had m.p. 178–179° after recrystallization from ethyl acetate. It was identical with the product of reaction of *p*-methoxyphenyl isocyanate with 2-mercaptoethyl *p*-methoxycarbanilate in the same proportions.

Anal. Calcd. for $C_{18}H_{20}N_2SO_5$: C, 57.4; H, 5.3; S, 8.5. Found: C, 57.3; H, 5.3; S, 8.5; λ_{co}, 6.10 and 5.97 μ.

(b) 2-(1-Naphthylcarbamoylthio)-ethyl 1-Naphthylcarbamate (V, R = $C_{10}H_7$).—A solution of 2-hydroxyethyl 1-naphthylthiolcarbamate (2.0 g., 0.009 mole), 1-naphthyl isocyanate (0.5 g., 0.01 mole) and one drop of diethylcyclohexylamine in 30 ml. of benzene was refluxed for two hours. The product which separated on addition of ligroin had m.p. 177–178° after recrystallization from ethyl acetate. It was identical with the reaction product of 1-naphthyl isocyanate and 2-mercaptoethyl 1-naphthylcarbamate.

Anal. Calcd. for $C_{24}H_{20}N_2SO_3$: C, 69.1; H, 4.8; S, 7.7. Found: C, 69.0; H, 4.8; S, 7.5; λ_{co}, 6.02 and 5.87 μ.

(c) 2-Carbaniloylthioethyl carbanilate (V, R = C_6H_5) was prepared by reaction of 2-mercaptoethyl carbanilate or 2-hydroxyethyl thiolcarbanilate with phenyl isocyanate. It had m.p. 148–150°; (lit.[4] gives 146°), λ_{co} 6.00 and 5.85 μ.

Preparation of Disulfides. (a) Dithiodiethylene Carbanilate.—2-Mercaptoethyl carbanilate (10 g., 0.051 mole) in 50 ml. of ethanol was stirred during the addition of a solution of ferric chloride (10 g. anhydrous, 0.062 mole) in 50 ml. of ethanol. The copious precipitate which separated was filtered off, washed with ethanol and recrystallized from ethyl acetate to give dithiodiethylene carbanilate (III, R = C_6H_5), m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4S_2$: C, 55.0; H, 5.0. Found: C, 55.1; H, 5.1; λ_{co}, 5.83 μ.

The same compound was obtained by oxidation of 2-mercaptoethanol and reaction of the product with phenyl isocyanate.

(b) Dithiodiethylene *p*-methoxycarbanilate (III, R = C_6H_4OMe) was prepared by a similar oxidation of 2-mercaptoethyl *p*-methoxycarbanilate. It had m.p. 147–148° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{20}H_{24}N_2O_6S_2$: S, 14.1. Found: S, 14.1; λ_{co}, 5.87 μ.

(c) Dithiodiethylene 1-naphthylcarbamate (III, R = $C_{10}H_7$) had m.p. 147–148°. It was prepared by a similar oxidation of 2-mercaptoethyl 1-naphthylcarbamate.

Anal. Calcd. for $C_{26}H_{24}N_2O_4S_2$: S, 12.9. Found: S, 12.9; λ_{co}, 5.87 μ.

Action of Alkali on 2-Mercaptoethyl Carbamates. (a) Aqueous Sodium Hydroxide.—2-Mercaptoethyl carbanilate (3.94 g., 0.02 mole) was melted on a steam-bath and treated with 10% sodium hydroxide solution (8 ml., 0.02 mole). The clear solution, which formed initially, quickly clouded and began to deposit solid with a slight evolution of heat (40–50°). After 30 minutes the solid was filtered off, washed with water and recrystallized a number of times from ethyl acetate to give the polysulfide (VI, R = C_6H_5, n = 3–4), m.p. 112–114°.

Anal. Calcd. for $C_{15}H_{23}NO_2S_4$: C, 47.7; H, 6.1; N, 3.7; S, 33.9; mol. wt., 377. Found: C, 48.8; H, 5.7; N, 3.4; S, 32.9; mol. wt., 353; λ_{co}, 5.87 μ.

Aniline was obtained from the aqueous filtrates from the initial preparation, and identified by conversion to carbanilide, m.p. 238–240°.

(b) Methanolic Potassium Hydroxide.—2-Mercaptoethyl carbanilate (10 g., 0.05 mole) was dissolved in 50 ml. of anhydrous methanol and treated with 10% methanolic potassium hydroxide (56 ml., 0.15 mole). A slight increase in temperature occurred (30–40°) and a solid began to precipitate in two minutes. The mixture of potassium carbonate and product was filtered off, washed with methanol (dried yield 7.0 g.), dilute hydrochloric acid (vigorous effervescence) and water. Recrystallization (once) from ethyl acetate gave the polysulfide (IV, R = C_6H_5, n = 4), m.p. 112–114° (yield 1.2 g.).

Anal. Calcd. for $C_{15}H_{23}NO_2S_4$: C, 47.7; H, 6.1; S, 33.9; N, 3.7. Found: C, 47.8; H, 5.6; S, 33.5; N, 3.7.

Similarly, 2-mercaptoethyl *p*-methoxycarbanilate (10 g.) afforded a polysulfide (VI, R = C_6H_4OMe, n = 3–4), m.p. 145–147° (1.2 g.) on reaction with methanolic potassium hydroxide.

Anal. Calcd. for $C_{14}H_{21}NO_3S_3$: C, 48.8; H, 6.1; S, 27.6. Found: C, 48.6; H, 5.7; S, 29.8.

(c) Sodium *t*-Butoxide.—2-Mercaptoethyl carbanilate (10 g., 0.05 mole) in tetrahydrofuran (100 ml.) was treated at room temperature with a solution of sodium *t*-butoxide in tetrahydrofuran (20 ml., 0.05 mole). The solid which precipitated was filtered off, washed with water and recrystallized from ethyl acetate to give the polysulfide (VI, R = C_6H_5, n = 7–8), m.p. 118–120° (3.02 g.).

Anal. Calcd. for $C_{23}H_{39}NO_2S_8$: C, 44.7; H, 6.3; N, 2.3; S, 41.4. Found: C, 44.5; H, 6.1; N, 2.1; S, 39.6.

Acknowledgment.—The authors wish to express their appreciation to Professor J. D. Roberts of California Institute of Technology, for helpful discussion and advice.

WILMINGTON, DEL.

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

Synthetic Oxytocics. II.[1] Condensation of Indolylmagnesium Bromide with Heterocyclic Aldehydes. Synthesis of 2,3-Benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine

BY HENRY BADER AND WILLIAM OROSHNIK

RECEIVED JULY 25, 1958

Indolylmagnesium bromide, although it fails to react normally with aliphatic and aromatic aldehydes, was found to give 3-indolylcarbinols with 2- and 4-pyridine- and 3-isoquinoline-aldehydes. 3-Indolyl-3′-isoquinolylcarbinol was converted by the route described in Part I[1] to the pentacyclic 2,3-benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine and its methochloride.

The finding, in Part I of this series, that 3-indolealdehyde condenses normally with 2-pyridyllithium made possible a very convenient synthesis of 2-skatylpiperidine (II) through the pyridylcarbinol I (Chart I). In endeavoring to extend the scope of this synthetic route, we also investigated the alternative possibility of obtaining carbinols, such as I, through the condensation of indolylmagnesium bromide with the readily available pyridine-,[2] quinoline-,[3] or isoquinoline[4]-aldehydes.

Actually, the reported experiences with indole Grignard reagents and various aliphatic and

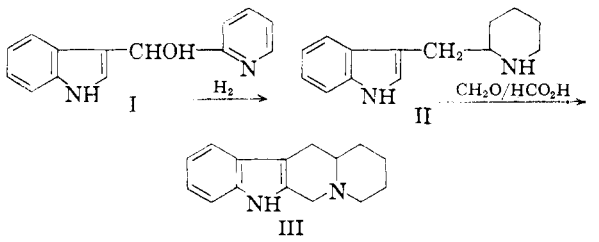
(1) Part I, H. Bader and W. Oroshnik, THIS JOURNAL, **79**, 5686 (1957).

(2) W. Mathes, W. Sauermilch and T. Klein, *Chem. Ber.*, **84**, 452 (1951); V. M. Micovic and M. Lj. Mihailovic, *Rec. trav. chim.*, **71**, 970 (1952); J. P. Wibaut and R. Huls, *ibid.*, **71**, 1021 (1952); V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1956).

(3) A. H. Cook, I. M. Heilbron and L. Steger, *J. Chem. Soc.*, 413 (1943).

(4) B. R. Brown, D. Ll. Hammick and B. H. Thewlis, *ibid.*, 1145 (1951); C. E. Teague and A. Roe, THIS JOURNAL, **73**, 688 (1951).

Chart I



aromatic carbonyl compounds[5] offered little encouragement for this approach. Aliphatic aldehydes are reported to produce 3,3'-diindolylalkanes or the symmetrical ethers of the desired carbinols, and aromatic aldehydes yield only 3,3'-diindolylarylmethanes, the so-called "rosindoles." Formaldehyde has been claimed to produce skatyl alcohol, but more recent work has demonstrated that the reaction product is in fact diindolylmethane.[6,7] Ketones similarly yield 3,3'-diindolyldialkyl- or arylmethane.[8]

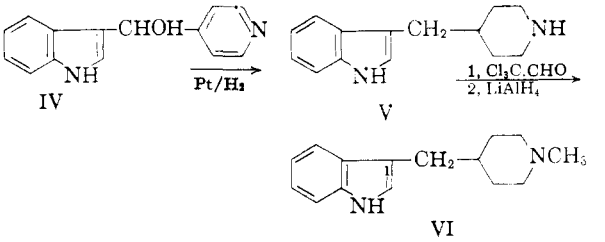
Nevertheless, since no heterocyclic aldehydes had been reported to have been tried with indolylmagnesium bromide, an attempt was made with 2-pyridylaldehyde. At −25°, with a mixture of ether and methylene dichloride as solvent, a 50% yield of the desired 3-indolyl-2'-pyridylcarbinol was obtained. The product I was identical with that obtained by the previous route (Chart I). A small amount of the "rosindole"[9] (6.5%) was also isolated. At 0°, the yield of carbinol dropped to 25%, while that of rosindole correspondingly rose to 44%.

Condensation with 4-pyridylaldehyde at 0° gave good yields of carbinol IV (58%). At 25° with only ether as solvent, the yield dropped to 22%. At 60°, even with methylene dichloride as co-solvent, the yield dropped to 6.5%. In the latter case, considerable quantities of the symmetrical ether of IV (16%) and of the "rosindole" (13%) were formed.

3-Isoquinolinealdehyde gave a 20% yield of the carbinol VII at room temperature. The nature and quantities of the by-products varied with the reaction temperature and with the ether–methylene dichloride ratio.

The success of these condensations in contrast to those with ordinary aldehydes and ketones suggested the possibility that the use here of low temperatures, methylene dichloride as co-solvent, or perhaps the presence of a base (afforded above by the basic aldehydes) may have been responsible. These conditions were therefore applied both singly and collectively to the condensation of indolylmagnesium bromide with benzaldehyde, but with no more success than had been previously reported.[10]

Attempted condensations with other heterocyclic aldehydes were likewise unsuccessful; 2-thenaldehyde gave only the corresponding rosindole, while indolealdehyde failed to react at all.



The new 3-indolylcarbinols obtained above were hydrogenated under the conditions elaborated in Part I (Adams catalyst in 20% absolute ethanolic acetic acid) for the selective reduction of the pyridine ring. The 4'-pyridyl derivative IV gave only 4-skatylpiperidine (V), which could be N'-methylated in good yield to VI by the method of Blicke and Lu[11] (formylation with chloral, followed by reduction with lithium aluminum hydride). The exclusive formation of V in the catalytic hydrogenation of IV differs from the result observed when compound I was similarly reduced (Part I), since in that case some of the corresponding indolylpiperidylcarbinol could be isolated. In contrast to both these results the 3'-isoquinolyl derivative (VII) gave excellent yields of the tetrahydroisoquinolylcarbinol VIII as the only product.

Reductive removal of the hydroxy group from VIII to yield IX (R = H) was readily accomplished with lithium aluminum hydride in (82–85°) boiling 1,2-dimethoxyethane. Similar treatment of the N'-formyl derivative of VIII gave IX (R = Me). In this case removal of the hydroxyl group was combined with the Blicke and Lu method of N-methylation.[11] These reductions are in accord with the previously reported conversion of skatyl alcohol to skatole with lithium aluminum hydride.[7] However, the action of the reagent does not appear to be general with this class of compounds. Both the 2'-pyridyl- and the 2'-piperidylcarbinols failed to react under the identical conditions, while the 4'-pyridylcarbinol led to an intractable mixture.

It seemed of interest to carry out a ring closure of IX (R = H) with formaldehyde in a Pictet–Spengler reaction to obtain the hitherto unknown 2,3-benzo-7,8-(2',3'-indolo)-tetrahydroquinolizine

(5) This subject was reviewed in W. C. Sumpter and F. M. Miller's "Heterocyclic Compounds with Indole and Carbazole Systems," (Interscience Publishers, Inc., New York, N. Y., 1954, pp. 52, 59, 60). In the present paper mention is made only of work not cited by these authors.

(6) H. V. Dobeneck and G. Maresch, *Angew. Chem.*, **63**, 469 (1951).

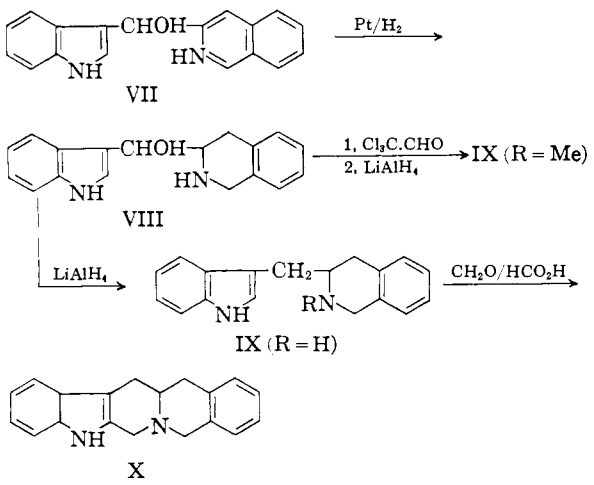
(7) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

(8) However, a claim was made recently by T. Hoshino, *Chem. Ber.*, **85**, 858 (1952), that with a proper method of working up, the main product with acetone is 2-(N-indolyl)-isopropyl alcohol.

(9) A. P. Gray and W. L. Archer, THIS JOURNAL, **79**, 3554 (1957), describe two diindolylmethylpyridines, obtained through an acetic acid condensation of indole and 2- and 4-pyridylaldehydes, respectively, which differ from the "rosindoles" described in this work both in physical properties and chemical stability. Our di-(3-indolyl)-2'-pyridylmethane melts at 223–226°, that of Gray and Archer at 208–210°; our 4'-pyridylmethane melts at 114–116°, that of Gray and Archer at 152–155° dec. These authors report well-crystallized hydrochlorides of their bases, while in our experience treatment of the "rosindoles" with inorganic acids even in non-aqueous medium produced intense violet solutions from which no product could be isolated. Non-identity of the products obtained from indoles and ketones through Grignard condensation or through acetic acid condensation was recently reported by W. E. Noland, M. H. Fischer, D. N. Robinson and H. Sorger-Domenigg, Abst. of Paper, 131st A.C.S. Meeting, April, 1957, 24-O.

(10) *Cf.* R. Majima and M. Kotake, *Ber.*, **55B**, 2859 (1922). None of the desired carbinol was produced even when the condensation with benzaldehyde was tried in presence of pyridine.

(11) F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, **74**, 3933 (1952).



(X). This was readily accomplished in formic acid at room temperature, in yields averaging 40%. The structure X was corroborated by elemental analysis, a positive β-carboline test, and infrared and ultraviolet spectra. As was demonstrated previously in Part I, the ultraviolet spectrum of the ring-closed quinolizidine exhibits a bathochromic shift due to an additional alkylation of the indole nucleus (Table I).

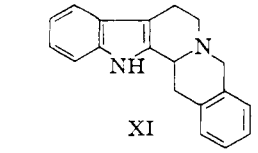
TABLE I

ULTRAVIOLET ABSORPTION DATA[a]

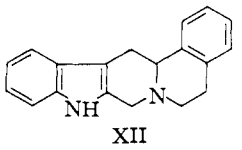
Compound	λ_{max}, mμ	ϵ_{max}	Compound	λ_{max}, mμ	ϵ_{max}
IV[c]	217.5	36,750	VIII[f]	220.5	40,000
	265–265.5	7,800		272.5	6,600
	288.5	5,000		278	
				279.5	6,500
I[c,i]	218.5	35,300		281.5	
	265	8,100		289	5,500
	270				
	277.5	7,450	IX, R = H[f]	219.5	30,500
	287.5	6,100		273	6,100
				282	6,250
VII[d]	223.5	46,450		290.5	5,450
	270–272.5	5,850			
	280[b]	5,600	X[f]	225.5	42,500
				275	7,900
II[e,i]	221.5	32,800		278.5	
	282	5,900		280	7,700
	289.8	5,000		282–282.5	
				289.5	6,400
			III[e,i]	225.5	35,000
				283	6,950
				289.5	5,700

[a] Solvent: 95% ethanol. [b] Inflection. [c] Indole and pyridine chromophores. [d] Indole and quinoline chromophores. [e] Indole chromophore. [f] Indole and *o*-xylene chromophores.

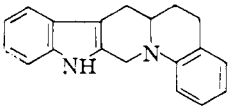
Compound X represents the third known benzoindolotetrahydroquinolizine, derived from β-carboline, the other two previously reported members of this class being yobyrine (XI)[12] and the structure XII.[13] The methods used in the synthesis of X seem to afford a practical route to the synthesis of the isomeric benzoindolotetrahydroquinolizine XIII. The three structures X, XII, and XIII were of interest at the time when this work was being carried out, as alternative formulations for the parent bases of the calabash curare alkaloids (*cf.* ref. 13), although the most recent work no longer supports this view.[14]



XI



XII



XIII

None of the compounds reported herein proved to have any significant oxytocic activity.

Experimental

3-Indolyl-2′-pyridylcarbinol (I).[15]—(a) A solution of 19.3 g. (0.165 mole) of indole in 100 ml. of ether was added at −10° over a period of 10 min. to a solution of ethylmagnesium bromide (50 ml., 3.35 *N*, 0.165 mole). The mixture was stirred 30 min. at room temperature, then 200 ml. of methylene dichloride was added in order to bring the complex into solution. The latter was cooled again to −25° and 16.0 g. (0.15 mole) of 2-pyridylaldehyde in 125 ml. of methylene dichloride were added at this temperature over a period of 10 min. Stirring was continued at −25° for 4.5 hr. and the reaction mixture decomposed with ammonium chloride solution (12 g. in 65 ml. water) at −30°. A methylene chloride-insoluble solid was filtered off and discarded, and the aqueous layer was re-extracted three times with methylene dichloride. When the combined extracts were concentrated, 5.6 g. of 3-indolyl-2′-pyridylcarbinol, m.p. 154–156°, separated. The mother liquors were freed of solvent, unreacted indole and aldehyde by steam distillation, and the crude residue was filtered and recrystallized from methylene dichloride and aqueous ethanol, yielding a further 11.2 g. of the carbinol, m.p. 1153–158° (total yield 16.8 g., 50%). After recrystallization from toluene the compound melted at 161–162°, undepressed on admixture of a sample obtained by the alternative route.[1]

From the final mother liquors of I a solid separated (1.3 g., 4.9%), m.p. 219–221°, which on four recrystallizations from 50% aqueous ethanol gave di-(3-indolyl)-2′-pyridylmethane, in white rosettes, m.p. 223–226°. Solutions of this product in acidic media had the dark violet color characteristic of "rosindoles."

Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 13.00. Found: C, 81.70; H, 5.20; N, 12.78.

(b) The reaction was performed in the same manner as described above, but the aldehyde was added at −10° and the reaction mixture was kept subsequently at 0° for 4.5 hr. Upon isolation of the products, 8.5 g. (25.3%) of the carbinol and 11.6 g. (43.6%) of the rosindole were obtained.

3-Indolyl-4′-pyridylcarbinol (IV).—(a) The procedure described for I was repeated on the same scale, substituting 4-pyridylaldehyde for 2-pyridylaldehyde. In this case both during the addition of the aldehyde and afterwards the reaction temperature was kept at −10°. The reaction mixture was decomposed with ammonium chloride solution (12 g. in 65 ml. water). The solid which separated was Soxhlet-extracted with methylene dichloride for 20 hr. and from the extract crystallized 3-indolyl-4′-pyridylcarbinol (13.3 g.), m.p. 151–152°. The aqueous layer of the original reaction mixture was extracted with methylene dichloride, the extracts joined to the organic layer and concentrated, yielding more carbinol (4.1 g.). From the mother liquors of both main crops through concentrations and recrystallizations from ethanol or methanol–benzene mixture, a further amount of the carbinol (2.0 g.) was obtained bringing the total yield to 19.4 g. (57.7%). The thimbles of the Soxhlet contained 7.3 of a product melting at 201° which was not investigated further.

(12) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946).

(13) V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2134 (1950); V. Boekelheide and C. T. Liu, *ibid.*, **74**, 4920 (1952).

(14) W. von Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **39**, 913 (1956); A. Zürcher, O. Ceder and V. Boekelheide, THIS JOURNAL, **80**, 1500 (1958).

(15) With R. A. Mallory.

The analytical sample of the carbinol crystallized from methanol–benzene mixture in rosettes of needles and melted at 156.5–157.5° after softening at 152.5°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.47; H, 5.43; N, 12.04.

(b) To a solution of indolylmagnesium bromide prepared as previously described from ethylmagnesium bromide (0.55 mole) and 58.55 g. (0.55 mole) of indole in 600 ml. of benzene, 53.55 g. (0.5 mole) of 4-pyridylaldehyde in 100 ml. of benzene was added at 60° over a period of 20 min. The thick voluminous precipitate which formed was redissolved by addition of methylene dichloride (250 ml.). Reflux at 60° was maintained for 4 hr., after which the reaction mixture was cooled and decomposed with an aqueous solution of 40 g. of ammonium chloride. The solid floating on the interface of the two layers was separated, refluxed with water and again separated, yielding 7.3 g. (6.5%) of 3-indolyl-4'-pyridylcarbinol. m.p. 152–153°. The organic layer was steam distilled and from the distillate 13.8 g. (23.5%) of recovered indole, m.p. 49–49.5°, was isolated. The distillation residue solidified and after crystallization from methanol yielded 17.8 g. (16%) of a presumed di-(3-indolyl-4'-pyridylmethyl) ether in rosettes of needles, m.p. 140.5–141.5°. Several recrystallizations from methanol left the m.p. unchanged.

Anal. Calcd. for $C_{28}H_{22}N_4O$: C, 78.12; H, 5.15; N, 13.02. Found: C, 79.40; H, 5.55; N, 12.54.

The walls of the reaction flask were coated with a semi-solid jelly, which was extracted with hot ethanol (2 l.). The extract was evaporated to dryness and the residue dissolved in benzene and water. The benzene layer was steam distilled and the solidified residue reprecipitated from methylene dichloride–petroleum ether (b.p. 40–60°) mixture as a red solid (5.0 g.), m.p. 100°, which gave red solutions in organic solvents and dark violet solutions in acidic media characteristic of "rosindoles." It was twice reprecipitated from its acetic acid solution with aqueous sodium hydroxide, yielding orange needles of di-(3-indolyl)-4'-pyridylmethane, m.p. 114–116° after softening at 106°.

Anal. Calcd. for $C_{22}H_{17}N_3$: N, 13.00. Found: N, 12.76.

From the mother liquor of the ether, more of the rosindole (16.0 g.) was isolated in a similar manner, bringing its total yield to 13%.

3-Indolyl-3'-isoquinolylcarbinol (VII).—To a solution of indolylmagnesium bromide (from 0.055 mole of ethylmagnesium bromide and 6.45 g. (0.055 mole) of indole in 80 ml. of ether) 100 ml. of methylene dichloride was added, followed by a solution of 7.86 g. (0.05 mole) of 3-isoquinolinealdehyde (prepared by the method of Teague and Roe[4]) in 100 ml. of methylene chloride, which was introduced at −10° over a period of 10 minutes. The solution was kept at room temperature for 18 hours, then decomposed with an aqueous solution of 10 g. of ammonium chloride. The organic layer was filtered and concentrated, when on cooling 3.05 g. (22.0% of theory) of 3-indolyl-3'-isoquinolylcarbinol separated in clusters of feathery needles, m.p. 159–160°. Recrystallization from 70% aqueous methanol did not affect the melting point.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.78; H, 5.14; N, 10.34.

A by-product (3.5 g.), m.p. 207°, which was isolated from the mother liquors, was not further investigated.

Condensation of 2-Thenaldehyde with Indolylmagnesium Bromide.—To a solution of indolylmagnesium bromide (from 0.055 mole of ethylmagnesium bromide and 6.45 g. (0.055 mole) of indole in 75 ml. of ether) 50 ml. of methylene dichloride was added, followed by a solution of 5.6 g. (0.05 mole) of 2-thenaldehyde in 50 ml. of methylene chloride, which was introduced at −10° over a period of 10 minutes. The solution was stirred at 0° for 2 hours and then kept at −5° for a further 16 hours. After decomposing the mixture with an ammonium acetate solution, the aqueous layer was extracted with methylene dichloride, extracts joined to the main organic layer and together steam distilled. The solidified residue was filtered, redissolved in benzene–cyclohexane mixture, decolorized with charcoal, and after discarding successive oily precipitates, induced to crystallize by addition of cyclohexane and a small amount of pentane. After being kept at 0°, 2.3 g. (28.0%) of crystalline di-(3-indolyl)-2'-thienylmethane, m.p. 149–150°, was obtained. The compound became pink after short exposure to air and gave pale yellow solutions in neutral media and red solutions in acids.

Anal. Calcd. for $C_{21}H_{16}N_2S$: C, 76.81; H, 4.91. Found: C, 77.44; H, 5.19.

4-Skatylpiperidine (V).—A solution of 6.0 g. (0.0267 mole) of 3-indolyl-4'-pyridylcarbinol (IV) and 5 ml. of glacial acetic acid in 30 ml. of absolute alcohol was shaken under hydrogen at three atmosphere pressure with 0.5 g. of Adams platinum oxide catalyst. Absorption ceased when 0.080 mole of hydrogen was taken up. The mixture was then filtered and poured into a solution of 15 g. of sodium hydroxide in 1 liter of water. The oily precipitate was extracted with benzene, the extract concentrated to 125 ml. and excess of petroleum ether (b.p. 40–60°) added, precipitating a gum. The latter was redissolved in benzene and a benzene solution of hydrogen chloride added precipitating 2.2 g. (33.0%) of crude 4-skatylpiperidine hydrochloride. m.p. *ca.* 210°. On reprecipitation with cyclohexane from a benzene–isopropyl alcohol solution the pure hydrochloride was obtained, m.p. 253–254°.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64. Found: C, 67.10; H, 7.57.

From an aqueous methanolic solution of the hydrochloride the base was liberated with 10% aqueous sodium hydroxide, then twice recrystallized from a methanol–benzene mixture (by dissolving in methanol, adding benzene and removing azeotropically almost all methanol) as a colorless solid, m.p. 155°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.21; H, 8.10.

N-Methyl-4-skatylpiperidine Hydrochloride (VI).—The crude 4-skatylpiperidine obtained by reduction of 7.3 g. (0.0325 mole) of 3-indolyl-4'-pyridylcarbinol (IV) was dissolved in 20 ml. of chloroform, and 2.0 ml. of anhydrous chloral was added, producing an oily precipitate. After overnight standing at room temperature the excess reagent and solvent were removed *in vacuo* and the residue was treated with 0.48 g. (0.0325 mole) of lithium aluminum hydride in 130 ml. of dioxane at 37° for 6 hours. The mixture was decomposed by addition of 10 ml. of water, the inorganic salts were filtered out and the filtrate evaporated to dryness *in vacuo*. The residue was extracted several times with hot benzene, the extract concentrated and treated with ethereal hydrogen chloride, precipitating 2.3 g. (26.6% based on IV) of the crude hydrochloride. Two recrystallizations from a methanol–isopropyl alcohol–benzene mixture gave pure N-methyl-4-skatylpiperidine hydrochloride, m.p. 224.5–225.5°.

Anal. Calcd. for $C_{15}H_{21}ClN_2$: C, 68.03; H, 8.00; N, 10.58. Found: C, 68.32; H, 7.74; N, 10.10.

3-Indolyl-3'-(1',2',3',4'-tetrahydroisoquinolyl)-carbinol (VIII).—(a) A solution of 9.9 g. (0.036 mole) of 3-indolyl-3'-isoquinolylcarbinol (VII) and 12 ml. of glacial acetic acid in 40 ml. of absolute ethanol was shaken under hydrogen at three atmospheres pressure with 1.0 g. of Adams platinum catalyst. Absorption ceased after 110 minutes when 0.070 mole of hydrogen had been taken up. The mixture was then filtered and poured into 1 liter of a 1% aqueous solution of sodium hydroxide. The solid precipitate was separated and dried over phosphorus pentoxide *in vacuo* for 15 hours. Extraction with 50 ml. of hot chloroform left behind 8.3 g. (83.0%) of 3-indolyl-3'-(1',2',3',4'-tetrahydroisoquinolyl)-carbinol, m.p. 213–215°. Recrystallization from acetone–chloroform yielded micro-crystals, m.p. 215–216°.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.60; H, 6.38; N, 9.98.

(b) In another experiment when only 1.5 g. of Adams catalyst was used with 18.0 g. of the carbinol VII, the hydrogenation took 23 hours and only 7.9 g. (43.3%) of the carbinol VIII was obtained. The chloroform extract was evaporated to dryness and the residual oil solidified by continuous extraction with ether. The crude solid so obtained (10.9 g., 55%) melted after several crystallizations from benzene–cyclohexane at 154–155°, and analyzed for the symmetrical ether of the carbinol VIII.

Anal. Calcd. for $C_{36}H_{34}N_4O$: C, 80.34; H, 6.36; N, 10.40. Found: C, 80.16; H, 6.65; N, 9.66.

3-Skatyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IX, R = H).—One gram of 3-indolyl-3'-(1',2',3',4'-tetra-

hydroisoquinolyl)-carbinol was added in portions to a stirred solution of 0.3 g. of lithium aluminum hydride in 60 ml. of 1,2-dimethoxyethane at room temperature. After the exothermic reaction subsided the mixture was heated under reflux for 30 minutes, then cooled and decomposed with 15 ml. of wet ether. Filtration and evaporation of the filtrate to dryness gave 1 g. of a light-colored oil, which crystallized from a 2:1 cyclohexane–benzene mixture as the crude base (0.65 g., 69%) m.p. 108°. Treatment in benzene solution with hydrogen chloride and recrystallization of the product from isopropyl alcohol gave 3-skatyl-1,2,3,4-tetrahydroisoquinoline hydrochloride hemihydrate, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{18}ClN_2 \cdot {}^1/_2H_2O$: C, 71.29; H, 6.48. Found: C, 71.22; H, 6.78.

The anhydrous hydrochloride was obtained by drying a sample still wet with isopropyl alcohol at 150° (10^{-3} mm.). It melted at 209–211°.

Anal. Calcd. for $C_{18}H_{19}ClN_2$: C, 72.35; H, 6.42; N, 9.38. Found: C, 72.04; H, 6.46; N, 8.87.

3-Skatyl-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IX, R = Me).—(a) One-half milliliter of chloral was added at room temperature to a suspension of 1.2 g. of 3-indolyl-3′-(1′,2′,3′,4′-tetrahydroisoquinolyl)-carbinol (VIII) in 10 ml. of chloroform and 30 ml. of 1,2-dimethoxyethane, and the mixture was heated under reflux for 45 minutes. Then another 0.5 ml. of chloral was added and the resulting solution was kept under reflux for one additional hour. The solution was evaporated to dryness *in vacuo* and the residue crystallized from 20 ml. of chloroform, yielding 0.490 g. of 3-skatyl-2-formyl-1′,2′,3′,4′-tetrahydroisoquinoline sesquisolvate, m.p. 175–176°. By evaporation of the mother liquor to dryness and crystallization of the residue from methylene dichloride a further amount of the solid was obtained (0.460 g., bringing the total yield to 0.950 g.).

Anal. Calcd. for $C_{19}H_{18}N_2O \cdot 1{}^1/_2\ CHCl_3$: C, 50.72; H, 4.05; N, 5.77. Found: C, 50.28; H, 3.99; N, 5.79.

Attempted recrystallizations gave products which contained varying amounts of chloroform.

(b) A solution of 0.85 g. of the above formyl derivative in 50 ml. of 1,2-dimethoxyethane was added at reflux to a stirred solution of 0.5 g. of lithium aluminum hydride in 30 ml. of dimethoxyethane over a period of 5 min. The mixture was kept under reflux for 6 hours, then cooled and decomposed with 2 ml. of water. The inorganic solid was washed several times with methylene dichloride, the washings were combined with the original organic phase, and the solvents evaporated *in vacuo*. The residual gum was dissolved in benzene and ethereal hydrogen chloride was added, causing the precipitation of 0.55 g. (41.0% yield based on VIII) of 3-skatyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, as a creamy solid, m.p. 135°. Reprecipitation from a mixture of isopropyl alcohol–acetone–ether raised the melting point to 137°.

Anal. Calcd. for $C_{19}H_{21}ClN_2$: C, 72.95; H, 6.77; N, 8.96. Found: C, 72.87; H, 6.88; N, 8.59.

2,3-Benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine (X).—To 2.8 g. of a crude oil, containing the free base of IX (R = H), obtained in the above-described manner by reduction of 2.78 g. (0.01 mole) of VIII, a mixture of 0.5 ml. of formic acid and 1 ml. of 37% formalin was added at −10°. The mixture was warmed to 40°, when an exothermic reaction could be noted. After standing at room temperature for 16 hours, a little methanol was added and the solution was poured into aqueous sodium hydroxide, precipitating 2.3 g. of a solid, m.p. 120–125°. Treatment with a small amount of methanol left behind 0.71 g. (25.9% yield based on two stages) of 2,3-benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine as an insoluble colorless solid, m.p. 240°. Crystallization from benzene–acetone mixture (containing only a trace of benzene) gave spherical clusters, m.p. 240°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 83.40; H, 6.63; N, 9.81.

Methochloride of X.—One gram of X was suspended in 100 ml. of methanol, and gaseous methyl chloride was added during 2 hours at room temperature and then for a further 6 hours at reflux temperature, by which time all the solid had dissolved. The solution was concentrated to a volume of 20 ml., a little ether was added, and after keeping overnight at 0°, 0.1 g. of the original base, m.p. 235–240°, was filtered off. The filtrate was evaporated to dryness under reduced pressure, and the residue solidified by trituration with ether containing a little methanol, yielding 0.95 g. of the crude methochloride, m.p. 220–226°. Recrystallization from a mixture of 12 ml. of methanol, 15 ml. of isopropyl alcohol and a little ether gave 0.8 g. of the methochloride, m.p. 263–265° after softening at 261°. The analytical sample was dried at 100° (1 mm.) for 2 hours.

Anal. Calcd. for $C_{20}H_{21}ClN_2 \cdot {}^1/_4H_2O$: C, 72.93; H, 6.58. Found: C, 72.96; H, 6.78.

A sample was allowed to come to equilibrium with atmospheric moisture.

Anal. Calcd. for $C_{20}H_{21}ClN_2 \cdot 1{}^2/_3H_2O$: C, 67.69; H, 6.90; N, 7.90; Cl, 9.99. Found: C, 67.85; H, 7.04; N, 7.87; Cl, 9.61.

Hydrochloride of X.—Dry hydrogen chloride was added to a solution of 100 mg. of X in 100 ml. of benzene and 20 ml. of isopropyl alcohol. The solution was evaporated to dryness and the solid residue was redissolved in benzene containing a trace of methanol. Dry ether was added to cloudiness and after standing at 0° overnight a jelly precipitated. It became crystalline when benzene was replaced with ether as a washing solvent. Filtration gave 110 mg. of the hydrochloride hemihydrate, m.p. 185° after softening at 177°.

Anal. Calcd. for $C_{19}H_{19}ClN_2 \cdot {}^1/_2H_2O$: C, 71.36; H, 6.30; N, 8.76. Found: C, 71.78; H, 6.49; N, 8.76.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Isoasparagine-oxytocin: The Isoasparagine Isomer of Oxytocin[1]

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The synthesis of *isoasparagine-oxytocin*, a cyclic polypeptide isomeric with oxytocin with respect to the asparagine residue, is presented. The oxytocic, avian vasodepressor and pressor activities of oxytocin were not detected in the isomer. Isoasparagine-oxytocin was compared with oxytocin also with respect to physical properties, several of which were found to be the same for the two polypeptides. It afforded a crystalline flavianate derivative. This synthesis, besides yielding information on the relationship of structure to biological activity and other properties in the posterior pituitary hormones, shows that intramolecular closure of an appropriate disulfhydryl intermediate to a 21-membered disulfide polypeptide ring can occur with facility.

In proposing the structure[2,3] for oxytocin, the chief oxytocic principle of the posterior pituitary gland, as the cyclic disulfide of L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide, several assumptions were made. These involved the position of

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