where these have even a greater net negative charge than I_0 at pH 10, indicates that factors other than simple electrostatic repulsion are involved. Charged groups located in the bonding region or regions of two 6,000 units probably are required to dissociate the monomer. The negative charges furnished by the *p*-carboxyphenylazo groups most likely are distributed over the surface of the monomer and not in the bonding regions. Since dissociation occurs near the pK for the ionization of the hydroxyl groups of tyrosine, the stabilization of the 12,000 unit may involve tyrosine residues either by hydrogen bonding or non-polar interactions.

Of considerable interest is the increased association in acid solution, leading to the formation of soluble polymers in equilibrium with monomer. The facts that (1) there appears to be a critical micelle concentration below which no polymer is detected, (2) this concentration decreases as more p-carboxyphenylazo groups are added and (3) the size of the polymer is relatively independent of total protein concentration but increases if the ionic strength is raised or more non-polar groups are attached, suggest that the formation of polymers may be a micellar phenomenon. The factors operating to limit the polymer size may resemble those responsible for determining the size of soap micelles as discussed by Debye²⁸ and Reich²⁹ and by Waugh¹³ in connection with protein associations.

If the Debye theory is applied to account for the formation of soluble polymers of azoinsulins, the

(28) P. Debye, J. Phys. Chem., 53, 1 (1949).

(29) I. Reich, *ibid.*, **60**, 257 (1956).

results shown in Table II, columns 7–10, are obtained.³⁰ Extrapolation of $W_{\rm m}$, the attractive energy per monomer, leads to a value of approximately -7,000 cal. for unreacted insulin which is in good agreement with that reported by Oncley and Ellenbogen.¹⁰ The increase of $W_{\rm m}$ per added azo group is about -2,000 cal.

Recently Reich²⁹ has shown that the Debye theory leads to incorrect calculations of the micelle size distribution. Reich's theory, which minimizes the free energy of the system rather than the free energy per micelle, leads to an unsymmetrical micelle size distribution. A sharp rise occurs as the number of molecules, N per micelle approaches the most energetically favored number, N_0 , whereas a more gradual decline is expected for $N > N_0$. A similar asymmetric distribution of polymers formed by the azoinsulins is observed upon ultracentrifugation. The size of the most stable micelle is shown to depend not only on the ionic strength but on the ratio, S/A, where A is the total surface of the molecule and S is the fraction covered by polar groups. At zero ionic strength, A - S, the fraction of hydrocarbon surface of $I_{3.9}$, is estimated to be 0.40, which is suggestively close to the fraction of non-polar amino acids in insulin, 0.41.13 Further possible application of Reich's theory to the azoinsulin system would require knowledge of entropy and enthalpy changes per monomer occurring upon aggregation.

(30) Debye's equations which apply to disk shaped micelles were used, although the micelle size was determined assuming a spherical structure.

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[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY OF THE ORTHO RESEARCH FOUNDATION]

Synthetic Oxytocics. I. Synthesis and Reactions of 3-Indolyl-2'-pyridylcarbinols and of 2,3-(2',3'-Indolo)-hexahydroquinolizines

By Henry Bader and William Oroshnik

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3-Indolyl-2'-pyridylcarbinol was prepared from 3-indolealdehyde and 2-pyridyllithium. It was catalytically reduced to 3-indolyl-2'-piperidylcarbinol (V) and to 2-skatylpiperidine. The latter compound could be N-methylated by lithium aluminum hydride reduction of its N-formyl derivative. It also was transformed by a modified Pictet-Spengler condensation into the 2,3-(2',3'-indolo)-hexahydroquinolizine (VII, R = H) or its 1'-hydroxymethyl derivative, according to reaction conditions. A similar condensation with the carbinol V gave VII, R = OH.

The highly complex structure of ergonovine, the isopropanolamide of lysergic acid (I), has motivated many searches for a potent oxytocic drug among simpler compounds, particularly those which represent fragments of the lysergic acid molecule. In some recent work along these lines, Akkerman and Veldstra¹ accomplished the synthesis of compound II and several of its derivatives, thereby attaining the ring structure of dihydrolysergic acid opened at the 10, 11-junction. The method of synthesis consisted essentially of the condensation of isatin with the appropriate α -picoline and reduction of the resulting dioxindole (after N'-methylation) with sodium in butanol. The

(1) A. M. Akkerman and H. Veldstra, Rec. trav. chim., 73, 629 (1954).

over-all yields obtained were only about 5%. Unfortunately, none of the compounds showed very significant oxytocic activity.



In a similar program in this Laboratory, the synthesis of compound II also was achieved, and its pharmacological properties were found to closely parallel those reported by the Dutch workers. Nevertheless, the superiority of the method of synthesis used in the present work (Chart I) and its extension to the formation of indolohexahydroquinolizines appeared to warrant an account of its details.



3-Indolyl-2'-pyridylcarbinol (III) readily was formed on condensing 3-indolealdehyde² with 2pyridyllithium.³ This appears to be the first instance of a successful condensation of indolealdehyde with an organometallic reagent. Vields as high as 80% can be obtained when two equivalents of pyridyllithium are used. With one equivalent, the yield was only 55%. However, 35% of the aldehyde was recovered in this case, indicating that part of the organometallic reagent is consumed by the acidic nitrogen atom of the indole nucleus.

In a similar manner, 5-chloro-2-pyridyllithium (prepared from 2-bromo-5-chloropyridine) gave 3-indolyl-(5-chloro-2-pyridyl)-carbinol.

The carbinol III and its chloro derivative proved to be considerably more stable to air oxidation than the parent compound, skatyl alcohol,⁴ showing no deterioration after several months storage either in the solid state or in solution. Although these carbinols are as susceptible as skatyl alcohol to the action of mineral acids or aqueous organic acids, they appeared to be relatively stable in anhydrous ethanolic acetic acid.

Selective hydrogenation of the pyridine ring in III, with simultaneous hydrogenolysis of the hydroxyl group, occurred with platinum oxide catalyst in 20% ethanolic acetic acid. The resulting skatylpiperidine (IV) was isolated in 52% yield. Its properties were identical with those reported by Akkerman and Veldstra¹ for the sodiumbutanol reduction product of the dioxindole VI. A very small amount (3.5%) of the corresponding carbinol V was also obtained and, in addition, a 30% yield of what appeared to be, judging from its

(3) H. Gilman and S. M. Spatz, J. Org. Chem., 16, 1485 (1951).

(4) This compound has only recently been prepared in a pure state by E. Leete and L. Marion, Can. J. Chem., **31**, 775 (1953).

ultraviolet and infrared spectra, the symmetrical ether of V.



In neutral or alkaline media (*i.e.*, ethanol at pH 7 and 10) virtually no reduction occurred with Adams catalyst. The slightly acidic hydrogenation conditions used here are unique in affording for the first time a method whereby a pyridine nucleus can be selectively reduced catalytically in the presence of the indole group. Such selective reductions have been accomplished in the past only by the use of sodium in alcohol. In glacial acetic acid Adams catalyst appears to show a preference for the benzene ring of the indole nucleus; *e.g.*, skatylisoquinoline gives tetrahydroskatylisoquinoline,⁵ tetrabyrine and yobyrin give the corresponding tetrahydroindole derivatives.⁶

Lithium aluminum hydride effected no change in III, even at the temperature of boiling 1,2-dimethoxyethane $(82-85^{\circ})$. This is rather surprising inasmuch as the related skatyl alcohol is readily reduced to the corresponding hydrocarbon by this reagent.⁴

The structures assigned to compounds III, IV and V were corroborated by their ultraviolet spectra. Those of III and its 5-chloro derivative exhibit both the indole $(\lambda\lambda_{max} 220, 280 \text{ and } 290 \text{ m}\mu)$ and pyridine $(\lambda\lambda_{max} 265 \text{ and } 270 \text{ m}\mu)$ chromophores. Compounds IV and V, and the presumed ether of V, show only the indole chromophore.

N'-Methylation of compound IV readily was accomplished by the method of Blicke and Lu⁷ wherein the amine is first formylated by reaction with chloral and the resulting N-formyl derivative then reduced with lithium aluminum hydride. The product proved identical with that obtained by Akkerman and Veldstra on reducing the methiodide of VI with sodium and butanol.¹

When methylation of IV was attempted by the standard Clarke–Eschweiler reaction with formalin and formic acid, a Pictet–Spengler ring closure occurred instead, giving rise to 2,3-(2',3'-indolo)-hexahydroquinolizine (VII, R = H).⁸ Evidence of the formation of quinolizine was obtained by the analytical formula, C₁₅H₁₈N₂, and the positive "carboline blue" color test,^{9,10} characteristic of the tetrahydro- β -carboline ring system. Corroborative evidence also was obtained from the ultraviolet spectrum, which corresponded to that of tetrahydroharman or of 2,3-dimethylindole (Table I). In these compounds the absorption maximum

(5) V. Boekelheide and Chu-Tsin Liu, THIS JOURNAL, 74, 4920 (1952).

(6) M. Janat, J. Keufer and J. LeMen, Bull. soc. chim. France, 230 (1952); P. Karrer and P. Waser, Helv. Chim. Acta, 32, 409 (1949);
H. Schwarz and E. Schlittler, *ibid.*, 34, 629 (1951).

 F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, 74, 3933 (1952).
 (8) The only other example of the tetracyclic ring system VII in the literature is the 9-keto derivative of VII prepared by J. Keufer, Ann. Pharm. Franc., 8, 818 (1950), from tetrahydronorharmane.

(9) D. G. Harvey, E. J. Miller and W. Robson, J. Chem. Soc., 153 (1941).

(10) G. R. Clemo and G. A. Swan, ibid., 617 (1946).

⁽²⁾ Several excellent methods of preparation of this aldehyde have been described recently by: F. T. Tyson and J. T. Shaw, THIS JOUR-NAL, **74**, 2273 (1952); H. R. Snyder, S. Swaminathan and H. J. Sims, *ibid.*, **74**, 5110 (1952); E. Campaigne and W. L. Archer, *ibid.*, **75**, 989 (1953); Jan Thessing, *Chem. Ber.*, **87**, 507 (1954); S. Swaminathan and S. Ranganathan, *Chemistry & Industry*, 1774 (1955).

Compound	λ_{max} , $m\mu$	€max	Compound	$\lambda_{max}, m\mu$	€max
III, $X = H^b$	218.5	35,300	Skatole ⁴	224	28,200
	265	8,100		282.5	5,400
	270			290	4,700
	277.5	7,450			,
	287.5	6,100	VII, $R = H^{a}$	225.5	35,000
				283	6,950
III, $X = Cl^b$	219-219.5	43,450		289.5	5,700
	272.5	10,200			,
	277.5	10,000	VII, $R = OH^c$	223.7	33,600
	290	7,200		282.5	7,850
				291.5	6,600
IV ^e	221.5	32,800			
	282	5,900	VII, $R = H_1 1'$ -CH ₂ OH ^c	227.5	32.750
	289.8	5,000	, , ,	275	7,250
				280-281 5	7 350
				290.5-291	5,550
V ^e	220	36,300			0,000
	281	5,800			
	289.8	5,000	2,3-Dimethylindole4	227.5	29,500
Skatyl alcohol ⁴	219	29.500		283	7.100
	279	5,800		290	6,100
	287.5	5,000			0,200

TABLE I

^a Solvent: 95% ethanol. ^b Indole and pyridine chromophores. ^c Indole chromophore.

is shifted bathochromically by 3.5 to $4 \text{ m}\mu$ from that of 3-alkylated indoles as a result of the additional alkylation at the 2 position.



In a similar manner, compound V was cyclized to the 9-hydroxy derivative of VII. Its absorption characteristics agreed with those of the compound VII, R = H.

N'-Methyl derivatives of III and IV were not obtained in the reactions described above, although these products might have been expected from competition by a Clarke-Eschweiler reaction. A similar instance of an exclusive Pictet-Spengler reaction under such conditions has been reported by Castrillon with mescaline.¹¹ Baltzly¹² has offered evidence that the pH is a controlling factor in competition between the Pictet-Spengler and Clarke-Eschweiler reactions, the former being favored when the ρ H falls below 7. However, the reactivity of the amine involved appears to be an even more important determining factor, for certain phenolic amines undergo Pictet-Spengler cyclization exclusively even under alkaline conditions. A similar reactivity has also been observed here with compound IV, which yields the N-methylol derivative of VII when it is heated with formalin in the absence of acids. In this connection it should be noted that the 4,5-benzo analog of IV has been reported to give high yields of VIII with formalin at a pH of only 5.5.5

(11) J. C. Castrillon, THIS JOURNAL, 74, 558 (1952).

(12) R. Baltzly, ibid., 75, 6038 (1953).

Neither VII nor its hydroxy derivative showed significant oxytocic activity. The methiodide of VII was likewise inactive as an oxytocic.

Experimental

3-Indolyl-2'-pyridylcarbinol (III).—A solution of 2-pyridyllithium was prepared by the method of Gilman and Spatz³ from 158 g. (1.0 mole) of 2-bromopyridine and 171 g. (1.25 moles) of *n*-butyl bromide in 1300 ml. of dry ether. This solution was cooled to -18° , and 72.6 g. (0.5 mole) of solid 3-indolealdehyde was added in portions with vigorous stirring. In spite of an external cooling bath at -50° , the temperature rose to 4°. Stirring was continued at -18° for 90 minutes and the reaction complex decomposed with ammonium chloride solution. The crude solid which separated was filtered and extracted with methylene dichloride in a Soxhlet apparatus. The cooled extract yielded 90.9 g. (81.1% theory) of 3-indolyl-2'-pyridylcarbinol, m.p. 154-155°. It crystallized from water in silvery plates and from benzene in fine feathery needles, both melting at 160-161°. The infrared absorption spectrum showed a hydroxyl band at 3.03μ .

Anal. Caled. for $C_{14}H_{12}N_2O\colon$ C, 74.98; H, 5.39; N, 12.49. Found: C, 75.18; H, 5.40; N, 12.58.

3-Indolyl-5'-chloro-2'-pyridylcarbinol.—The above procedure was repeated on an 0.08-mole scale substituting 2-bromo-5-chloropyridine¹³ for the 2-bromopyridine. The crude solid obtained was fractionally crystallized from methanol, then recrystallized from chloroform and finally from hot water. The yield was 4.9 g. (23.2%) of material melting at 164–167°. The recovered indolealdehyde weighed 4.8 g. (41.7%). The analytical sample of the carbinol was recrystallized consecutively from water and benzene; the rosettes of needles melted at 166–167°.

Anal. Caled. for $C_{14}H_{11}ClN_2O$: C, 64.98; H, 4.28; N, 10.82; Cl, 13.71. Found: C, 65.42; H, 4.37; N, 10.75; Cl, 13.31.

2-Skatylpiperidine (IV) and 3-Indolyl-2'-piperidylcarbinol (V).—A solution of 26.0 g, (0.116 mole) of 3-indolyl-2'-pyridylcarbinol and 40 ml. of glacial acetic acid in 120 ml. of absolute alcohol was shaken under hydrogen at three atmosphere pressure with 0.65 g, of Adams platinum oxide catalyst. Absorption ceased when 0.333 mole of hydrogen was taken up. The mixture was then filtered and poured into a solution of 30 g, of sodium hydroxide in 2 liters of

(13) Prepared by the method of F. H. Case, ibid., 68, 2576 (1946).

water, and the oil which precipitated was induced to solidify by keeping it at 0°. The solid was filtered and the aqueous filtrate was set aside for further work-up. Crystallization of the solid from benzene after a prior treatment of its solution with charcoal gave 12.8 g. of 2-skatylpiperidine (51.6% theory) as needles, m.p. 156–156.5°. (Akkerman and Veldstra¹ report m.p. 156–157°.)

Anal. Caled. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.59; H, 8.29; N, 12.93.

When ethereal hydrogen chloride was added to a benzene solution of the base, the **hydrochloride** precipitated. After two precipitations from isopropyl alcohol-benzene solution by means of ether, the hydrochloride melted at 78-82°.

Anal. Calcd. for $C_{14}H_{19}ClN_2\cdot H_2O\colon$ N, 10.42; Cl, 13.19. Found: N, 10.47; Cl, 13.00.

By adding cyclohexane to the concentrate of the benzene mother liquor, obtained from the recrystallization of IV, 6.6 g. (30% theory) of product, m.p. 95°, was obtained. After recrystallization from cyclohexane it melted at 119.5-121.5°. Solubility and absorption properties suggested this product to be the **ether of V**.

Anal. Calcd. for $C_{28}H_{34}\mathrm{N}_4\mathrm{O}\colon$ N, 12.65. Found: N, 12.75.

The aqueous filtrate mentioned above was extracted with ether and the extract dried and concentrated. Trituration of the solid residue with hot benzene left 0.8 g. (3.5%) of colorless microplates, m.p. 197°, which crystallized from acetone in plates melting at 200–201.5°. The infrared spectrum (in potassium chloride) showed a hydroxyl band at 3.2μ and C–O stretching band at 9.35μ . This and the ultraviolet spectrum (Table I) indicate 3-indolyl-2'-piperidylcarbinol (V).

Anal. Caled. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.11; H, 7.86; N, 12.37.

1-Methyl-2-skatylpiperidine (II).—Chloral (2 ml., 0.02 mole) was added at 0° to a suspension of 4.3 g. (0.02 mole) of 2-skatylpiperidine in 20 ml. of chloroform. The solution was refluxed for 1 hr., the solvent was removed *in vacuo* and the oily residue dissolved in 60 ml. of a 1:1 benzene-dry ether mixture. When this solution was added to a solution of 0.76 g. (0.02 mole) of lithium aluminum hydride in 40 ml. of ether, refluxing commenced spontaneously and was further maintained for 6 hr. The mixture was then cooled to -20° and decomposed with 10 ml. of water. The precipitated inorganic solids were extracted repeatedly with benzene and ether, the extracts combined with the main ether layer, dried and concentrated. The residual oil was dissolved in benzene and treated with ethereal hydrogen chloride. The precipitated gum on crystallization from isopropyl alcohol yielded 3.4 g. (64%) of N-methyl-2-skatylpiperidine hydrochloride, m.p. 221.5°. Recrystallization from an isopropyl alcohol-benzene mixture gave microplates, m.p. 222.5-226.5°.

Anal. Calcd. for $C_{15}H_{21}ClN_2$: C, 68.03; H, 8.00; N, 10.58; Cl, 13.39. Found: C, 68.07; H, 8.00; N, 10.64; Cl, 13.48.

The base was liberated from an aqueous solution of the hydrochloride with alkali, taken up in benzene and, after removal of solvent, crystallized from cyclohexane-petroleum ether (b.p. $40-60^{\circ}$) in pale yellow spherical clusters of crystals, m.p. 109–110°. (Akkerman and Veldstra¹ give m.p. 113–114°.)

Anal. Caled. for $C_{15}H_{20}N_2;$ C, 78.90; H, 8.83. Found: C, 78.98; H, 9.05.

2,3-(2',3'-Indolo)-hexahydroquinolizine (VII, $\mathbf{R} = \mathbf{H}$).— A total of 6.4 g. (0.03 mole) of 2-skatylpiperidine was introduced, in portions, at 0° into 3.5 g. of 98% formic acid. To the paste thus obtained, 2.7 g. of 37% formalin was added, followed with 4 ml. of water and the mixture rerefluxed for 13 hr. The resulting solution was poured into 300 ml. of a 3% solution of sodium hydroxide and the precipitated solid collected. The aqueous solution was extracted with benzene and this yielded a further crop of the crude product. Both crops were treated with charcoal in hot benzene solution, and the solution was concentrated, yielding 3.75 g. (55.0%) of a solid, m.p. 213-216°. Further recrystallization from benzene-cyclohexane mixture and then from cyclohexene gave 2,3-(2',3'-indolo)-hexahydroquinolizine in microprisms which melted at $218-219^\circ$.

Anal. Caled. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.60; H, 7.97; N, 12.29.

The base (VII, R = H) produced a β -carboline color reaction with concentrated sulfuric acid-ferric chloride or sodium nitrite mixtures. A strong violet color was produced immediately, passing slowly into olive-green.

immediately, passing slowly into olive-green. The hydrochloride, precipitated by passing hydrogen chloride into a benzene solution of the base, was recrystallized from isopropyl alcohol or water; the needles melted at 236.5–238.5°. It was much less soluble in hydroxylic solvents than the hydrochlorides of II and IV.

Anal. Calcd. for $C_{15}H_{19}ClN_2$: C, 68.55; H, 7.29; N, 10.66; Cl, 13.49. Found: C, 68.02; H, 7.38; N, 10.25; Cl, 14.07.

The methiodide was formed in benzene-ethanol solution (1 g. of base, 200 ml. of benzene, 10 ml. of ethanol) with a slight excess of methyl iodide. After 3 days at room temperature, the methiodide separated in a 67% yield as pale yellow clusters of microcrystals, m.p. 277° (recrystallization from ethanol did not alter the melting point).

Anal. Caled. for $C_{16}H_{21}IN_2$: C, 52.17; H, 5.75; N, 7.61. Found: C, 52.42; H, 5.95; N, 7.43.

2,3-(1'-Hydroxymethyl-2',3'-indolo)-hexahydroquinolizine.—A solution of 6.4 g. (0.03 mole) of 2-skatylpiperidine in 22.5 ml. of 37% formalin and 20 ml. of isopropyl alcohol was kept for 5.5 hr. in a sealed tube at 140-150°. The contents of the tube were poured into 1 l. of water, the solution made alkaline with sodium hydroxide and extracted with ether. When the dried extract was partly concentrated, 3.85 g. (50%) of the product (VII, $R = H, 1'-CH_2OH$) separated in rosettes of prisms which melted at 180.5°, then resolidified and melted again at 213-214°. Recrystallization from benzene or benzene-cyclohexane did not alter the melting points.

Anal. Calcd. for C₁₀H₂₀N₂O: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.24; H, 7.87; N, 10.78.

The compound produced a β -carboline color reaction analogous to that given by VII, R = H.

The hydrochloride was precipitated from a benzene solution with ethereal hydrogen chloride. After several reprecipitations from isopropyl alcohol-benzene-ether mixture, it melted at $218-219^{\circ}$ dec.

Anal. Caled. for C₁₆H₂₁ClN₂O: N, 9.57; Cl, 12.11. Found: N, 9.33; Cl, 12.58.

9-Hydroxy-2,3-(2',3'-indolo)-hexahydroquinolizine (VII, $\mathbf{R} = \mathbf{OH}$).—To a suspension of 0.6 g. of 3-indolyl-2'-piperidylcarbinol in 2 ml. of water were added, at room temperature, first 0.3 ml. of formic acid (which caused dissolution of the solid) and then 0.3 ml. of 37% formalin. The solution was kept for 3 days at room temperature and then 10% sodium hydroxide was added, precipitating a solid, m.p. 220°, which crystallized from isopropyl alcohol in creamy microcrystals, m.p. 234-236° after softening at 225°. It gave a positive β -carboline test and showed a hydroxyl band at 3.15 μ in the infrared.

Anal. Caled. for $C_{15}H_{18}N_2O;\ C,\ 74.35;\ H,\ 7.49;\ N,\ 11.56.$ Found: C, 73.81; H, 7.45; N, 11.11.

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