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Gelsemine. II. The Chemistry and Rearrangements of Spiroöxindoles[1]

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The reactions, interconversions and rearrangements in the spiro-(cyclopentane-1,3′-pseudoöxindole) series are described (Chart I). The rearrangement of the carbinol amine XIX to 9-methyltetrahydrocarbazole is likely to prove useful in the structural elucidation of gelsemine. N^a-Methyl derivatives of gelsemine and dihydrogelsemine were prepared and found identical with the so-called "des-bases." Experiments to prepare carbinol amines in the gelsemine series (XXV) have been started.

The revisions in the chemistry of spiroöxindole derivatives were made almost simultaneously and independently by two different groups of investigators[3-5] prompted either by observations of the rearrangement of quinamine to isoquinamine[6,7] or by studies on the mechanism of oxidation in the indole series.[8] Occupation with another alkaloid, gelsemine[9] (having hypotensive properties), led us to extend and investigate the chemistry and rearrangements of spiroöxindoles.

The reactions summarized in the Chart show three different routes to the spiroöxindoles V and XIV.

(i).—Starting with the spiroindoxyl VI,[10] methylmagnesium iodide effects a twofold Wagner–Meerwein rearrangement[11] to give the methylindolenine VII, in which the methyl is activated by the adjacent —C=N— group.[12,13] Reaction with nitrous acid yields the oximino compound XI,

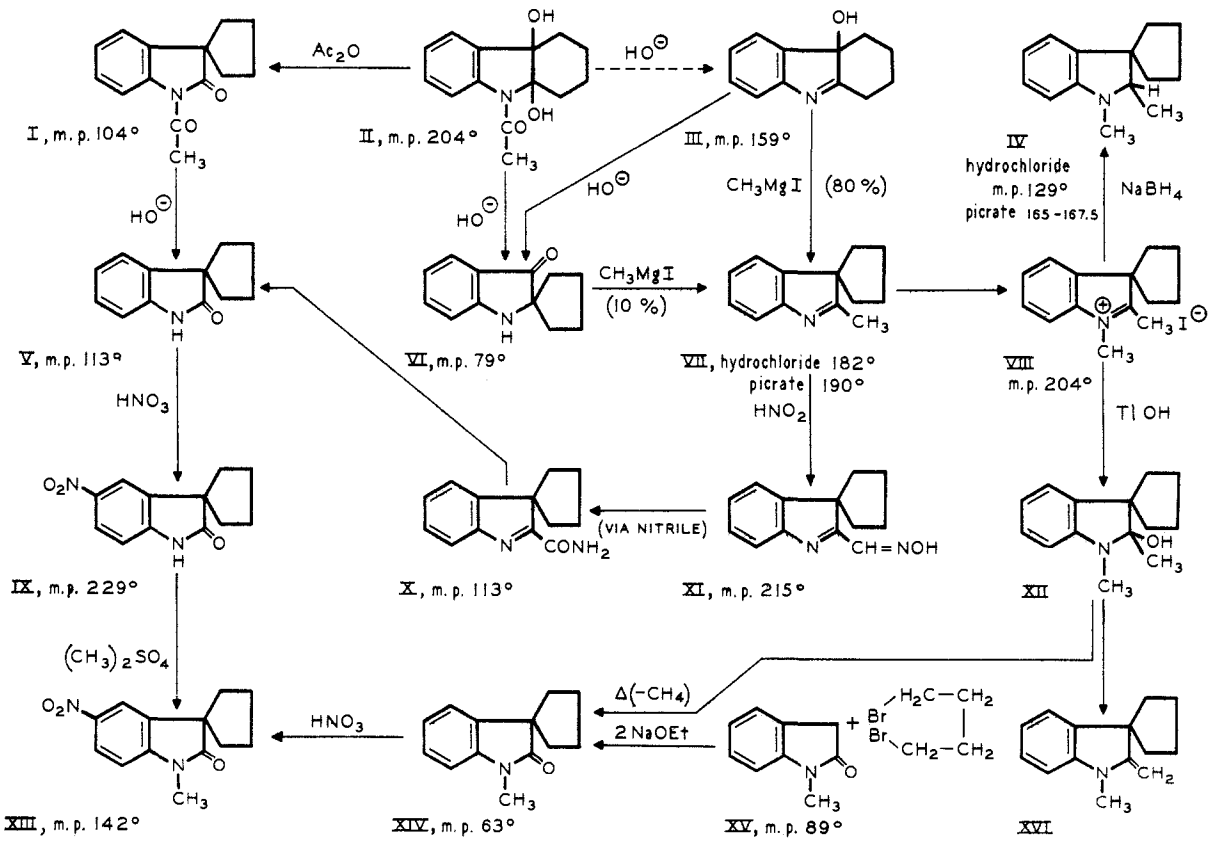
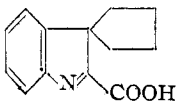


Chart I.—Interconversions and rearrangements of spiroöxindoles and indoxyls.

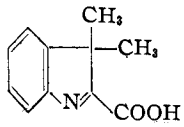
convertible, *via* the liquid nitrile (not isolated in pure form) and the amide X, to the spiroöxindole V[14] identical with the (acetic anhydride-catalyzed)

(1) Preceding paper in this series, THIS JOURNAL, **70**, 1424 (1948).
(2) National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md.
(3) S. G. P. Plant and R. Robinson, *Nature*, **165**, 36 (1950).
(4) J. B. Patrick and B. Witkop, THIS JOURNAL, **72**, 633 (1950).
(5) B. Witkop and J. B. Patrick, *Experientia*, **6**, 183 (1950); THIS JOURNAL, **73**, 2188 (1951).
(6) C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby and R. Robinson, *J. Chem. Soc.*, 1485 (1950).
(7) B. Witkop, THIS JOURNAL, **72**, 2311 (1950).
(8) B. Witkop and A. Ek, *ibid.*, **73**, 5664 (1951).
(9) M. Kates and L. Marion, *ibid.*, **72**, 2308 (1950); *Can. J. Research*, **29B**, 37 (1951).
(10) *Cf.* B. Witkop, THIS JOURNAL, **72**, 614 (1950).
(11) B. Witkop and J. B. Patrick, *ibid.*, **73**, 1558 (1951).
(12) G. Plancher and D. Bettinelli, *Gazz. chim. ital.*, **29I**, 106 (1899).
(13) H. Leuchs and H. Schulte Overberg, *Ber.*, **64**, 1903 (1931).
(14) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **123**, 688 (1923).

deacetylated rearrangement product from II.[15] The same correlation has been carried out recently by Plant[16] using the oxindole synthesis of Brunner. In this sequence the acid XVII was not obtained from the amide X by acid treatment.[17] The



XVII



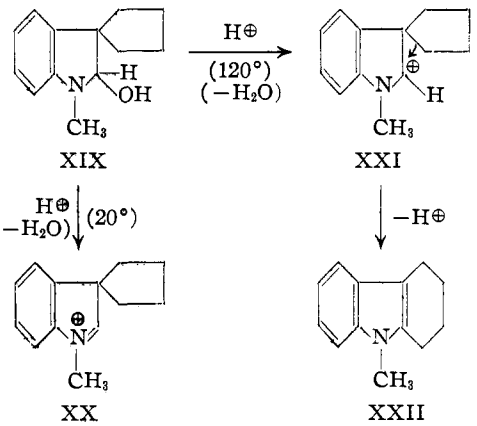
XVIII

analogous 3,3-dimethylindolenine-2-carboxylic acid[18] is known to undergo an acid-catalyzed decarboxylation[19] and rearrangement to 2,3-dimethylindole. We tried to effect a Hammick reaction[20] with 3,3-dimethylindolenine-2-carboxylic acid (XVIII). When XVIII was refluxed in benzophenone solution, there was formed instead the trimer of 3,3-dimethylindolenine,[18,21,22] m.p. 214–215°.

(ii).—The methiodide of the methylindolenine VII, which could be reduced to the N-methylindoline IV by sodium borohydride[23] gave a free ether-soluble oily carbinol base XII or "Fischer base" XVI. The picrate of this base, m.p. 159°, is probably derived from the original quaternary compound VIII in accordance with the rules of tautomerism in this series.[24] The free base (XII or XVI) on pyrolysis lost methane (or was oxidized) to give the spiroöxindole XIV.[25] If a loss of methane were involved, the reaction would be reminiscent of the base-catalyzed transformation of 2,2-dialkylbenzimidazolines to 2-alkylbenzimidazoles.[26]

(iii).—The condensation of N-methyloxindole (XV) with tetramethylene bromide in the presence of sodium methoxide gives the spiroöxindole XIV in good yield.[4] The reaction is patterned after similar condensation reactions.[27,28] Nitration of XIV gave the 5-nitro derivative XIII identical with the product obtained by nitration (IX) and methylation from V.[14]

The partial reduction of the spiroöxindole XIV with lithium aluminum hydride[29] gave the carbinolamine XIX, the picrate of which was derived



XIX XXI XX XXII

from the anhydro form in accordance with the general mechanism of salt formation of open and cyclic Schiff bases.[30] The action of hydrochloric or polyphosphoric acid at elevated temperature (100–150°) caused the carbinolamine XIX to rearrange to 9-methyltetrahydrocarbazole (XXII) (*via* the intermediate carbonium structure XXI). The same sequence of reactions was carried out by Ciamician in the conversion of 1,3,3-trimethyloxindole to 1,2,3-trimethylindole *via* 1,3,3-trimethyl-2-hydroxyindoline.[31] It may be recalled that rearrangement and/or loss of water in the case of the alkanols XXIII[10] and XXIV[5] occurred already at room temperature with dilute acetic or picric acids.

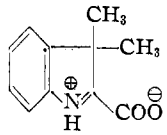
(15) 9-Acetyl-10,11-*cis*-dihydroxyhexahydrocarbazole, previously prepared by the addition of nitric acid[14] to, or the osmium tetroxide oxidation of, 9-acetyltetrahydrocarbazole [D. W. Ockenden and K. Schofield, *Nature*, **168**, 603 (1951)] can also be obtained by the procedure of Milas and Sussman [THIS JOURNAL, **58**, 1302 (1936)] from 9-acetyltetrahydrocarbazole; see Experimental.

(16) R. F. Moore and S. G. P. Plant, *J. Chem. Soc.*, 3475 (1951).

(17) Likewise the liquid 3,3-dimethyl-2-cyanoindolenine, on the action of either acid or base, lost hydrogen cyanide to give 3,3-dimethyloxindole (ref. 12), whereas Leuchs (ref. 13) was able to isolate 3,3-dibenzylindolenine-2-carboxylic acid from the parent nitrile by basic hydrolysis.

(18) R. Robinson and H. Suginome, *J. Chem. Soc.*, 298 (1932).

(19) The thermal decarboxylation (ref. 18) probably proceeded through the zwitterion XVIIIa [B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 659 (1949); *cf.* B. R. Brown, *Quarterly Rev.*, **5**, 131 (1951)].



XVIIIa

However, there seems to be no indication for the presence of the carboxyl anion of XVIIIa [band at 6.35 mμ, *cf.* I. M. Klotz and D. M. Gruen, *J. Phys. Colloid Chem.*, **52**, 961 (1948); H. W. Thompson, D. L. Nicholson and N. L. Short, *Faraday Soc.*, Discussion 9, Spectroscopy and Molecular Structure, 1951] in the infrared spectrum of XVIII in chloroform. The position of the carboxyl band of a few representatives of this series are:

Compound	Absorption of carboxyl	Measured in
3,3-Dimethylindolenine-2-carboxylic acid	5.66 (5.86[δ] unassigned)	Chloroform
α-Picolinic acid	5.65	Chloroform
α-Picolinic acid hydrochloride	5.75	Nujol
Nicotinic acid	5.81	Nujol
Quinolinic acid	6.32	Nujol
Quinaldinic acid	5.64	Chloroform

The shift to red in the ultraviolet absorption spectrum of the zwitterion XVIIIa (*cf.* ref. 30) is not found: 3,3-dimethylindolenine-2-carboxylic acid absorbs λ_{max} (log ε) 289 mμ (3.93) in ethanol at somewhat shorter wave length than the methyl ester, λ_{max} (log ε) 295 mμ (3.99); the amide (X) absorbs in between these two values at 292 mμ (4.10).

(20) P. Dyson and D. L. Hammick, *J. Chem. Soc.*, 1724 (1937).

(21) K. Brunner, *Monatsh.*, **16**, 854 (1895).

(22) The trimerization happened also when XVIII was refluxed with acetic anhydride in an attempt to prepare the mesionic condensation product analogous to Besthorn's red quinoline dye [*cf.* B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 628 (1950)].

(23) *Cf.* B. Witkop and J. B. Patrick, THIS JOURNAL, in press; K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 951 (1952).

(24) For an up-to-date discussion *cf.* P. L. Julian, E. W. Meyer and H. Printy in R. C. Elderfield's "Heterocyclic Compounds," Vol. 3, New York, 1952, p. 74.

(25) The pyrolysis of comparable 1,2,3,3-tetrasubstituted 2-hydroxyindolines [K. Brunner, *Monatsh.*, **26**, 1359 (1905); G. Jenisch, *ibid.*, **27**, 1223 (1906)] would be of interest in this connection.

(26) R. C. Elderfield, 12th National Organic Chemistry Symposium, Denver, Col., June, 1951, Abstracts, p. 86.

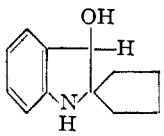
(27) O. Eisleb, *Ber.*, **74**, 1433 (1941).

(28) E. Kretz, J. M. Müller and E. Schlittler, *Helv. Chim. Acta*, **35**, 520 (1952).

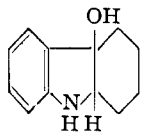
(29) F. Galinowsky, *Monatsh.*, **82**, 551 (1951).

(30) B. Witkop, J. B. Patrick and H. M. Kissman, *Ber.*, **85**, 949 (1952).

(31) G. Ciamician and A. Piccinini, *ibid.*, **29**, 2467 (1896); *Gazz. chim. ital.*, **27I**, 341 (1897).

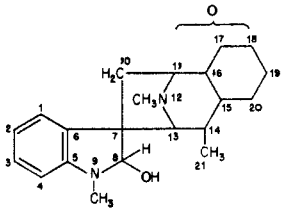


XXIII

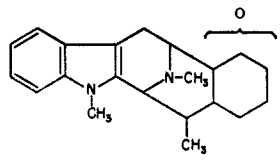


XXIV

The analogous rearrangement of the corresponding carbinolamine (XXV)[32] from what is currently pictured as N-methyldihydrogelsemine should remove the main obstacle in the pathway of degradation of gelsemine, *viz.*, the quaternary carbon in position 7[32] to yield XXVI. The significance of this change would be comparable to the strychnine → strychnone conversion in which the acid-catalyzed loss of water proceeds with fission rather



XXV



XXVI

than rearrangement of the carbon skeleton.[33] When the required N^a-methyl derivatives of gelsemine and dihydrogelsemine were prepared, they were found to be identical with the corresponding "des-bases."[34,35]

A wide variety of conditions was tried for the selective reduction of N-methyldihydrogelsemine, N-methylgelsemine and their methiodides and hydrochlorides: lithium aluminum hydride in varying proportions (one, two and four equivalents of hydrogen) in solvents such as ether, tetrahydrofuran, N-methylmorpholine, carbitol[36] and HCl-saturated ether[37] applying normal as well as inverse addition; sodium borohydride in cold and refluxing methanol and ethanol; sodium in ethyl and isopropyl alcohols. Polarographic analysis[38] indicated a high potential is required for the reduction; electrolytic reduction, therefore, has not been tried yet,[39] but could possibly lead directly to rearrangement when applied in strong acid at elevated temperature. If an O-methyl ether of the oxindole could be prepared, its reduction would offer promise. Our reduction attempts in some cases have led to small amounts of the desired carbinolamine (typical infrared bands at 2.75 and 2.92 μ, no more carbonyl).[40] The work had to be discontinued at this point.

(32) R. Goutarel, M.-M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta*, **34**, 1139 (1951); *cf.* M. S. Gibson and R. Robinson, *Chemistry and Industry*, 93 (1951).

(33) R. B. Woodward, W. J. Brehm and A. L. Nelson, THIS JOURNAL, **69**, 2250 (1947).

(34) T. Habgood, L. Marion and H. Schwartz, *Helv. Chim. Acta*, **35**, 638 (1952).

(35) V. Prelog, J. B. Patrick and B. Witkop, *ibid.*, **35**, 640 (1952).

(36) I. Goodman, *J. Chem. Soc.*, 2209 (1951).

(37) H. M. Doukas and T. D. Fontaine, THIS JOURNAL, **73**, 5917 (1951).

(38) *Cf.* W. C. Sumpter, P. H. Wilken, T. L. Williams, R. Wedemeyer, F. L. Boyer and K. W. Hunt, *J. Org. Chem.*, **16**, 1777 (1951).

(39) *Cf.* Electrolytic reduction of spirothioöxindoles, ref. 27.

(40) Drs. Marion and Schwarz informed us that by reduction of N-methylgelsemine with sodium in liquid ammonia they had obtained a dihydro compound the infrared spectrum of which was indicative of a carbinolamine. A sample of this dihydro compound, which could not be reduced to the tetrahydro compound, also failed to undergo any changes in polyphosphoric acid at 220°. We are most obliged to Drs. Marion and Schwarz for placing some of the compound at our disposal.

Experimental[41]

Methyl Cyclopentyl Ketone.[42,43]—In a 500-ml. 3-necked flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel was placed 41 g. of crystalline sodium dichromate followed by 19 cc. of concentrated sulfuric acid in 200 cc. of water. About 5 cc. of methylcyclopentylcarbinol[44] was added with stirring. The solution assumed a dark brown color and the temperature rose. The carbinol was then added dropwise at a rate determined by the rate of heat evolution. Occasional application of an ice-bath to the flask was used to keep the temperature at or below 55°. When all the carbinol was added (45 min.), stirring was continued until the temperature had fallen to 50°. The flask was cooled and about 200 cc. of ether was added. After thorough mixing, the layers were separated and the brown ether layer was washed with three 35-cc. portions of 1 *N* alkali solution. The pale yellow ether solution was dried over sodium sulfate and the ether was then evaporated. The crude ketone (21.6 g.) was transferred to a 25-cc. flask and distilled *in vacuo* yielding 15.0 g. (57%) of a colorless fragrant liquid boiling 80–85° (65 mm.) (approx.), which in the Fischer indole synthesis gave directly the spiroindolenine VII.[11]

Spiro-(cyclopentane-1,3′-pseudo-2′-formoximinoindole) (XI).—To 2.1 g. of VII, dissolved in 15 cc. of glacial acetic acid, was added with stirring an ice-cold solution of 0.67 g. of sodium nitrite in 5 cc. of water. The solution assumed a dark orange color, became somewhat warm, and suddenly set to an orange sludge. After ten minutes stirring the mixture was diluted slowly with 60 cc. of water and filtered. The yellow filter cake was thoroughly washed with water, sucked dry at the pump, and stored overnight in a vacuum desiccator over phosphorus pentoxide. The crude product amounted to 1.724 g. of yellow solid, m.p. 207–212°.

On recrystallization from methanol, the analytical sample formed long silky yellow needles, m.p. 213–215° (crystalline transformation to short prisms 145°; softening, 193°; sublimation 210°; clear light yellow melt).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.58; N, 13.08. Found: C, 73.39; H, 6.77; N, 13.05.

Spiro-(cyclopentane-1,3′-pseudoöxindole) (V).—A mixture of 1.6 g. of the oxime (XI) and 40 cc. of acetic anhydride was refluxed for two hours. The resulting dark solution was stirred with 400 cc. of hot water to destroy the excess anhydride. The brown, oily organic layer was then taken up in ether, washed with 2 *N* potassium hydroxide solution and with saturated sodium chloride solution and dried over anhydrous potassium carbonate. The solution was then filtered from the drying agent and the ether was evaporated. The residual oil was thoroughly extracted with cold pentane. The yellow pentane solution was evaporated, and the residual oil then crystallized. The sticky crystalline mass was washed with pentane until the washings were colorless, and the combined washings set aside (see below). The residual colorless crystals, after drying overnight *in vacuo*, amounted to 202 mg. of light tan granules, m.p. 113.5–114° (sublimation, 100°; clear colorless melt). A mixed melting point with the spiro-oxindole (V) prepared from 9-acetyl-10,11-*cis*-dihydroxyhexahydrocarbazole by the method of Perkin and Plant[14] showed no depression, and the infrared spectra of the two compounds were identical.

Spiro-(cyclopentane-1,3′-pseudoindole-2′-carboxamide) (X).—Evaporation of the combined pentane washings left an oil possessing strong absorption at 4.5 μ in the infrared (cyano group), but also showing a strong oxindole band at 5.8 μ. Both bands were still present after the oil had been subjected to vacuum distillation, giving 469 mg. of clear

(41) All melting points are corrected (Kofler block); all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and associates in the Microanalytical Laboratory of the National Institutes of Health.

(42) This ketone, previously prepared by a less satisfactory method,[11] was needed for the Fischer synthesis of the indolenine VII.

(43) *Cf.* M. Godchot and P. Bedos, *Bull. soc. chim.*, **43**, 522 (1928).

(44) From acetaldehyde and cyclopentylmagnesium bromide (ref. 11 and 43).

yellow oil, b.p. 93–134° (1 mm.). This oil was chromatographed on a 20-mm. diameter column of 15 g. of Fisher alumina, made in hexane. The chromatography was carried out by the general procedure of Reichstein and Shoppee.[45] Elution with 80% chloroform in benzene yielded 181 mg. of crystalline material (and 200 mg. of less pure substance) which was obtained, after two recrystallizations from benzene–ligroin, as large brilliant birefringent prisms, m.p. 113–115° (sublimation from 95°; melting and resolidification 98.5°; clear colorless melt).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.58; N, 13.08. Found: C, 73.49; H, 6.67; N, 12.52.

The substance melted 60–103° when admixed with the spiroöxindole (V). The infrared spectrum of the material showed no cyano band.

Spiro-(cyclopentane-1,3′-pseudo-2′-methylindole) Methiodide (VIII).—A mixture of 590 mg. of the tertiary base VII, in 10 cc. of methanol with 4 cc. of methyl iodide was refluxed for three hours and allowed to stand overnight. Evaporation *in vacuo* left a purple crystalline residue (weight, 1.085 g.). This residue was thoroughly washed, first with ether, then with acetone. After drying, the crystalline residue amounted to 669 mg. (70%); colorless needles, m.p. 203–204° (darkening and distillation in yellow drops at 190°; clear yellow melt).

Anal. Calcd. for $C_{13}H_{15}N{\cdot}CH_3I$: C, 51.39; H, 5.54; N, 4.28. Found: C, 51.52; H, 5.59; N, 4.16.

Spiro-(cyclopentane-1,3′-1′,2′-dimethylindoline) (IV).—Three hundred and fifty mg. of the methiodide VIII was added, with external ice cooling, to a suspension of 350 mg. of sodium borohydride in 10 cc. of alcohol. The addition was accompanied by vigorous gas evolution. The mixture was then refluxed for two hours, decomposed with water, and filtered. The filtrate was thoroughly extracted with ether and the ether extract was washed, first with water, then with saturated salt solution, and finally dried over magnesium sulfate. Evaporation of the dry ether solution left 276 mg. of a clear light-yellow oil which could not be induced to crystallize. Infrared spectrum in chloroform: no NH or OH bands; strong band at 6.21 μ (Ph–N). This oil was divided into two portions. One portion was converted into the picrate in aqueous solution. The water-insoluble picrate, after recrystallization from methanol, formed yellow prisms, m.p. 165–167.5° (sublimation at 136°, darkening 146°, sublimate crystallizes 157°, dark melt-decomposition).

Anal. Calcd. for $C_{14}H_{19}N{\cdot}C_6H_3N_3O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.68; H, 5.34; N, 13.14.

Hydrochloride.—On recrystallization from isopropyl alcohol–ethyl acetate, the hydrochloride, prepared from the second portion in ethereal solution, formed colorless birefringent prisms, m.p. 123–129° (clear colorless melt). The compound sublimes very strongly.

Anal. Calcd. for $C_{14}H_{19}N{\cdot}HCl$: C, 70.72; H, 8.48; N, 5.89. Found: C, 70.79; H, 8.45; N, 5.83.

Spiro-(cyclopentane-1,3′-pseudo-2′-methylindole) Picrate.—A solution of 550 mg. of the methiodide VIII in approximately 10 cc. of methanol was added to an aqueous solution of thallous hydroxide prepared from 504 mg. of thallous sulfate with barium hydroxide. A copious orange precipitate formed which was removed by centrifugation and allowed to stand, still moist, overnight, whereupon it developed a reddish color. The precipitate was thoroughly washed with water (which took up most of the red color) and ether, then discarded. The water layer was made strongly basic by addition of 2 *N* potassium hydroxide and extracted with ether. The red color disappeared. The tan ether extract was dried over magnesium sulfate. On standing a red coloration appeared. The oily residue of the ether extract in chloroform solution showed the following infrared absorption bands: 2.95^m (bonded OH?); 3.37^s; 3.50^s; 6.07^s ($>$N—C$\overset{\wedge}{=}$CH$_2$?); 6.22^s; 6.70^s; 6.85^w; 6.93^w; 7.24^s; 7.42^m; 7.47^m; 7.21^w; 8.72^s; 9.02^s; 9.31^m; 9.60^w; 9.78^m; 10.65^m; 11.85^m. Treatment of two aliquots, one with perchloric, the other with ethereal oxalic acid, produced only oils, but a third aliquot yielded a crystalline picrate, on treatment with picric acid in benzene. On recrystallization from methanol the picrate formed clear yellow birefringent plates, m.p. 158.5–159.5° (darkening from 148°, sublimation from 150°, clear, dark yellow melt).

Anal. Calcd. for $C_{14}H_{17}N{\cdot}C_6H_3N_3O_7$: C, 56.08; H, 4.71; N, 13.08. Found: C, 56.41; H, 4.89; N, 12.85.

When silver oxide was used instead of thallous oxide the ether-soluble compound was an oil showing a strong carbonyl band (5.83 μ) indicative of oxidation to the oxindole (XIV).

Spiro-(cyclopentane-1,3′-pseudo-1′-methyloxindole) (XIV). A. By Pyrolysis of XII.—The rest of the ether solution was transferred to a small Hickman still and the ether evaporated. Distillation of the residue *in vacuo* yielded four drops of a single colorless liquid, b.p. 88–121° (0.17–0.18 mm.). The infrared spectrum was identical with that of a specimen of the spiroöxindole (XIV) synthesized by the method described below.

B. By Condensation of N-Methyloxindole with Tetramethylene Dibromide.—To a refluxing mixture of 2 g. of N-methyloxindole and 3 g. of tetramethylene dibromide in 30 cc. of absolute ethanol was added a solution of 0.65 g. of sodium in 15 cc. of absolute ethanol. The addition was carried out dropwise over a period of about 25 minutes. The mixture was refluxed for half an hour after the addition of all the sodium alcoholate; then the solvent was removed *in vacuo*. Microdistillation of a portion of the residual red oil produced colorless crystals which were used to seed the rest of the oil. The entire mass then crystallized in large needles. On recrystallization from petroleum ether magnificent hexagons were obtained, m.p. 61–63° (yield 60–70%).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.57; H, 7.51. Found: C, 77.81; H, 7.67.

Spiro-(cyclopentane-1,3′-pseudo-1′-methyl-5′-nitroöxindole) (XIII).—Three hundred fifty milligrams of the spirooxindole XIV was added to 10 cc. of nitric acid (1:4). The mixture was slowly heated and boiled for three minutes. The greenish oil which first formed set to a yellow paste on washing and after drying in a vacuum desiccator, solidified to yellow crystals, which were recrystallized from alcohol, m.p. 141–142° (sublimation from 100°; clear, pale yellow melt).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.57; H, 5.96.

A mixed melting point of the above compound with a sample of the spiroöxindole (XIV), prepared from II *via* I $\rightarrow$ V $\rightarrow$ IX,[14] showed no depression.

9-Acetyl-10,11-*cis*-dihydroxyhexahydrocarbazole (II) by Addition of Hydrogen Peroxide to N-Acetyltetrahydrocarbazole.—To a solution of 2 g. of 9-acetyltetrahydrocarbazole in 25 cc. of *t*-butyl alcohol was added 12 cc. (100% excess) of a 1.67 *M* solution of hydrogen peroxide in the same solvent. The mixture was chilled to 0° and 1 cc. of a 1% solution of osmium tetroxide in *t*-butyl alcohol was added. Within ten minutes a product began to crystallize from the mixture. After standing overnight the mixture was worked up at ice temperature by dilution with ether and thorough extraction with water and a little 2 *N* potassium hydroxide to remove osmium. The residual ether solution, after drying with sodium sulfate, was evaporated, leaving an orange oil. The oil was taken up in benzene–petroleum ether (1:3) and allowed to crystallize. There was obtained a quantity of prisms, m.p. 124–133°, and a number of small lumps of purer crystalline material, clusters of prisms, m.p. 205–208° (clear melt, after considerable sublimation), identical with 9-acetyl-10,11-dihydroxyhexahydrocarbazole prepared according to Perkin and Plant.[14] The yield under these conditions was poor and no attempt was made to improve it.

Spiro-(cyclopentane-1,3′-N-methyl-2′-hydroxyindole) (XIX).—To a solution of 200 mg. of spiro-(cyclopentane-1,3′-N-methyl-pseudo-oxindole) (XIV) in 30 cc. of dry ether was added 36 mg. of lithium aluminum hydride and the mixture refluxed for one hour. After decomposition with ice, the dried ether layer left 185 mg. of a colorless oil which showed (in chloroform solution) the following infrared bands: 2.81 (hydroxy), 6.21, 6.74, 6.89. The same compound was obtained in subsequent experiments even when more than 1/4 mole of lithium aluminum hydride was employed for the reduction.

Spiro-(cyclopentane-1,3′-N-methylindoleninium) Picrate (XX).—While the oxalate and hydrochloride of the above alkamine were obtained oily, a crystalline picrate was formed in benzene solution. Recrystallized from methanol it

(45) T. Reichstein and C. W. Shoppee, *Disc. Faraday Soc.*, 305 (1949).

formed long yellow birefringent prisms, m.p. 162–164° (sintering at 153°, yellow-green melt).

Anal. Calcd. for $C_{13}H_{16}N\cdot C_6H_3N_3O_7$: C, 54.94; H, 4.60. Found: C, 54.99; H, 4.94.

Rearrangement to 9-Methylcarbazole (XXII).—When the free alkamine (XIX) is left in a mixture of methanol and concentrated hydrochloric acid at room temperature, the unchanged free base can be recovered. With methanolic concentrated HCl (1:1) on the steam-bath or in polyphosphoric acid at 150° for a few minutes the alkamine is rearranged to a non-basic compound which crystallizes out of the acid- and base-washed and dried ether extract in colorless plates, m.p. 48°. The ultraviolet and infrared spectra were in agreement with an N-methyl indole compound. The picrate, prepared in benzene solution, formed red-brown needles, m.p. 114°.

The literature records m.p. 50°[46,47] for 9-methyltetrahydrocarbazole and 114.5°[46] and 116°[47] for the picrate.

N-Methylgelsemine.—A mixture of 2.41 g. of gelsemine, 300 mg. of potassium metal and 30 cc. of benzene was refluxed and stirred. Within 15 minutes a copious creamy precipitate had formed. After an hour 1.09 g. of methyl iodide in 4 cc. of benzene was added and refluxing was continued for two more hours. After standing overnight the mixture was filtered. Evaporation of the filtrate (steam-bath) left 552 mg. (22%) of a yellow oil which crystallized on scratching. Decomposition of the filter cake with water, followed by ether extraction, recovered 275 mg. of gelsemine, bringing the corrected yield to 25%. The crude N-methyl compound was taken up in boiling ligroin, decolorized with diatomaceous earth, and allowed to crystallize; colorless prisms, m.p. 141–142.5° (sublimes in small prisms 126°; clear colorless melt).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 75.01; H, 7.20; N, 8.33. Found: C, 74.72; H, 7.27; N, 8.23.

The reduction of N-methylgelsemine with lithium aluminum hydride gave N-methyldesoxydihydrogelsemine, m.p. 117–119°, identical with des-N-methyldesoxydihydrogelsemine.[35]

N-Methyldihydrogelsemine. A. By Hydrogenation.—A solution of 50 mg. of N-methylgelsemine in 4 cc. of methanol was stirred with 20 mg. of platinum oxide under hydrogen. In 19 minutes the hydrogen uptake was 21.65 cc. The solution was filtered and evaporated to leave colorless birefringent prisms, m.p. 164–168° identical (infrared spectrum) with the product obtained by methylation of dihydrogelsemine.

B. **By Methylation.**—A mixture of 213 mg. of dihydrogelsemine, 40 mg. of metallic potassium and 20 cc. of benzene was refluxed for 4 hours, 120 mg. of methyl iodide in 2 cc. of benzene was added dropwise and refluxing continued overnight. The mixture was filtered and the filtrate evaporated to leave 260 mg. (80%) of a yellow oil which crystallized readily on trituration with hexane. On recrystallization from hexane (and decolorization with diatomaceous earth) there were obtained large colorless birefringent prisms, m.p. 167–169° (sublimes in long needles 134°, sinters 157°, clear colorless melt).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.75; N, 8.28. Found: C, 75.17; H, 8.18; N, 8.12.

The reduction of N-methyldihydrogelsemine with lithium aluminum hydride led to N-methyltetrahydrodesoxygelsemine, m.p. 148°, identical with des-N-methyl-desoxytetrahydrogelsemine.[35]

Methiodide.—A mixture of 200 mg. of N-methyldihydrogelsemine, 10 cc. of methanol and 0.5 cc. of methyl iodide was refluxed for 30 minutes, left overnight, and evaporated on the steam-bath. The residue, amounting to 300 mg., crystallized readily on trituration with acetone. After washing with acetone, a portion was recrystallized from ethanol. Small hard glossy birefringent cubes, m.p. 305–306.5° (slow darkening from 200°, spalling and crystalline transformation 250–265°, melts with decomposition, brown melt).

Anal. Calcd. for $C_{22}H_{29}N_2O_2I$: C, 55.00; H, 6.08; N, 5.83. Found: C, 55.34; H, 6.07; N, 5.78.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF SMITH, KLINE AND FRENCH LABORATORIES]

C^{14}-Labeled Colchicine Derivatives[1]

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Six derivatives of colchicine, each labeled with C^{14} in a known position of the molecule, have been prepared. As an adjunct to the preparations involving labeled diazomethane, a method was developed for the quantitative estimation of this reagent in solutions containing it based upon the well-known ferric reaction of colchiceine.

Discussion

In order to study the fate of colchicine derivatives in biological studies, the preparation of a series of representative compounds labeled with C^{14} was undertaken. Walaszek[3] recently reported the biosynthesis of such compounds by growth of colchicum plants in an atmosphere of $C^{14}O_2$. Extraction of the plants gave the C^{14}-alkaloids. With this method, however, the positions of the labeled carbon atoms are not known, and thus the identification of labeled metabolic products is more difficult. Through the use of radioactive diazomethane and radioactive acetyl chloride we have prepared a number of colchicine derivatives labeled in rings A, B and C as shown in formulas I, II and III.

Ordinarily, in reactions involving the use of diazomethane, a liberal excess of the reagent is employed. In the present problem, however, it became necessary to obtain maximum methylation with a minimum expenditure of the C^{14} reagent. This involved the determination of the diazomethane equivalent of the nitrosomethylurea, optimum conditions for the methylation of the various colchicine derivatives, and adequate separation of isomeric products when these were formed.

The usual methods[4] for the determination of diazomethane were unsuitable inasmuch as they would have consumed the reagent to give C^{14} products of no immediate interest to our problem. A method was therefore devised based on the well-

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