	4.31
	282	3.78

[a] Spectra determined using a Beckman Model DU spectrophotometer; solvent: 95% ethanol. [b] 4-(1-Methyl-3-indolylethyl)-1-methylpiperidine.[2] [c] Shoulder.



with morphine-like analgesia and it may be that these rather than analgesic potency *per se* are what are associated with morphine-like structural features. The *N*-aralkylpiperidines listed in Tables I and II (and other, related derivatives) quite generally display marked depressant effects on the central nervous system (mice and dogs), whereas, as can be seen from the tables, only a limited group of the compounds have analgesic activity. This structural specificity supports the view that the observed analgesic effects actually are associated with blocking of the perception of pain and are not merely evidence of general central depression.[13]

Inspection of Tables I and II reveals that in this series analgesic efficacy requires the 4-(indolylethyl)-*N*-aralkylpiperidine structure (IV *vs.* II; IV *vs.* XX; VII *vs.* XVIII). Optimum activity attends those compounds in which an *N*-unsubstituted indole nucleus is attached through its 3-position [IV and VII *vs.* XV (more toxic) and XVI; IV *vs.* XIX], and in which a two carbon chain links the benzene ring with the piperidine nitrogen (IV *vs.* III and VI). It is interesting to note, however, that the benzyl derivative III is a highly effective compound, almost as active as the phenethyl compound IV and appreciably more so than the phenylpropyl analog VI. This sharply contrasts with the pethidine series in which the highest potency is associated with a three carbon separation.[11c]

From an over-all standpoint, the optimum compounds of this series are IV, and its piperideine V and phenacyl VIII analogs, all of which are comparable to morphine in analgesic activity in mice and rabbits. The structural specificity found in this series invites efforts to clarify the observed empirical relationships. It will be of particular interest to ascertain whether or not analgesic activity resides in only one of the enantiomorphic forms.

EXPERIMENTAL[14]

Intermediates. Synthesis of the requisite indolylethylpyridines was reported earlier.[2] *p*-Nitrophenethyl bromide was prepared as described in the literature.[15] 4-Phenethylpiperidine, b.p. 120–127° (3 mm.), n_D^{25} 1.5301, hydrochloride salt m.p. 182–184°,[16] was prepared by the hydrogenation of 4-phenethylpyridine[17] in aqueous acetic acid with Adams platinum oxide, conditions previously defined for the reduction of 4-benzylpyridine.[18]

Hydrogenation of indolylethylpyridine bases. 4-(3-Indolylethyl)piperidine (I). A. *In glacial acetic acid.* A solution of 53.0 g. (0.24 mole) of 4-(3-indolylethyl)pyridine in 200 ml. of glacial acetic acid was hydrogenated over 1.2 g. of platinum oxide (Adams catalyst) at room temperature and 50 p.s.i. in an Adams-Parr apparatus. Hydrogen absorption was slow, the calculated amount being absorbed in 45 hr. The filtered solution was concentrated *in vacuo* to a thick, red oil which was taken up in dilute aqueous acid. The aqueous solution was washed with ether and made alkaline to precipitate an oil which solidified. The solid was recrystallized (with charcoal) from isopropyl alcohol to yield 37.7 g. (69%) of I as off-white crystals, m.p. 162–163°.

B. *In acidified aqueous ethanol.* When a solution of 44.5 g. (0.2 mole) of 4-(3-indolylethyl)pyridine in a mixture of 100 ml. of water, 80 ml. of ethanol and 20 ml. of concd. hydrochloric acid was shaken in an Adams-Parr apparatus with 1.0 g. of platinum oxide at room temperature and 50 p.s.i., hydrogen absorption was complete in less than 20 hr. Work-up afforded 36 g. (78% yield) of I, m.p. 161–162°; mixture melting point with the product obtained in A showed no depression.

Alkylation of indolylethylpiperidines. The following examples will illustrate the procedures used for the preparation of many of the compounds described in Tables I and II.

A. *4-(3-Indolylethyl)-1-phenethylpiperidine* (IV). A stirred mixture of 125 g. (0.55 mole) of I, 150 g. (1.2 moles) of sodium carbonate (monohydrate) and 750 ml. of isopropyl alcohol was heated to reflux and a solution of 102 g. (0.55 mole) of phenethyl bromide in 125 ml. of isopropyl alcohol was added, dropwise. Stirring and heating was continued for 16 hr. The hot reaction mixture was filtered, the filtrate was concentrated *in vacuo* to a smaller volume and cooled in an ice bath. Recrystallization of the resultant precipitate from ethanol provided 148 g. (81% yield) of IV, m.p. 129–130°.

(13) On the other hand, P. A. J. Janssen *et al.*, *J. Med. Pharm. Chem.*, 1, 281 (1959); also Jansen *et al.*[10] appear to regard the lack of morphine-like extra-analgesic properties to be evidence of the lack of analgesic action.

(14) 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.

(15) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1435 (1940).

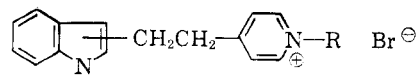
(16) C. F. Bailey and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 1633 (1930), report b.p. 126–130° (3 mm.), n_D^{25} 1.5293, hydrochloride salt m.p. 171–173°, for this compound obtained by the nickel catalyzed hydrogenation of 4-stilbazole.

(17) F. W. Bergstrom, T. R. Norton, and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945).

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

TABLE IV

4-(INDOLYLETHYL)PYRIDINIUM SALTS



	R	Indole Position	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Bromine, %[a] Calcd.	Bromine, %[a] Found
XXI	Phenethyl	3	157–157.5	$C_{23}H_{23}BrN_2$	67.81	67.42	5.69	5.86	19.62	19.59
XXII	γ-Phenylpropyl	3	[b]	$C_{24}H_{25}BrN_2$					18.97	18.87
XXIII	Phenoxyethyl	3	149–151	$C_{23}H_{23}BrN_2O$	65.25	65.66	5.48	5.81	18.88	18.64
XXIV	Phenethyl	1	151–154	$C_{23}H_{23}BrN_2$	67.81	68.08	5.69	5.68	19.62	19.60

[a] Ionic bromine by potentiometric titration. [b] Shrinks and melts gradually above 65°

The hydrochloride salt, recrystallized from isopropyl alcohol, melted at 225–226°.

B. *4-(3-Indolylethyl)-1-(p-nitrophenethyl)piperidine* (XII). This alkylation may proceed *via* *p*-nitrostyrene.[15,19] To a mixture of 22.8 g. (0.1 mole) of I and 32 g. (0.3 mole) of anhydrous sodium carbonate in 150 ml. of isopropyl alcohol, stirred and heated to reflux on a steam-bath, was added, dropwise, a solution of 23.0 g. (0.1 mole) *p*-nitrophenethyl bromide in 100 ml. of isopropyl alcohol. After 21 hr. at reflux the reaction mixture was diluted with water and the precipitate was recrystallized from chloroform–petroleum ether (b.p. 60–70°) to give 23.4 g. (64% yield) of XII, m.p. 173–175°.

C. *4-(3-Indolylethyl)-1-phenacylpiperidine* (VIII). To a stirred mixture of 22.8 g. (0.1 mole) of 4-(3-indolylethyl)-piperidine, 33.0 g. (0.2 mole) of hydrated potassium carbonate and 150 ml. of boiling toluene was added, dropwise, a solution of 15.5 g. (0.1 mole) of phenacyl chloride in 50 ml. of toluene. After being stirred and heated for 8 hr., the reaction mixture was diluted with 500 ml. of hot benzene, filtered and the filtrate was allowed to cool. The crystalline precipitate that formed was recrystallized from benzene to yield 23.0 g. (70%) of VIII, white flakes, m.p. 173–174°.

D. *4-(3-Indolylethyl)-1-(β-hydroxyphenethyl)piperidine* (VII). A mixture of 11.4 g. (0.05 mole) of I and 6.0 g. (0.05 mole) of styrene oxide was heated in an oil bath at a bath temperature of 150° for 7 hr. The cooled melt was crystallized from ethanol to yield 10.0 g. (58%) of VII, m.p. 133–135°.

4-(Indolylethyl)pyridinium salts. 4-(3-Indolylethyl)-1-phenethylpyridinium bromide (XXI). An example will illustrate the procedure used for obtaining the salts listed in Table IV. A solution of 235 g. (1.05 moles) of 4-(3-indolylethyl)pyridine and 226 g. (1.2 moles) of phenethyl bromide in a liter of acetonitrile was heated at reflux on a steam bath for 8 hr. The oily precipitate, which crystallized on cooling, was recrystallized from isopropyl alcohol to yield 345 g. (81%) of XXI, m.p. 157–157.5°.

Hydrogenation of 4-(indolylethyl)pyridinium salts. 4-(3-Indolylethyl)-1-phenethylpiperidine (IV). A solution of 102 g. (0.25 mole) of XXI in 1 l. of 75% aqueous methanol was stirred with 2.5 g. of Adams platinum oxide catalyst at 65° and a hydrogen pressure of 400 p.s.i. in a 2-l. Magne Dash autoclave. Absorption of hydrogen was complete in 2–4 hr. The hot mixture was filtered and the catalyst thoroughly washed with hot methanol. The combined filtrates were diluted with water, made alkaline with aqueous ammonia, and the precipitate was recrystallized from ethanol to yield 73 g. (88%) of IV, m.p. 130–132°. The melting point of a mixture with the product obtained by the reaction of I with phenethyl bromide was not depressed. The hydrochloride salt melted at 225–226° after recrystallization.

4-(3-Indolylethyl)-1-phenethyl-Δ³-piperideine (V). To a stirred solution of 20.0 g. (0.05 mole) of XXI in 200 ml. of methanol was added, dropwise at a rate sufficient to maintain gentle reflux, a solution of 15.2 g. (0.4 mole) of sodium borohydride in 100 ml. of methanol. After the addition was complete the solution was heated under reflux on a steam bath for 2 hr., concentrated to about one-half its volume and cooled to provide a crystalline precipitate. This was thoroughly washed with water, dried and recrystallized from benzene-petroleum ether (b.p. 60–70°) to give 12.6 g. (76% yield) of V, colorless crystals, m.p. 132–133°. The melting point on admixture with IV was depressed to 119°.

4-(3-Indolylethyl)-1-(p-aminophenethyl)piperidine (XIII). An exothermic reaction and vigorous evolution of gas took place when a rapidly stirred solution of 10.0 g. (0.026 mole) of XII and 5.0 g. of 85% hydrazine hydrate (0.085 mole) in 200 ml. of ethanol was treated with approximately 2 g. of Raney nickel catalyst (W-2) and warmed gently on a steam bath. The steam bath was removed and the rate of gas evolution controlled by ice-cooling of the reaction flask. At the end of 5 min. the initial reaction had subsided and the reaction mixture was heated under reflux with stirring for 5 hr. Concentration of the filtered solution under reduced pressure left a residue which was extracted with hot benzene. The benzene solution was diluted with ether and acidified with etheral hydrogen chloride. Recrystallization of the precipitate from methanol–ethyl acetate afforded 5.8 g. (55% yield) of XIII as the dihydrochloride salt, melting with decomposition at 293°.

1-(3-Indolylethyl)-4-phenethylpiperidine (XX). To a mixture of 17.0 g. (0.09 mole) of 4-phenethylpiperidine and 27.0 g. (0.2 mole) of anhydrous potassium carbonate in 250 ml. of dried ethylene glycol dimethyl ether was added, dropwise with stirring, a solution of 20.7 g. (0.1 mole) of 3-indoleglyoxylyl chloride[20] in another 250 ml. of the diether. The reaction mixture was stirred at room temperature for 2 hr. and then heated on a steam bath for 1 hr. The reaction mixture was filtered, the filtrate was evaporated to dryness and the residue was crystallized from chloroform–petroleum ether and recrystallized from isopropyl alcohol to yield 16.5 g. (51%) of *1-(3-indoleglyoxylyl)-4-phenethylpiperidine*, m.p. 179–183°.

The whole of this product (0.05 mole) dissolved in 300 ml. of ethylene glycol dimethyl ether (dried over sodium hydride) was added, dropwise with stirring, to a slurry of 5.6 g. (0.15 mole) of lithium aluminum hydride in 200 ml. of the glycol ether. After the addition was complete, the reaction mixture was heated at reflux for 9 hr. Ethyl acetate was added to the cold reaction mixture followed by water and dilute hydrochloric acid. The resultant acid mixture was treated with 90 g. (0.3 mole) of potassium sodium tartrate, made strongly alkaline and extracted with ether. When the ether extract was shaken with 2% hydrochloric acid, a water-insoluble hydrochloride salt precipitated. Recrystalli-

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zation from methanol afforded 10.5 g. (69% yield) of the hydrochloride salt of XX as small, colorless crystals, m.p. 233–235°.

Decomposition of the salt provided XX, colorless needles from benzene–petroleum ether, m.p. 119–120° (lit.[8] gives m.p. 119°).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOPE COLLEGE]

Synthesis of a Series of Derivatives of Ethyl 2-Pyridylacetate

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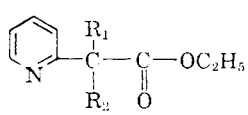
Monosubstitution on the methylene group of ethyl 2-pyridylacetate (I) was effected by allowing its sodium derivative to react with alkyl, allyl, and aryl halides. Substitution was shown to be on the methylene group by hydrolyzing and decarboxylating the butyl derivative of (I) to give α-amylpyridine. Benzoyl chloride reacted with I to give α-dibenzoyl-α-(2-pyridyl)-acetate. The aldehyde functions of benzaldehyde and of hexaldehyde were condensed with the methylene group in the presence of a basic catalyst. Acrolein underwent a Michael addition with I in the presence of sodium ethoxide. Nitrosation yielded the oxime.

A number of reactions of I have been reported by previous investigators: the Michael condensation[1] with acrylonitrile to form γ-carbethoxy-γ-(2-pyridyl)butyronitrile (II), the reactions[2] with ethyl chloroacetate and potassium ethoxide to form ethyl 2-pyridylsuccinate (III), with ethyl formate and potassium to form ethyl hydroxymethylene(2-pyridyl)acetate (IV), and with γ-phenoxypropyl bromide and potassium in diethyl ether to for ethyl phenoxy-α-(2-pyridyl)valerate (V), the condensation[3] with β-phenoxyethyl bromide to form ethyl α-(2-pyridyl)-γ-phenoxy-*n*-butyrate (VI), and the preparation of ethyl α-bromo-2-pyridylacetate[4] (VII) by the addition of I to a solution of bromine in carbondisulfide.

Chart 1

Reaction Products of Ethyl(2-Pyridyl)acetate



I. $R_1 = H$; $R_2 = H$
II. $R_1 = H$; $R_2 = CH_2CH_2CH_2CN$
III. $R_1 = H$; $R_2 = CH_2—C(=O)—OC_2H_5$
IV. $R_1R_2 = =CHOH$
V. $R_1 = H$; $R_2 = CH_2CH_2CH_2OC_6H_5$
VI. $R_1 = H$; $R_2 = CH_2CH_2OC_6H_5$
VII. $R_1 = H$; $R_2 = Br$
VIII. $R_1 = H$; $R_2 = CH_2CH_2CH_2CH_3$
IX. $R_1 = H$; $R_2 = CH_2CH_2CH_2CH_2CH_2CH_3$
X. $R_1 = H$; $R_2 = CH_2C_6H_5$
XI. $R_1 = H$; $R_2 = CH_2CH=CH_2$
XII. $R_1 = CC_6H_5(=O)$; $R_2 = CC_6H_5(=O)$
XIII. $R_1R_2 = =CHC_6H_5$
XIV. $R_1R_2 = =CH(CH_2)4CH_3$
XV. $R_1 = H$; $R_2 = CH_2CH_2CHO$
XVI. $R_1R_2 = =NOH$
XVII. $R_1 = H$; $R_2 = NH_2$

In our laboratory the sodium derivative of I, prepared in benzene, reacted with butyl bromide giving a 50% yield of ethyl α-(2-pyridyl)caproate (VIII). By using hexyl bromide, a similar yield of ethyl α-(2-pyridyl)caprylate (IX) was obtained. Lesser yields were obtained when such basic reagents as sodium hydride, sodium amide, sodium ethoxide, phenyllithium, or butyllithium were employed. The butyl derivative of I was converted to amylpyridine by hydrolysis and decarboxylation according to the method described by Doering and Pasternak.[5] The sodium derivative of I, prepared by using sodium ethoxide, reacted with benzyl chloride to give ethyl α-(2-pyridyl)-β-phenylpropionate (X) in 52% yield. X was hydrolized and decarboxylated to 2-phenylethylpyridine (dihydro-α-stilbazole).

As a representative aliphatic unsaturated compound, allyl bromide was added to the sodium salt of I and gave a 27% yield of ethyl α-(2-pyridyl)-Δ^4-pentenoate (XI). Sodium in benzene when used as a basic catalyst provided a better yield than sodium ethoxide in ethanol.

Benzoyl chloride was found to react spontaneously with I to give what proved to be ethyl α-dibenzoyl-α-(2-pyridyl)acetate (XII) in 38%

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