THE JOURNAL OF Organic Chemistry®

Volume 27, Number 12 January 10, 1963

Gelsedine[1]

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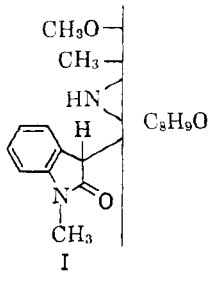
Received July 2, 1962

The alkaloid gelsedine is shown to be demethoxygelsemicine. Some degradation experiments and a p.m.r. spectral investigation are described. A chemical and spectral study of oxindole model compounds is discussed.

As the consequence of a thorough investigation of the alkaloidal constituents of yellow jasmine, *Gelsemium sempervirens* (L.) Ait., Schwarz and Marion reported in 1953[3] the isolation of three minor alkaloids—gelsemicine ($C_{20}H_{26}O_4N_2$), gelsedine ($C_{19}H_{24}O_3N_2$), and gelsevirine. Gelsemicine was considered to have many of the characteristics of an indole alkaloid and gelsevirine those of a 1,3,3-trisubstituted oxindole, while more structure data were collected, for gelsedine, the first oxindole alkaloid to be a secondary base. On the basis of elemental analysis, O-, N-, and C-methyl determinations, Zerewitinow determination and ultraviolet and infrared spectral analyses of the alkaloid and its N_b-acetyl derivative part structure I was suggested for gelsedine. Its methoxyl group was considered



I

to be in a position α or β to the oxindole carbonyl function because of its loss on catalytic hydrogenation of the alkaloid to a hydroaromatic system as well as on lithium aluminum hydride reduction of gelsedine to a noncrystalline, probably indoline substance and because of the slow appearance of a 405-mμ band in the ultraviolet spectrum of an alkaline solution of gelsedine which was considered to be characteristic of a β-alkylideneoxindole or isatin chromophore.

In view of our interest in the *Gelsemium* alkaloids[4] and in the chemistry of oxindole compounds[5] we have been drawn to the unsolved problem of the structure of gelsedine and have been involved in its investigation intermittently for the last six years. The present report represents the summation of our efforts.

The previously recorded[3] infrared spectral characteristics of gelsedine[6] were corroborated and support the presence of an N-substituted oxindole moiety. The oxindole carbonyl group could be shown to be in close proximity of N_b since the 5.84 μ ($CHCl_3$) band shifted to 5.81 μ ($CHCl_3$) in N_b-tosylgelsedine and to the hydrogen-bonded 5.94-μ ($CHCl_3$) position in gelsedine hydrobromide[7] and 6.08 μ ($CHCl_3$) in N_b-methylgelsedine hydroiodide. The ultraviolet spectrum of the alkaloid was in accord with previous observation,[3] but in contrast to the latter no change was noticed in alkaline

(1) This work was supported by U.S. Army Chemical Corps Contract DA 18-108-405-CML-269 and by a grant (MY 1301) from the U.S. Department of Health, Education, and Welfare.

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(3) H. Schwarz and L. Marion, *Can. J. Chem.*, **31**, 958 (1953).

(4) E. Wenkert and J. H. Hansen, *Iowa State J. Sci.*, **34**, 163 (1959).

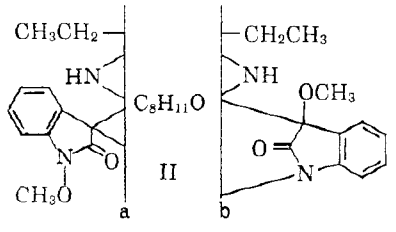
(5) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959), and previous papers.

(6) Gelsedine and gelsemicine were isolated according to the published procedure[3] from a generous supply of *Gelsemium* extract kindly furnished by the Ciba Pharmaceutical Co. The authors are most grateful to Dr. E. Schlittler and his colleagues for this gift.

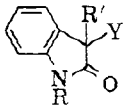
(7) This salt, m.p. 144–147°, was prepared especially for X-ray structure analysis. Unfortunately it changed color and gave changes of intensities of the X-ray reflections on exposure to the X-ray beam, presumably due to chemical transformation (Mr. D. E. Williams, private communication, April, 1959).

solution. A controlled Kuhn–Roth determination of gelsedine revealed that the C-alkyl group present in the alkaloid was a C-ethyl function.[8]

The most plausible explanation for the reported extrusion of the methoxy group on both catalytic and chemical reduction of the alkaloid[3] appeared to be its location on a benzylic or analogous position and, on this basis, gelsedine seemed to be a N-methoxy-3,3-disubstituted or 3-methoxy-N,3-disubstituted oxindole derivative. This argument suggested that lithium–liquid ammonia reduction of the alkaloid might lead to a demethoxy derivative. Since this reduction could be shown to convert the model compound, 1,3-dimethyl-3-methoxyoxindole (IIIa),[9] prepared by exhaustive alkylation of dioxindole with dimethyl sulfate and aqueous base, into 1,3-dimethyloxindole (IIIb), it was tried on gelsedine. The latter was transformed into demethoxygelsedine by this reduction process as well as by a reduction with sodium and *t*-butyl alcohol. The product could be acetylated to a N_b-acetyl derivative. The spectral properties of both substances showed them to be oxindoles. The diamide revealed a weak, but distinct peak (2.93 μ) in the OH and NH stretching region of the infrared spectrum which could be ascribed to a non-acetylable (even with ketene) hydroxyl group or, more likely, to the NH group of an oxindole moiety. These data suggested IIa or b as possible part structures of the alkaloid.



In view of the unusual expulsion of the methoxy group on lithium aluminum hydride reduction of gelsedine[3] it was of interest to study the behavior of its possible model IIIa toward this reagent. While the reduction of N-methyldioxindole (IIIc) has been shown to yield mostly N-methylindole and some N-methyloxindole (IIId),[10] the reduction of the more methylated compound IIIa had not been investigated. When this reaction was carried out for a half hour in ether as solvent, 1,3-dimethyloxindole (IIIb) and its dioxindole (IIIe) were obtained. The first indication of the latter substance not being a product of unprecedented demethylation of the starting material but rather one of oxidation of its companion product was the isolation of the even more unusual oxidation product, 1,3-dimethyloxindole dimer (IIIf),[11] from some of the reductions. Careful exclusion of air and reductive pretreatment of the solvent failed to prevent the formation of the dioxindole IIIe but merely added 1,3-dimethylindole to the products. The latter and its dihydro derivative are the known products of lithium aluminum hydride reduction of 1,3-dimethyloxindole (IIIb).[10] It now could be shown that the indole is the sole product of the reduction of IIIe. Finally, exposure of the lithium enolate of 1,3-dimethyloxindole (IIIb) to lithium aluminum hydride reduction afforded the same mixture of products which had been isolated from the reduction of IIIa. These results suggest that the only true product of the reduction of IIIa is the aluminum-complexed enolate of IIIb (formed presumably by hydride addition to the oxindole carbonyl group and loss of methanol from the resulting carbinolamine aluminate) which under ideal conditions would yield the demethoxy product IIIb but which is oxidized to the dioxindole IIIe (conceivably by ether peroxides) which, in turn, is partly reduced to 1,3-dimethylindole.



IIIa. R = R′ = Me, Y = OMe
b. R = R′ = Me, Y = H
c. R = Me, R′ = H, Y = OH
d. R = Me, R′ = Y = H
e. R = R′ = Me, Y = OH
f. R = R′ = Me, Y = —)$_2$
g. R = Y = H, R′ = Me
h. R = OMe, R′ = Y = H

With the advent of nuclear magnetic resonance spectroscopy as a tool of structure analysis an inspection of the proton magnetic resonance spectra of gelsedine, its derivatives and various simple oxindole model compounds was undertaken.[12] Gelsedine's p.m.r. spectrum in deuteriochloroform solution revealed a four-proton multiplet at 6.81–7.44 p.p.m. (relative to an internal TMS standard), in consonance with the presence of an *ar*-unsubstituted oxindole ring, a methoxyl singlet at 3.96 p.p.m. and the two-proton quartet, δ = 1.72 (J = 7.5 c.p.s.), and three-proton triplet, δ = 1.00 (J = 7.5 c.p.s.), characteristic of an ethyl group. The spectrum failed to support the previously suggested presence of a N-methyl group.[3] There was neither a 3.2-p.p.m. signal characteristic of N-methyloxindoles [$\delta_{N\text{-}Me}$ = 3.22 (IIIa), 3.18 (IIIb), 3.17 (IIIc), 3.17 (IIIe), 3.25 (N-methylisatin)], nor was there any absorption ascribable to a N_b-methyl function. Furthermore, the spectrum negated the assumed presence of an active hydrogen

(8) The authors are indebted to Mr. L. Dorfman (Ciba Pharmaceutical Co.) for this determination.

(9) M. Kohn and A. Ostersetzer, *Monatsh.*, **32**, 905 (1911).

(10) P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949).

(11) J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.*, 4782 (1958). It has been possible to prepare the two diasteromeric dimers IIIf by the reaction of the sodium enolate of IIIb and butyl nitrite (D. B. R. Johnston, unpublished observation).

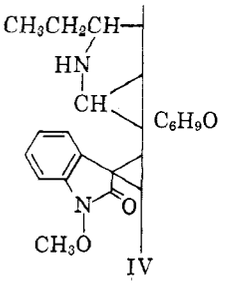
(12) The authors are most grateful to Dr. N. R. Trenner (Merck, Sharpe and Dohme) for the early p.m.r. spectra and their interpretation which initiated this study in 1958–1959.

at C-3 of the oxindole nucleus.[3] This atom showed up as a doublet at 3.40 p.p.m. (J = 7.7 c.p.s.) and 3.45 p.p.m. (J = 7.5 c.p.s.) in IIIb and IIIg, respectively, being coupled by the adjacent 3-methyl groups whose signals appeared at 1.46 p.p.m. (J = 7.7 c.p.s.) and 1.48 p.p.m. (J = 7.5 c.p.s.), respectively. [The p.m.r. signals of 3-methyl groups of dioxindoles appear at somewhat lower field, δ = 1.62 (IIIa), 1.62 (IIIe).] Thus, gelsedine is a 1,3,3-trisubstituted oxindole.

Unfortunately, neither the methylated dioxindole IIIa nor N-methoxyoxindole (IIIh)[13] proved to be good models for locating the methoxy group in gelsedine. Their signals were at 2.97 and 3.65 p.p.m., respectively, and thus both upfield from the 3.96 p.p.m. singlet of the alkaloid. (The C-3 methylene group of IIIh appears as a singlet at 3.38 p.p.m.) However, this problem was resolved by inspection of the p.m.r. spectrum of demethoxy-N_b-acetylgelsedine. The methoxy signal had vanished and in its stead a one-proton peak at 8.97 p.p.m. had appeared. The latter is characteristic of the highly concentration-dependent (δ = 9–10) oxindole NH group. This observation was in consonance with the infrared data of the gelsedine derivative (*vide supra*) and indicated that the alkaloid possessed an N-oxygenated oxindole moiety (IIa), a heretofore unencountered alkaloid structure unit.

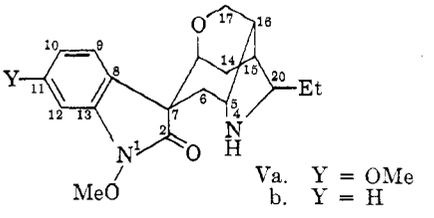
Information regarding the more subtle structural features of gelsedine could be acquired from a comparison of its p.m.r. spectrum and that of its N_b-acetyl derivative. The latter exhibited an expected extra methyl signal at 2.46 p.p.m., but, more importantly, revealed a downfield shift of three groups of saturated hydrogens. The methylene of the ethyl group had moved from 1.72 p.p.m. to $\delta \geq 1.88$ and two broad one-proton multiplets had migrated from δ = 2.71–3.17 and 3.17–3.83 to δ = 3.48–3.94 and 4.11–4.76. The chemical shift of these hydrogens and their downfield drift on acetylation of the alkaloid located their position on N_b-substituted carbon atoms and suggested the presence of a $R_2CHNHCHR'Et$ unit in gelsedine. The remaining two-proton multiplet at δ = 4.20–4.30 and one-proton signal at $\delta \simeq 3.5$ had to be associated with carbons holding the presumed[3] ether oxygen of the alkaloid. Unfortunately even this additional information was insufficient to permit a complete formulation of the structure of the natural product without introduction of many assumptions. However, part structure IV could account for all the accumulated data.

At this point of our work there appeared a report on the X-ray analysis of gelsemicine hydroiodide[14] which revised completely previous views[3] on the structure of gelsemicine. In view of the presence of a N-methoxyoxindole moiety in the latter



IV

and the previously cited[3] great similarity of the alkaloid's infrared spectrum with that of gelsedine a comparison of the p.m.r. spectra of the two alkaloids became of utmost importance. Such collation as well as one of the spectra of the N_b-acetyl derivatives of the alkaloids showed them to be superposable everywhere except for the aromatic region and for an extra 3.80-p.p.m. aromatic methoxyl signal in the gelsemicine spectra. The three-proton aromatic absorption in the p.m.r. spectrum of gelsemicine showed a C(9)-H[15] quartet at 7.26 p.p.m. (J = 1.3, 8.5 c.p.s.), a C(10)-H quartet at 6.55 p.p.m. (J = 3.0, 8.5 c.p.s.), and a C(12)-H multiplet at 6.48, quite reminiscent of the aromatic peak pattern of 11-methoxy indole alkaloids.[16] These results show that gelsemicine (Va) is 11-methoxygelsedine and in combination with the X-ray data[14] they permit the assignment of structure Vb to gelsedine.



Va. Y = OMe
b. Y = H

The structures of the two secondary *Gelsemium* bases bear a close relationship to the constitution of gelsemine, one of two major *Gelsemium* alkaloids. Their formation in the plant probably follows a similar biosynthetic path.[4] The most interesting and novel feature in Va and b is the absence of C-21 in the non-tryptamine part of their molecular framework. This moiety is usually derived from the C_{10} unit VI.[17] In the case of gelsemicine and gelsedine C-21 may have been extruded from VI, presumably by a retroaldol process, or may never have been incorporated initially into VI, especially should it arise from one-carbon precursors.[18]

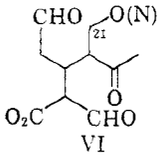
(13) W. B. Wright, Jr., and K. H. Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956).

(14) M. Przybylska and L. Marion, *Can. J. Chem.*, **39**, 2124 (1961).

(15) The numbering system follows that of yohimbine. It is suggested that this also be the nomenclature of all biosynthetically and, hence, structurally related indole alkaloids.

(16) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961).

(17) E. Wenkert, *ibid.*, **84**, 98 (1962).



VI

Experimental

N_b-*p*-Toluenesulfonylgelsedine.—A solution of 137 mg. of gelsedine and 145 mg. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine was left for 1 hr. on a steam bath and at room temperature for 12 hr. Addition of water, extraction with ether, and evaporation of the organic solution yielded 150 mg. of a solid, m.p. 215–216°, which on crystallization from ethyl acetate gave N_b-*p*-toluenesulfonylgelsedine, m.p. 220–221°; $[\alpha]_D^{EtOH}$ −143°; infrared spectrum ($CHCl_3$): C=O 5.81 (s), C=C 6.19 (m), 6.23 (w) μ.

Anal. Calcd. for $C_{27}H_{31}N_2O_5S$: C, 64.71; H, 6.27; N, 5.81. Found: C, 64.69; H, 6.04; N, 5.84.

N_b-Methylgelsedine Hydroiodide.—A mixture of 85 mg. of gelsedine, 23 mg. of sodium bicarbonate, 1 ml. of methyl iodide, and 1 ml. of absolute ethanol was refluxed for 24 hr. The mixture was concentrated and cooled whereupon 73 mg. of needles deposited. Recrystallization from ethanol yielded N_b-methylgelsedine hydroiodide, m.p. 245–248°; $[\alpha]_D^{EtOH}$ −114° (*c*, 1.07); infrared spectrum ($CHCl_3$): OH, NH 2.97 (w), 3.80 (m), 3.90 (m), 4.05 (w), 4.20 (w) μ, C=O 6.08 (s) μ, C=C 6.24 (m) μ.

Anal. Calcd. for $C_{20}H_{26}N_2O_3 \cdot HI$: N, 5.97. Found: N, 5.83.

Demethoxygelsedine.—A solution of 86 mg. of gelsedine in 1 ml. each of ether and tetrahydrofuran was added to a solution of 20 mg. of lithium in 7 ml. of liquid ammonia. After 30 min. the blue solution was poured into aqueous ammonium chloride solution and extracted with ether and ethyl acetate. The extract was dried and evaporated and the residue crystallized four times from benzene. This led to 22 mg. of colorless prisms of demethoxygelsedine, m.p. 233–235°; $[\alpha]_D^{EtOH}$ −182° (*c*, 2.66); spectra: ultraviolet (95% ethanol), λ_{max} 255 mμ (log ϵ 3.83); infrared (Nujol), OH, NH 2.97 (w) μ, C=O 5.87 (s) μ, C=C 6.16 (w), 6.20 (w) μ.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.57; N, 9.47.

Treatment of demethoxygelsedine with acetic anhydride and pyridine for 18 hr. at room temperature followed by the usual work-up yielded a solid which on crystallization from methanol gave N_b-acetyldemethoxygelsedine, m.p. 309–311°; infrared spectrum ($CHCl_3$): OH, NH 2.93 (w), 3.18 (w) μ, C=O 5.83 (s), 6.15 (s) μ.

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.56; N, 7.11. Found: C, 70.27; 7.08.

A solution of 30 mg. of gelsedine in 1 ml. of benzene and 1 ml. of *t*-butyl alcohol was refluxed, while 150 mg. of sodium was added slowly over a 2.5-hr. period. The mixture was diluted with water and extracted with benzene. Upon concentration of the solution plates of demethoxygelsedine crystallized. This crude reduction product, m.p. 214–218°, did not depress the melting point of the lithium–ammonia product, had an infrared spectrum identical with that of the latter and yielded N_b-acetyldemethoxygelsedine on treatment with acetic anhydride and pyridine.

(18) It has been suggested recently that a similar biosynthetic unit lacking C-21 may be responsible for the nontryptamine portion of the structure of mitragynine [J. B. Hendrickson, *Chem. Ind.* (London), 713 (1961)].

1,3-Dimethyl-3-methoxyoxindole (IIIa).—To a cooled and stirring suspension of 31.0 g. of crude dioxindole, prepared by the reduction of 37.6 g. of isatin with sodium hydrosulfite,[19] there was added 150 g. of dimethyl sulfate slowly. After 3 hr. more sodium hydroxide, 200 ml. of 10% solution, and dimethyl sulfate, 58 g., was added. At the end of two more hours the resulting precipitate was filtered and crystallized from hexane–methylene chloride yielding 18.6 g. of 1,3-dimethyl-3-methoxyoxindole (IIIa) m.p. 78–79° (lit.[9] m.p. 78.5°), spectra: ultraviolet (95% ethanol), λ_{max} 258 mμ (log ϵ 3.78), no change on admixture with 5% sodium hydroxide solution; infrared (Nujol), C=O 5.81 (s) μ, C=C 6.27 (s) μ.

The reduction of IIIa (311 mg.) by lithium (105 mg.) in liquid ammonia (25 ml.) followed the above procedure. Chromatography of the product on alumina and elution with 7:3 petroleum ether–carbon tetrachloride yielded 150 mg. of 1,3-dimethyloxindole (IIIb), m.p., m.m.p. 54–55°, spectra identical with those of an authentic sample.

Lithium Aluminum Hydride Reductions of Oxindoles.—An ethereal solution of 710 mg. of IIIa was added to a stirring ethereal suspension of excess lithium aluminum hydride and the mixture refluxed 0.5 hr. Careful addition of water destroyed the excess hydride. The resulting precipitate was filtered and washed with aqueous ethanol. The basic filtrate was extracted with ethyl acetate. The organic solution was washed with *N* hydrochloric acid, sodium carbonate solution, and water and then dried over anhydrous magnesium sulfate. The solution was evaporated under vacuum and the residue, 550 mg., chromatographed on alumina. Elution with 3:1–1:3 benzene–chloroform gave 250 mg. of a solid which on sublimation yielded 162 mg. of 1,3-dimethyloxindole (IIIb), m.p. 52–53°; m.p., m.m.p. 55° after crystallization from petroleum ether; spectra identical with those of an authentic sample. Elution with 50:1 chloroform–methanol gave 167 mg. of a solid which on sublimation yielded 101 mg. of 1,3-dimethyldioxindole (IIIc), m.p. 151–152°; m.p., m.m.p. 152° after crystallization from acetone; spectra identical with those of an authentic sample.

When in a similar reduction of IIIa the products were separated by distillation, a solid, m.p. 202–204°, appeared in the fraction boiling at 120°/1 mm. Crystallization thereof from ethanol yielded 3,3-(1,3-dimethyl)oxindolyl (IIIf), m.p., m.m.p., 215–217° (lit.,[11] m.p. 219–221°); spectra identical with those of an authentic sample.

A similar reduction of 198 mg. of IIIa, however run under nitrogen, gave IIIb and IIIc along with 8 mg. of 1,3-dimethylindole as an oil (petroleum ether elution λ_{max}; 220 mμ, 289 mμ, λ_{min} 247 mμ); its picrate, m.p. m.m.p. 137–139°.

A reduction of 205 mg. of IIIa under nitrogen for 18 hr. yielded 80 mg. of crude products whose separation led to 51 mg. of 1,3-dimethylindole, 5 mg. of IIIb, and 5 mg. of IIIc.

A reduction of 92 mg. of IIIc under nitrogen for 0.5 hr. gave 30 mg. of only 1,3-dimethylindole.

A solution of 92 mg. of IIIb and lithium *t*-butoxide (8 mg. of lithium in 30 ml. of *t*-butyl alcohol) was evaporated to dryness under reduced pressure and suspended in 20 ml. of anhydrous ether. A solution of 250 mg. of lithium aluminum hydride in 30 ml. of ether was added and the mixture stirred under nitrogen for 0.5 hr. The usual work-up gave 65 mg. of crude product which could be separated into 16 mg. of 1,3-dimethylindole, 8 mg. of IIIb, and 5 mg. of IIIc.

(19) C. Marschalk, *J. prakt. Chem.*, **88**, 227 (1913).