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A DEGRADATION OF GELSEMINE

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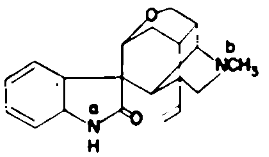
Abstract—An unusual reversible degradation of a quaternary gelsemine derivative is described.

THE structure of gelsemine (I), one of the main alkaloids of *Gelsemium sempervirens* has recently been ascertained by x-ray crystallographic means by Pepinsky *et al.*[2] and the degradative studies and biogenetic considerations of Conroy and Chakrabarti[3] published at the same time are in full agreement with this structure, independently deduced by them.



I

Conroy's degradative studies are especially noteworthy in that they describe for the first time a method by which the highly compact cage structure containing N(b) can be breached. The many earlier degradative studies[4] had utterly failed to open this system and in particular had demonstrated that no quaternary derivatives of this system will undergo a normal Hofmann elimination.

Thus, gelsemine and dihydrogelsemine methohydroxides on attempted Hofmann degradation yield N(a)-methylgelsemine and N(a)-methyldihydrogelsemine respectively,[5] and the methohydroxides of these N(a)-methyl derivatives when heated merely return the corresponding tertiary bases with loss of methanol.[5]

These results are readily understandable on the Pepinsky–Conroy structure since both hydrogen atoms β to N(b) are at bridgehead positions which cannot accommodate a double bond.

At the time our work was undertaken the structure of gelsemine was unknown, but there were strong biogenetic reasons for believing that the vinyl group was

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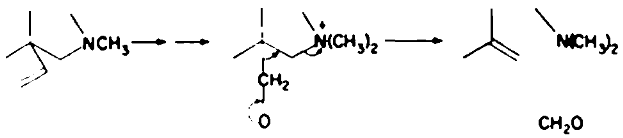
[2] F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Letters* No. 4, 1 (1959).

[3] H. Conroy and J. K. Chakrabarti, *Tetrahedron Letters* No. 4, 6 (1959).

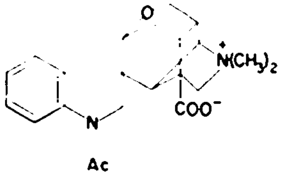
[4] These studies had indicated the presence of the 3,3-disubstituted oxindole system, a tertiary nitrogen carrying a methyl group in a 5 membered ring, a vinyl group, an inert oxygen atom in a system containing six rings, and had indicated the proximity of the oxindole oxygen and the vinyl group. cf. *inter alia*, L. Marion, *Canad. J. Res.* **B21**, 247 (1943); M. Kates and L. Marion, *J. Amer. Chem. Soc.* **72**, 2308 (1950); *Canad. J. Chem.* **29**, 37 (1951); R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta* **34**, 1139 (1951); G. Jones and T. S. Stevens, *J. Chem. Soc.* 2344 (1953); T. Habgood and L. Marion, *Canad. J. Chem.* **33**, 604 (1955); L. Marion and K. Sargeant, *J. Amer. Chem. Soc.* **78**, 5127 (1956); *Canad J. Chem.* **35**, 301 (1957).

[5] R. Goutarel, M. M. Janot, V. Prelog and R. P. A. Sneeden, *Helv. Chim. Acta* **34**, 1962 (1951); T. Habgood, L. Marion and H. Schwarz, *Ibid.* **35**, 638 (1952); V. Prelog, J. B. Patrick and B. Witkop, *Ibid.* **35**, 640 (1952). The methohydroxide of N(a)-methyl-nor-gelsemine aldehyde (IV) also loses methanol on pyrolysis, yielding the tertiary aldehyde; *vide infra*.

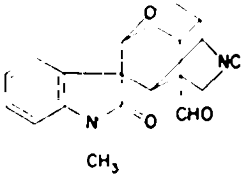
attached to a carbon atom which stood β to N(b). In this circumstance it should be possible to effect a degradation of the following type:



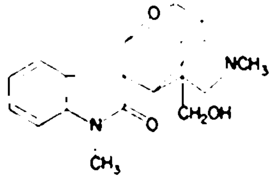
Reactions of this sort have been observed in simple systems,[6] particularly when the β carbon atom is disubstituted, and the reaction is similar in principle to the successful degradation carried out by Conroy[3] on the related betaine III, whose decarboxylation is accompanied by a ring opening of this type.



II



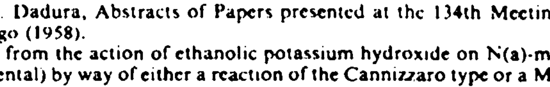
IV



V

We accordingly undertook a study of the thermal degradation of the methohydroxide of N(a)-methyl-nor-gelsemine carbinol (V), prepared by borohydride reduction[7] and methylation of Marion's N(a)-methyl-nor-gelsemine aldehyde (IV).[8] The results obtained were unexpected, and while they do not add to the structural conclusions already available, they are consistent with the structural proposals of Pepinsky and of Conroy and seem to be of sufficient intrinsic chemical interest to report.

When the crystalline N(a)-methylgelsemine-nor-carbinol methohydroxide trihydrate[9] is heated under reduced pressure, no formaldehyde is formed, but a highly fugitive anhydro-base which we formulate as the 3,3-spirotrimethylene oxide derivative VII sublimes in nearly quantitative yield. Analysis immediately after sublimation gives values corresponding to $C_{21}H_{28}O_3N_2$; after several days the



VI VII

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[6] V. J. Traynelis and J. G. Dadura, Abstracts of Papers presented at the 134th Meeting of the American Chemical Society, Chicago (1958).

[7] This carbinol also results from the action of ethanolic potassium hydroxide on N(a)-methyl-nor-gelsemine aldehyde IV (cf. Experimental) by way of either a reaction of the Cannizzaro type or a Meerwein–Ponndorf-Verley reduction. This is strong presumptive evidence that the carbon atom α to the aldehyde carbonyl does not bear a hydrogen atom and to this extent confirms Conroy's conclusion based on the NMR spectrum of N(a)-acetyldeoxo-nor-gelsemine aldehyde.

[8] L. Marion and K. Sargeant, *Canad. J. Chem.* 35, 301 (1957).

[9] The corresponding methiodide, from which this substance is produced by ion exchange, can be obtained in 55% yield by preparation of N(a)-methylgelsemine methiodide in one step followed by oxidative cleavage and borohydride reduction of the aldehyde in another step. (cf. Experimental).

analytical results indicate that water is being taken up by the sublimate. This formulation is strongly supported by the NMR spectrum of the substance. In Table 1 the gross features of its spectrum and that of dihydrogelsemine are compared. The appearance of a group of poorly resolved peaks corresponding to approximately 4 protons in the range 5·1 to 5·5 τ and a completely unsplit peak at 8·0 τ corresponding to 6 protons, the first assigned to the four non-equivalent hydrogens of the trimethylene oxide ring,[10] the second to two equivalent tertiary N-methyl groups,[11] is decisive.

Table 1. NMR spectra[a] of anhydro sublimate (VII) and dihydrogelsemine. Relative integrated areas and probable assignments

Proton	τ[b]	Anhydro-base (VII)		Dihydrogelsemine[c]	
		observed	calc	observed	calc
N(a) H	· 2·0	0	0	1	1
Aryl H-	2·3 3·7	4	4	4	4
O CH$_2$- C (trimethylene oxide)	5·1 5·5	3 4	4	0	0
O –CH (ether)	5·9	4–5	1	1	1
O CH$_2$– (ether)	6·1		2	2	2
N(b) CH	6·6 6·7		1	1	1
N(a) CH$_3$	6·9	3[d]	3	0	0
N(b) CH$_2$	6·9 7·6	5	0	3	2
C– CH	7·9–8·2		3	6	3
C–CH$_2$	7·9 8·2		2		4
N(b) CH$_3$	7·8 8·0	6[d]	6	3[d]	3
C CH$_3$	9·2	0	0	3[e]	3
			26		24

[a] Determined at 60 mc in deuterochloroform (conc approx 20%) with tetramethylsilane and chloroform as internal standards.

[b] Chemical shifts in p.p.m. relative to tetramethylsilane - 10. cf. G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

[c] The NMR spectrum of dihydrogelsemine has been reproduced in part and discussed in, J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 281. McGraw-Hill (1959).

[d] Singlet

[e] Triplet

The infrared spectrum of the sublimate also supports its formulation as VII. According to Barrow and Searles[12] the trimethylene oxide ring shows intense absorption at about 8·0 μ and at 10·2–10·3 μ, but the absence of absorption in the

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[10] NMR absorption at 5·81 τ and 5·64 τ has been observed for the ring methylene hydrogens of 3,3-diethyltrimethylene oxide (private communication from S. Searles) and of 3,3-dichloromethyltrimethylene oxide (private communication from G. V. D. Tiers) respectively. The ring methylene hydrogens adjacent to oxygen in 1-oxa[4 . 2 . 0] bicyclooctane (τ -- 5·54) and in 1-oxa-5-methyl[2 . 2 . 0] bicyclohexane (τ – 5·13, 5·61) also fall in this range (private communications from D. S. Tarbell and A. Rosowsky and from R. Srinivasan).

[11] In the starting quaternary carbinol hydroxide the two unsplit peaks corresponding to these two (non-equivalent in this case) N- CH$_3$ groups occur at 7·08 and 7·17 τ. Among the calabash curare alkaloids quaternary N—CH$_3$ groups also occur in this region (6·8–7·0 τ), 0·7–0·8 p.p.m. less than the corresponding tertiary N—CH$_3$ resonance. (Private communication from V. Boekelheide and O. Ceder.)

[12] G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.* **75**, 1175 (1953).

8·0 μ region in some trimethylene oxides has been noted by Campbell[13]. A comparison of the infrared absorption in this region of several 3,3-disubstituted trimethylene oxide derivatives and of our anhydro-base is given in Table 2.

Perhaps the most striking feature of the chemistry of the anhydro-base VII is the great ease with which the reaction by which it is formed is reversed. When freshly sublimed, it is readily soluble in non-polar solvents such as benzene, ether, methyl iodide, chloroform and the like as well as in simple alcohols, but its chloroform solution on standing deposits N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate in crystalline form. When dissolved in 50 per cent aqueous ethanol, the anhydro-base exhibits an initial pH of 6·9, but this rises to pH 12·3 in about half a minute,[14] and from such solutions the crystalline methohydroxide trihydrate can be isolated. The tendency of VII to revert to the quaternary alkoxide VI is in fact so great that attempts to stabilize the opened form VII by quaternization (with methyl iodide) so that further degradations could be carried out on it have uniformly given only N(a)-methyl-nor-gelsemine carbinol methiodide.

TABLE 2. SELECTED INFRARED ABSORPTION BANDS

3,3-Dimethyl trimethylene oxide[13a]	Bis-3,3-chloromethyl trimethylene oxide[13b]	Bis-3,3-bromomethyl trimethylene oxide[13b]	Bis-3,3-aminomethyl trimethylene oxide[13b] dihydrobromide	Anhydro-base (VII)[c]
8·05[d]	8·1		--	8·03
10·15	10·15	10·20	10·45	10·30
10·6	10·45	10·57	10·68	10·53

[a] Liquid sample
[b] Potassium bromide pellet or chloroform solution
[c] Potassium bromide pellet
[d] Microns

It may be remarked in passing that the reaction by which VII is formed from VI is merely the intramolecular counter-part of the reaction by which other quaternary hydroxides in this series return to the corresponding tertiary bases with loss of methanol, i.e. the nucleophilic attack of alkoxide (or hydroxide) on a carbon atom α to the quaternary nitrogen. Both this reaction and its reverse appear to be examples of reactions which are enormously facilitated by the proximity imposed on the reacting centers by the rigid geometry of this system.

EXPERIMENTAL[15]

N(a)-*Methyl*-nor-*gelsemine carbinol* (V). A solution of 425 mg N(a)-methyl-nor-gelsemine aldehyde (IV),[8] m.p. 197–200°, in 20 ml 50% aqueous methanol was treated with 400 mg sodium borohydride in portions. The solution was warmed gently for a few min, and after 1 hr the excess reagent was destroyed by the addition of dil acetic acid. The solution was made basic with ammonia and extracted with chloroform and the extracts were washed, dried and concentrated to yield a colorless residue which crystallized readily from benzene as colorless prisms, 378 mg, m.p. 243–250°. A second

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[13] T. W. Campbell, *J. Org. Chem.* **22**, 1029 (1957).

[14] Compare the similar rise in basicity which occurs during the reconversion of the anhydro-base from tetrahydroberberine (or l-canadine) methohydroxide to this quaternary hydroxide. cf. F. L. Pyman, *J. Chem. Soc.* **103**, 821 (1913).

[15] Melting points are uncorrected. Analyses were done by W. Manser, Zurich and Microtech Laboratories.

crop had m.p. 242–247.5°. Recrystallization from benzene raised the m.p. to 249–250° (Found: C, 70.56; H, 7.08; N, 8.12. $C_{20}H_{24}O_{3}N_{2}$ requires: C, 70.56; H, 7.11; N, 8.23%.)

The same substance resulted when the aldehyde IV (60 mg) was heated under reflux for 13 hr with a solution of 1.2 g potassium hydroxide in 6 ml ethanol. Dilution with water and extraction with chloroform yielded after concentration a pale orange oil (50 mg) which solidified under ether and whose infrared spectrum was indistinguishable from that of the sample described above.

N(a)-*Methyl*-nor-*gelsemine carbinol methiodide*. This was prepared in and crystallized from ethanol, colorless needles, m.p. 288–290° (dec). Highly purified samples occasionally melt as high as 304–305° (dec) (Found: C, 52.06; H, 6.03; N, 5.48; I, 25.20. $C_{21}H_{27}O_{3}N_{2}I$ requires: C, 52.28; H, 5.65; N, 5.81; I, 26.32%.) $[\alpha]^{\text{[illegible]}}_{D}$ +16 (c 1.05, water).

This methiodide can also and more conveniently be prepared directly from gelsemine as follows: A solution of 5.00 g of the acetone solvate of gelsemine in 140 ml reagent grade toluene was concentrated to about 100 ml by boiling to remove acetone and traces of water, cooled, and treated with 726 mg of a 49.6% dispersion of sodium hydride in mineral oil. After the immediate copious gas evolution had ceased, the mixture was heated under reflux for 2 hr, allowed to cool, treated with 4 ml methyl iodide, and refluxed for 30 min. More methyl iodide (5 ml) was added and the mixture allowed to stand at room temp for several days. The colorless crystalline solid, crude N(a)-methylgelsemine methiodide, was collected, washed with benzene, dried (8.88 g) and converted to the chloride by ion exchange over 70 g Dowex 2-x4 (chloride form) in 50% aqueous methanol. The resulting solution was concentrated under diminished pressure to yield the crude quaternary chloride as a yellow gum which in contrast to the iodide was readily soluble in methanol. Filtration of its solution in this solvent removed 0.61 g sodium chloride, and the resulting clear solution was concentrated to yield 5.69 g (theory 5.08 g) of the chloride. A solution of this substance in 85 ml water was treated with 150 mg osmium tetroxide with stirring. A chocolate brown color was produced, and after 10 min a solution of 5.90 g sodium meta periodate in the minimum amount of water was added dropwise. The brown but essentially homogeneous solution was allowed to stand 1 hr, then warmed on the steam bath for 20 min, during which it lightened to pale yellow, finally allowed to cool and treated with 2 g sodium borohydride. Much gas was evolved and a fine black precipitate of osmium dioxide was produced. After standing overnight the solution was filtered, concentrated to about 50 ml under diminished pressure (crystalline precipitate) and treated with 2.0 g sodium iodide. Crude crystalline N(a)-methyl-nor-gelsemine carbinol methiodide, 5.20 g (theory 6.31), m.p. 278–280° (dec), was obtained. Recrystallization from alcohol–water gave 3.47 g (55%) of material of acceptable quality, m.p. 279–286° (dec).

N(a)-*Methyl*-nor-*gelsemine carbinol methochloride*. This was prepared from the iodide (or the hydroxide) by ion exchange on Dowex 2-x4, m.p. 294–295° (dec) when crystallized from absolute ethanol–ether (Found: (on sample dried at 100° *in vacuo*) C, 62.78; H, 7.11; N, 6.99. $C_{21}H_{27}O_{3}N_{2}Cl\ \frac{1}{2}H_{2}O$ requires: C, 63.05; H, 7.06; N, 7.00%.)

N(a)-*Methyl*-nor-*gelsemine carbinol methohydroxide*. This was prepared from the iodide by ion exchange on Dowex 2-x4 (hydroxide form) and crystallized from 95% alcohol–ether, fine needles, m.p. 296–297° (dec). (Found: (on air-dried sample) C, 59.05; H, 8.14; N, 6.55; H_2O, 4.22, 4.39 (loss in wt. on drying at 100°). $C_{21}H_{28}O_{4}N_{2}\cdot 3H_{2}O$ requires: C, 59.13; H, 8.04; N, 6.57; H_2O (loss of 1 H_2O) 4.23%.) uv λ_{max} 254 mμ (log ε 3.8), 284 mμ (shoulder) (log ε 3.1), $[\alpha]^{\text{[illegible]}}_{D}$ +16 (c 0.88, water).

The O-acetyl derivative of N(a)-*methyl*-nor-*gelsemine carbinol methiodide*. This was prepared by heating a solution of 105 mg of the methiodide in 2 ml acetic anhydride to reflux for 30 min. The cooled solution was diluted with methanol, allowed to stand for a few min, then concentrated to dryness under diminished pressure. The colorless residue was dissolved in hot water, treated with sodium iodide and allowed to crystallize, small prisms, 51 mg, m.p. 260–265° (dec). Recrystallization from water raised the m.p. to 265–270° (dec). IR max *inter alia* 5.82, 5.88 and 7.98 μ (O-acetyl group and N(a)-methyl oxindole carbonyl). (Found: C, 51.71; H, 5.71. $C_{23}H_{29}O_{4}N_{2}I\ \frac{1}{2}H_{2}O$ requires: C, 51.79; H, 5.67%.)

Pyrolysis of N(a)-*methyl*-nor-*gelsemine carbinol methohydroxide*. *The anhydro-base* VII. When this methohydroxide (48 mg) was heated in a stream of nitrogen at temp ranging from 150–190°, extensive decomposition took place. The nitrogen stream was passed into 2 N hydrochloric acid saturated with 2,4-dinitrophenylhydrazine, but no formaldehyde 2,4-dinitrophenylhydrazone was detected. Sublimation of the residue at 10^{-4} mm and 150–200° afforded a sublimate (5 mg) whose infrared spectrum was identical with that of N(a)-methyl-nor-gelsemine carbinol.

When, however, N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate (205 mg) was sublimed at 160–170° and 10^{-4} mm, a colorless sublimate was produced, and an inappreciable residue (2 mg) remained. Analysis of a sample of sublimate prepared in this way immediately after sublimation (Found: C, 71·40; H, 7·73. $C_{21}H_{26}O_3N$ requires: C, 71·17; H, 7·39%) indicates that an anhydro-base has been produced. Analysis after a week or so suggests that water is being absorbed (Found: C, 70·24; H, 7·89; N, 7·69%). The sublimate is readily soluble in benzene, chloroform, ether, acetone and ethanol but insoluble in water. When a portion of the sublimate was dissolved in 50% aqueous ethanol, the pH as determined by a glass electrode increased from 6·9 to 12·3 in about ½ min. A solution of the sublimate in chloroform deposited on standing crystalline material whose infrared spectrum was indistinguishable from that of the starting N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate, which contained no iodide ion, whose solution in water had pH ca. 12 and whose electrophoretic mobility was the same as quaternary salts in this series.

Attempted quaternization of the anhydro-base VII *with methyl iodide*. The sublimate (10^{-3} mm, 160–170°) from 345 mg N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate (residue 4·2 mg) was taken into methyl iodide and allowed to stand 1 day. Removal of the methyl iodide and examination of the infrared spectrum of the residue showed that the residue was essentially unchanged sublimate, so the residue was warmed with methyl iodide in acetonitrile. The solvents were removed, and the residue yielded 247 mg of material soluble in chloroform, which, when passed in methanol through an ion exchange column (Dowex 2-x4) in the iodide form, yielded N(a)-methyl-nor-gelsemine carbinol methiodide, m.p. 282–284° (dec), not depressed by admixture of authentic methiodide. Their infrared spectra were indistinguishable.

Attempted Hofmann degradation of N(a)-*methyl*-nor-*gelsemine aldehyde methohydroxide*. N(a)-Methyl-nor-gelsemine aldehyde methiodide (16 mg), prepared from the aldehyde in the usual way and crystallized from acetone–ether, m.p. 255–265° (variable with dec). (Found: C, 52·37; H, 5·46; N, 5·23. $C_{21}H_{25}O_3N_2I$ requires: C, 52·51; H, 5·25; N, 5·84%) was converted to the hydroxide in methanol over Dowex 2-x4 (hydroxide form), and the residue remaining after removal of the solvent was sublimed (at 170–180° and 2×10^{-4} mm). The infrared spectrum of the pale yellow sublimate (10 mg) was indistinguishable from that of N(a)-methyl-nor-gelsemine aldehyde.

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