153. *The Alkaloids of* Gelsemium Sempervirens. *Part I.*

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Gelsemine and sempervirine have been isolated in improved yields; and gelsemicine, most probably $C_{20}H_{24}O_4N_2$ and a secondary base, has been more fully characterised. Crystalline derivatives of further alkaloids have been obtained in small quantity. The catalytic hydrogenation of the three main components has been studied. Gelsemine is a powerful monoacid base ($K = 2{\cdot}3 \times 10^{-5}$); the oxygen atoms are extraordinarily inert and their function is still obscure. Moore's *apo*gelsemine and *isoapo*gelsemine (J., 1910, **97**, 2223; 1911, **99**, 1231) appear to be produced by hydration of an olefinic linkage in gelsemine. Numerous exploratory observations on the degradation of gelsemine and sempervirine are recorded.

The American "yellow jasmine," *Gelsemium sempervirens*, Ait., has afforded the following crystalline alkaloids: gelsemine ($C_{20}H_{22}O_2N_2$), sempervirine ($C_{19}H_{16}N_2$), and gelsemicine [$C_{20}H_{25}O_4N_2$ (*sic*), Chou, *Chinese J. Physiol.*, 1931, **5**, 131, 295], as well as amorphous constituents of doubtful individuality. Little is known of their constitution, although colour reactions and botanical relationships might suggest affinities with the *Strychnos* bases.

By submitting 22·5 kg. of powdered *Gelsemium* root, supplied by Messrs. Burroughs Wellcome and Co., to a modification of Sayre and Watson's procedure (*J. Amer. Pharm. Assoc.*, 1919, **8**, 708), we obtained in considerably improved yield gelsemine (29 g.) and sempervirine nitrate (19 g.). The fraction of amorphous bases having chloroform-soluble hydrochlorides—Sayre and Watson's "gelsemoidine"—afforded 1·5 g. of a new crystalline *methiodide* $C_{20}H_{22(24)}O_3N_2,CH_3I$; its specific rotation differed widely from that recorded by Moore (*loc. cit.*) for his *apo*gelsemine methiodide of the same composition and m. p. No gelsemicine could at first be identified; in isolating this rather unstable substance Chou worked up his material in a different manner. At a later stage of the investigation a sample of amorphous "gelsemoidine" picrate was re-examined and gelsemicine readily isolated through its benzoyl derivative (see below); and enough of this alkaloid had survived for identification in a specimen of free "gelsemoidine."

Concentrated *Gelsemium* tincture (8·2 l.), supplied by the same firm and similarly treated, afforded 6·75 g. of gelsemine, 1·75 g. of sempervirine nitrate, and 6—7 g. of "gelsemoidine" hydrochloride. There were also isolated 500 mg. of the crystalline *picrate*, $C_{20}H_{24}O_4N_2,C_6H_3O_7N_3$, m. p. 152°, of an amorphous base. Other materials of less certain homogeneity are recorded in the experimental section. This tincture was examined before the separation of gelsemicine as benzoyl derivative had been worked out, and the alkaloid was not identified.

Some 60 g. of "Nebenhydrochloride des Gelsemins" (Merck), from the late Professor Barger's collection, yielded no gelsemine, 2·5 g. of sempervirine nitrate, a little of the picrate, m. p. 152°, and 5·6 g. of what proved to be *gelsemicine picrate*, m. p. 203°.

Gelsemine.—This alkaloid, by hydrogenation over palladium, afforded dihydrogelsemine, described while this work was in progress by Chu and Chou (*J. Amer. Chem. Soc.*, 1940, **62**, 1955), whose findings agree with ours. Over Adams's platinum catalyst, the dihydro-derivative and then more slowly *hexahydrogelsemine* were produced. On the other hand, gelsemine was recovered unchanged after attempted reduction with sodium and *cyclo*hexanol.

By boiling gelsemine with hydrochloric acid, Moore (*loc. cit.*) obtained *apo*gelsemine, $C_{20}H_{24}O_3N_2$ (≡ gelsemine + H_2O), the isomeric *isoapo*gelsemine, and the miscalled "chloro*isoapo*gelsemine," $C_{20}H_{23}O_2N_2Cl$, which yields the *isoapo*-base on hydrolysis. Here the elements of water or hydrogen chloride are probably added to the double bond which is reduced in the formation of dihydrogelsemine, for this base is unaffected by hydrochloric or hydriodic acid (cf. Chu and Chou, *loc. cit.*). Moreover gelsemine, with hydriodic acid and red phosphorus, afforded the *hydriodide*, $C_{20}H_{23}O_2N_2I,HI$, of an amorphous base. This is presumably "iodo*isoapo*gelsemine," because of its mode of formation and since the product of its hydrolysis yielded a methiodide agreeing in properties with *isoapo*gelsemine methiodide; by reduction with zinc and acetic acid "iodo*isoapo*gelsemine" gave dihydrogelsemine.

Gelsemine is a tertiary base, sharply monoacid in titration against methyl-red, of such strength * that the basic nitrogen atom can neither be attached to a benzene nucleus nor form part of an unreduced pyridine ring; hexahydrogelsemine also is a tertiary monoacid base. Gelsemine contains one *N*-methyl group (Marion, *Canadian J. Res.*, 1943, **21***B*, 247). The methiodide reverts to gelsemine on attempted Hofmann degradation (Moore, *loc. cit.*), and Emde reduction of dihydrogelsemine methiodide gave only an organo-mercury compound. With cyanogen bromide, gelsemine afforded in good yield comparable quantities of its *hydrobromide* and of a well-crystallised, feebly basic, bromine-free product of sharp and reproducible m. p. Imperfectly concordant analyses of separate preparations of the latter substance suggested that these were mixtures of derivatives containing one and two cyano-groups in the intact or at most demethylated gelsemine system.

The function of the oxygen atoms in gelsemine is not clear. Dihydrogelsemine contains one reactive hydrogen atom, and Moore (*loc. cit.*) describes an acetylgelsemine. We failed to prepare this derivative or to benzoylate gelsemine or hexahydrogelsemine under Schotten–Baumann conditions (cf. Göldner, *Ber. deut. Pharm. Ges.*, 1895, **5**, 330), and Chu and Chou (*loc. cit.*) could not prepare an acetyl or a benzoyl derivative of

* We are indebted to Dr. J. A. Mair, of this Department, for the following measurements: E.M.F. of system, quinhydrone electrode in 0·0354N-gelsemine hydrochloride–saturated calomel element, 147, 148, 150 mv. at 13°; whence pH = 5·41 and $K_b = 2{\cdot}3 \times 10^{-5}$.

dihydrogelsemine. Gelsemine and its reduction products are not phenolic, as indicated by their insolubility in alkali and failure to couple with diazobenzene-*p*-sulphonic acid; hexahydrogelsemine is not brominated in cold aqueous solution, and Chou and Chu find (*J. Amer. Chem. Soc.*, 1941, **63**, 827) that gelsemine reacts additively with bromine. The alkaloid contains no methoxyl group (Moore, *loc. cit.*), and di- and hexa-hydrogelsemine were unchanged by prolonged refluxing with hydriodic acid and red phosphorus. Not only could no oxime be prepared, but gelsemine and dihydrogelsemine resisted long boiling with the Grignard reagent. Finally, gelsemine was unaffected by aqueous baryta or alcoholic sodium hydroxide solution at 150°.

Experiments on the general decomposition of gelsemine were not enlightening. Oxidation with permanganate, boiling dilute nitric acid, or hydrogen peroxide–osmium tetroxide gave no characterisable product, nor did treatment of dihydrogelsemine with the first two reagents. With selenium at 230° gelsemine yielded a substance, not fully studied, in which degradation had not proceeded to a useful extent. At a higher temperature Marion (*loc. cit.*) obtained a little 2 : 3-dimethylindole; gelsemine gives a positive Ehrlich reaction with *p*-dimethylaminobenzaldehyde. By heating gelsemine with palladium at 180—275° in presence or absence of air, or by distilling it over zinc dust, only ill-defined, readily resinifiable products were obtained. The only isolable product after potash fusion was a picrate, m. p. 152°, identical with that isolated from *Gelsemium* tincture.

Sempervirine.—Three molecules of hydrogen were absorbed over palladium, and five in all over Adams's catalyst. In the former case, neither the product, which quickly resinified, nor any derivative could be crystallised; in the latter, the crystalline material first isolated already contained oxygen and rapidly absorbed more in the air. Reduction of sempervirine by Clemmensen's method, or at a lead cathode, gave no useful result. Surprisingly, the alkaloid was recovered as *hydriodide* after long boiling with hydriodic acid and red phosphorus.

Sempervirine afforded a quaternary *monomethiodide* from which no definable product could be obtained on degradation by aqueous alkali. With cyanogen bromide, sempervirine gave the crude *hydrobromide* along with amorphous materials. No useful results were obtained by oxidation of sempervirine with permanganate, nitric acid, chromic acid, or hydrogen peroxide–osmium tetroxide, by heating it with palladium in air or oxygen, or by potash fusion.

Gelsemicine.—The picrate, m. p. 203°, isolated from Merck's " Nebenhydrochloride," afforded a base which agreed with Chou's gelsemicine in m. p., optical rotation, and m. p. of hydrochloride; the analytical data conform well to the formula $C_{20}H_{24}O_4N_2$, having one hydrogen atom fewer than Chou's unconventional expression. Gelsemicine was not hydrogenated over palladium; it absorbed one molecule of hydrogen rapidly, and a further two more slowly, in acetic acid over Adams's catalyst. It is notable that each of the three *Gelsemium* bases contains two double bonds (or their equivalent) which are hydrogenated in this way with some reluctance. Gelsemicine has three active hydrogen atoms (Zerevitinov), but is insoluble in aqueous alkali; it rapidly darkens and resinifies in alkaline media. Schotten–Baumann benzoylation gave a *monobenzoyl* derivative which was non-basic and presumably substituted on the nitrogen atom. Gelsemicine was unaffected by carbonyl reagents. With methyl iodide it behaved as a secondary base, yielding a *methylgelsemicine hydriodide.*

Experimental.

Isolation of the Alkaloids.—(a) *From the powdered root.* The powder was shaken with four parts of rectified spirit for 15—20 hours, and the extract evaporated in a vacuum. After basification with ammonia, the alkaloids were extracted with chloroform and taken up, after evaporation, in 0·5% hydrochloric acid, leaving much tar. Sempervirine nitrate was then precipitated by adding to the solution of hydrochlorides 1/20 of its volume of saturated sodium nitrate solution. The bases in the filtrate were liberated by ammonia, extracted with chloroform, and the concentrated extract shaken with 2N-hydrochloric acid until no more base was extracted. This acid solution was then basified with ammonia and shaken thrice with ether (A) and thrice with chloroform (B). The residue from extract (A) was dissolved in acetone, leaving an amorphous solid (200 mg.), m. p. 324° (decomp.), which could not be crystallised and gave no crystalline derivatives; from the acetone solution gelsemine was obtained in quantity, but the final mother-liquors afforded no gelsemicine when submitted to Chou's procedure (*loc. cit.*). An alcoholic solution of the residue from extract (B) was saturated with hydrogen chloride, and light brown, amorphous hydrochlorides precipitated with ether. These were mainly soluble in chloroform; from separate portions of this solution were obtained amorphous picrates of indefinite m. p., a non-crystalline base which resinified in air, and a crystalline *methiodide*, colourless prisms from 90% alcohol, m. p. 296—297° (decomp.) (Found : C, 52·5, 52·6, 52·5; H, 5·5, 5·6, 5·5; N, 5·9; I, 26·6. $C_{20}H_{24}O_3N_2,CH_3I$ requires C, 52·3; H, 5·6; N, 5·8; I, 26·3%). It had $[\alpha]_D^{20°}$ + 3·9° (c = 1·022 in water); for *apo*gelsemine methiodide Moore records $[\alpha]_D$ + 12·4° (c = 1·335). Subsequently, the amorphous picrates just referred to were reconverted into the free bases, and these were treated in cold chloroform with excess of benzoyl chloride and sodium hydroxide solution; an ethereal solution of the non-basic portion soon deposited benzoylgelsemicine (mixed m. p.).

A further extraction of the root with boiling spirit afforded about half as much gelsemine and sempervirine as the cold extraction, and subsequent treatment with alcohol–concentrated hydrochloric acid (9 : 1) extracted no more alkaloid.

(b) *From concentrated* Gelsemium *tincture.* This was treated in the same way as the alcoholic extract of the powdered root. Again the gelsemine mother-liquors afforded no gelsemicine, but uncrystallisable bases which were converted into picrates. Of these, a *picrate* (100 mg.), insoluble in cold acetone, crystallised from aqueous alcohol in yellow microplates which turned bright red and melted at 185° (Found : C, 47·2; H, 5·1; N, 14·2. $C_{19}H_{36}O_2N_2,2C_6H_3O_7N_3$ requires C, 47·6; H, 5·4; N, 14·3%). The free base and its other derivatives were amorphous. The acetone-soluble fraction gave a yellow microcrystalline *picrate*, from aqueous alcohol, m. p. 152° (Found : C, 53·4; H, 4·7; N, 11·6. $C_{20}H_{24}O_4N_2,C_6H_3O_7N_3$ requires C, 53·3; H, 4·6; N, 12·0%). No homogeneous picrate could be isolated from the mother-liquors, but treatment of the liberated bases in chloroform with methyl iodide gave a colourless *methiodide*, m. p. 261° (decomp.) after crystallisation from alcohol–ether (Found : C, 50·0; H, 5·2; N, 6·5. $C_{18}H_{20}O_2N_2,CH_3I$ requires C, 50·2; H, 5·1; N, 6·2%).

The amorphous, chloroform-soluble hydrochlorides obtained as from the fraction (B), above, were converted into picrates and crystallised from aqueous alcohol, giving first 500 mg. of the salt, m. p. 152°, just described, and on further

crystallisation from water successively two additional fractions, m. p. 140° (Found : C, 49·9; H, 4·5%) and 118° (Found : C, 51·6; H, 4·3; N, 12·9. $C_{18}H_{20}O_4N_2,C_6H_3O_7N_3$ requires C, 51·7; H, 4·1; N, 12·6%).

(c) *From Merck's "Nebenhydrochloride."* Sempervirine was separated in the usual way as nitrate. The ethereal extracts which previously afforded gelsemine here gave none of that base, but on treatment with picric acid yielded *gelsemicine picrate*, yellow plates from methyl alcohol, m. p. 203° (Found : C, 53·5; H, 4·7; N, 11·8. $C_{20}H_{24}O_4N_2,C_6H_3O_7N_3$ requires C, 53·3; H, 4·6; N, 12·0%). Small quantities of the picrates of m. p.'s 152° and 118° were also isolated as previously described.

Gelsemine.—The acetone-free base had $[\alpha]_D^{20°}$ + 17·8° in chloroform (c = 2·026); Moore and Chou (*locc. cit.*) give +15·9° and +10°, respectively, in that solvent. An alcoholic solution of gelsemine gave a deep pink coloration with *p*-dimethylaminobenzaldehyde in hydrochloric acid. On rapid heating, gelsemine hydrochloride melts at 333° (decomp.); Moore gives "about 300°." The *hydrobromide*, prepared in and crystallised from slightly aqueous alcohol, formed prisms, m. p. 325° (decomp.) (Found : C, 59·7; H, 5·9. $C_{20}H_{22}O_2N_2$,HBr requires C, 59·6; H, 5·7%). The *methobromide*, prepared in ether, crystallised from alcohol in needles, m. p. 313—314° (Found : C, 60·4; H, 6·1. $C_{20}H_{22}O_2N_2,CH_3Br$ requires C, 60·4; H, 6·0%). The methiodide [m. p. variable, 286—301° (decomp.)] had $[\alpha]_D^{18°}$ + 6·0° (in water, c = 0·928); Moore gives +8·9°.

Reduction of Gelsemine.—Gelsemine (100 mg.) was freed from acetone at 120—140° and treated in boiling *cyclo*hexanol (10 c.c.) with sodium (0·3 g.). Most of the base was recovered and no other substance could be detected.

In aqueous alcohol over palladium-black the alkaloid absorbed 1 mol. of hydrogen in an hour, and reaction then ceased. The product crystallised from acetone in needles, m. p. 220—221° [Chou (*loc. cit.*) gives 224—225°] (Found : C, 74·1; H, 7·3; active H, 0·32. Calc. for $C_{20}H_{24}O_2N_2$; C, 74·1; H, 7·4; 1 active H, 0·31%). A solution of dihydrogelsemine in 25% nitric acid turns bright green on warming, and passes through dark green, black, and violet to pale pink. The hydrochloride crystallises from alcohol in needles, m. p., air-dried, 328° (decomp.) [Chou records 318—320° (decomp.)] (Found : C, 63·3; H, 7·4; N, 7·7; Cl, 9·4. Calc for $C_{20}H_{24}O_2N_2,HCl,H_2O$; C, 63·5; H, 7·2; N, 7·4; Cl, 9·1%). The methiodide was prepared in acetone and crystallised from alcohol–ether (Found : C, 54·1; H, 5·8; N, 6·0; I, 27·1. Calc. for $C_{20}H_{24}O_2N_2,CH_3I$; C, 54·1; H, 5·8; N, 6·0; I, 27·3%); attempted Emde reduction with sodium amalgam gave a brown, amorphous solid which was insoluble in all solvents except aqueous alkali, and appeared to be an organo-mercury compound. Dihydrogelsemine was recovered unchanged after 2 hours' boiling with excess of methylmagnesium iodide in ether, and after 21 hours' refluxing with hydriodic acid (d 1·7) and red phosphorus.

Over Adams's catalyst in dry acetic acid, gelsemine absorbed 1 mol. of hydrogen rapidly, and two more slowly (5 hours at 19°; absorption 3·07, 3·02 mols.); the intermediate product was the known dihydrogelsemine. *Hexahydrogelsemine* was liberated by adding sodium hydroxide to the filtered solution after concentration in a vacuum. It crystallises from acetone in needles, m. p. 170° (Found : C, 73·2; H, 8·7; N, 8·4. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·5; N, 8·5%), and unlike gelsemine and dihydrogelsemine gives no characteristic colour reaction with concentrated sulphuric acid and potassium dichromate. It is somewhat soluble in water, and partly precipitated from aqueous solution by addition of sodium hydroxide. The *methiodide*, prepared in cold acetone and crystallised from alcohol–ether, melted at 296° (Found : C, 53·4; H, 6·8; N, 5·9. $C_{20}H_{28}O_2N_2,CH_3I$ requires C, 53·6; H, 6·6; N, 6·0%). Hexahydrogelsemine was recovered unchanged after attempted Schotten–Baumann benzoylation, and after 18 hours' boiling with excess of hydriodic acid (d 1·7) and red phosphorus. Addition of bromine-water to an aqueous solution of hexahydrogelsemine gave an orange precipitate, m. p. 220°, evidently a perbromide, the alcoholic solution of which became colourless on boiling and subsequently afforded unchanged hexahydrogelsemine.

"*Iodo*isoapo*gelsemine.*"—Gelsemine (150 mg.) was refluxed with hydriodic acid (12 c.c.; d 1·7) for 30 hours. Neither the basic reaction product nor its methiodide could be crystallised; but a concentrated solution of the former in boiling alcohol, treated with hydriodic acid (0·5 c.c.; d 1·7), at once gave crystalline "*iodo*isoapo*gelsemine*" *hydriodide*, needles from aqueous alcohol, m. p. 298° (decomp.) (Found : C, 41·8; H, 4·0; N, 4·8. $C_{20}H_{23}O_2N_2I,HI$ requires C, 41·5; H, 4·2; N, 4·8%). The base was refluxed with aqueous-alcoholic potassium formate for 6 hours. The resulting base could not be crystallised, but its methiodide, prepared in ether–chloroform, crystallised from aqueous alcohol–ether in plates, m. p. 266° (decomp.), in agreement with Moore's description of *isoapo*gelsemine methiodide. "Iodo*isoapo*gelsemine" hydriodide (200 mg.) was reduced by boiling in acetic acid with zinc dust (1 g.) for several hours. The basic product, crystallised from acetone, was identical (mixed m. p.) with dihydrogelsemine; the methiodide melted at 301—302° (decomp.) (Found : C, 54·0; H, 5·6; N, 6·1%). "Iodo*isoapo*gelsemine" (400 mg.) was refluxed with diethylaniline (15 c.c.) for several hours. After addition of sodium carbonate and steam-distillation, the residue was extracted with ether and crystallised thrice from acetone (charcoal). Colourless prisms were obtained, m. p. 106—108° (Found : C, 72·1; H, 7·1; N, 8·6. Calc. for $C_{20}H_{22}O_2N_2$; C, 74·5; H, 6·8; N, 8·7%), agreeing with Moore's description of the isomeride of gelsemine formed in the same way from "chloro*isoapo*gelsemine." The carbon value is discrepant, but owing to the very small yield a further preparation was not undertaken.

Action of Cyanogen Bromide.—A slight excess of dry, freshly prepared cyanogen bromide was added to gelsemine (1 g.) in ether–benzene, and the mixture refluxed (protected from moisture) for 6 hours. The colourless precipitate, after crystallisation from alcohol, melted at 326° (decomp.); two samples had the approximate composition of gelsemine hydrobromide (Found : C, 59·6, 59·6; H, 5·9, 6·0; N, 7·5, 7·4%), and the free base, purified with some difficulty, was identical (mixed m. p.) with gelsemine. The ethereal filtrate from the crude hydrobromide was evaporated, and the residue crystallised from alcohol in lustrous plates or prisms (0·5 g.). In several experiments the product melted sharply at 216°, but the analytical data suggest that all samples were mixtures [Found : C, 70·8, 71·7, 71·8; H, 5·6, 5·5, 5·6; N, 12·3, 13·2, 13·9, 14·1. Calc. for $C_{20}H_{21}O_2N_2(CN)$: C, 72·6; H, 6·1; N, 12·1%]. In a micro-hydrogenation over palladium, the substance absorbed 2·00 mols., on the basis of the same formula; the product was a weak base extracted incompletely from ether by dilute hydrochloric acid. The product of m. p. 216° gave an amorphous hydrochloride with dry hydrogen chloride in ether, but was insoluble in the aqueous acid and did not combine with methyl iodide in boiling benzene. Boiled for 6 hours with alcoholic potash, it afforded an uncrystallisable product which in cold acetone yielded a methiodide, m. p. 297—298° (decomp.) after recrystallisation from aqueous alcohol–ether (Found : C, 53·1; H, 5·7; N, 6·7; I, 27·7. Calc. for $C_{20}H_{22}O_2N_2,CH_3I$: C, 54·3; H, 5·4; N, 6·0; I, 27·4%).

Function of the Oxygen Atoms.—In an attempt to repeat Moore's preparation of acetylgelsemine, the product could be crystallised only from acetone, giving needles which melted at 106°, solidified at 120°, and remelted at 176°; after further drying in air it melted at 178°, alone or mixed with gelsemine. The alkaloid was also recovered unchanged after 6 hours' boiling with acetic anhydride and sodium acetate. Gelsemine was unaffected by prolonged refluxing with hydroxylamine hydrochloride in pyridine, with hydroxylamine acetate in aqueous alcohol, or with ethereal *n*-butylmagnesium bromide.

To diagnose a possible lactam system, the base was heated with excess of 10% barium hydroxide solution at 150° for 5 hours. Most of the gelsemine was recovered by extraction with ether, and nothing could be isolated as benzoyl derivative after treatment of the alkaline layer with benzoyl chloride. Gelsemine was similarly recovered after 10 hours' heating at 150° with 6N-aqueous–alcoholic potassium hydroxide solution.

Action of Selenium.—Gelsemine (500 mg.) was heated with selenium (250 mg.) in nitrogen at 230° for 18 hours. From

the cooled melt ether removed a little material, probably impure gelsemine; subsequent extraction with chloroform gave in small yield an acetone-insoluble, amorphous base. This combined with methyl iodide in boiling alcohol–chloroform, giving a methiodide, m. p. 270° (decomp.) after crystallisation from aqueous alcohol–ether and drying at 120° (Found: C, 52·4, 52·7; H, 5·8, 5·5; N, 6·5, 7·1; I, 25·9. Calc. for $C_{20}H_{24}O_3N_2,CH_3I$: C, 52·3; H, 5·6; N, 5·8; I, 26·3%).

Potash Fusion.—Gelsemine (400 mg.) was heated in a heavily-silvered glass tube with potassium hydroxide (800 mg.) in a current of pure, dry air for 15 minutes at 300°. No volatile product was detected. On treatment with water and acid, the melt dissolved completely, and on basification gave an insoluble amorphous base which afforded the picrate, m. p. 152°, already isolated from *Gelsemium* tincture (Found: C, 53·3; H, 4·7%). A similar fusion at 400° gave the same result.

Sempervirine.—The picrate, prepared by adding alcoholic picric acid to sempervirine in chloroform, and crystallised from alcohol, melted at 268° (decomp.) (Found: C, 5·98; H, 3·9. Calc. for $C_{19}H_{16}N_2,C_6H_3O_7N_3$: C, 59·9; H, 3·8%). The *hydrobromide*, m. p. 325° (decomp.) (Found: C, 59·2; H, 5·7; N, 7·6. $C_{19}H_{16}N_2,HBr,2H_2O$ requires C, 58·6; H, 5·4; N, 7·2%), and the *hydriodide*, m. p. 333—335° (decomp.) (Found: C, 57·1; H, 4·1. $C_{19}H_{16}N_2,HI$ requires C, 57·0; H, 4·3%), crystallised from alcohol in minute yellow needles. *Sempervirine methiodide*, prepared in chloroform as buff-coloured plates and crystallised from aqueous alcohol, melted at 348° (decomp.) (Found: C, 57·9; H, 4·9; N, 6·8. $C_{19}H_{16}N_2,CH_3I$ requires C, 58·0; H, 4·6; N, 6·8%). Heated for 4 hours at 195° with 20% potassium hydroxide solution, it yielded an amorphous basic solid which gave no crystalline derivatives.

Reduction.—In alcohol over palladium-black, sempervirine absorbed 2·8 mols. of hydrogen, yielding a colourless resin which darkened in air and gave no crystallisable derivatives. Over Adams's catalyst in acetic acid 3 mols. of hydrogen were absorbed in 30 minutes, and action ceased after 5 hours with absorption of 4·8, 5·0 mols. in all. The *decahydrosempervirine*, at first colourless, was liberated by sodium hydroxide and extracted with chloroform, the solution was concentrated in a vacuum, and the deep yellow residue crystallised from acetone. The pale yellow needles so obtained melted at 205° and contained oxygen (Found: C, 77·9; H, 8·1; N, 9·6. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·1; N, 9·5%); they slowly turned red and the oxygen content increased. Sempervirine was boiled for 30 hours with excess of hydriodic acid (*d* 1·7) and red phosphorus. A little solid separated on dilution with water and more was produced on partly neutralising the filtrate with sodium carbonate. It had the properties of sempervirine hydriodide (Found: C, 57·1; H, 4·1%), and afforded sempervirine (mixed m. p.) with sodium hydroxide.

Action of Cyanogen Bromide.—Sempervirine was warmed for 6 hours with excess of the reagent in ether–chloroform, and the dark brown precipitate collected; nothing crystalline could be prepared from the filtrate. The precipitate, crystallised several times from alcohol, formed bright yellow needles, m. p. 325° (decomp.), evidently impure sempervirine hydrobromide (Found: C, 61·0, 60·9; H, 5·3, 5·4; N, 8·3, 8·1%), since the liberated base yielded sempervirine picrate, m. p. and mixed m. p. 267° (decomp.) (Found: C, 59·2; H, 4·0; N, 13·8. Calc. for $C_{19}H_{16}N_2,C_6H_3O_7N_3$: C, 59·9; H, 3·8; N, 14·0%).

Gelsemicine.—The picrate was dissolved in 10% hydrochloric acid, the picric acid extracted with benzene, and the base freed by ammonia and extracted with ether. It crystallised from acetone in clusters of prisms, m. p. 170°, $[\alpha]_D^{20}$ −141° in chloroform (c = 1·10). In micro-hydrogenations, 3·00 mols of hydrogen were absorbed over Adams's catalyst in acetic acid, but none over palladium; micro-Zerevitinov (Weiler and Strauss) showed 2·81 active hydrogen atoms. The hydrochloride formed warty rosettes of micro-prisms, m. p. 140—142°. *Benzoylgelsemicine*, prepared by shaking the alkaloid in cold chloroform with benzoyl chloride and sodium hydroxide solution, crystallised from alcohol in colourless needles, m. p. 232°. It was hydrolysed cleanly and almost completely by 4 hours' boiling with 5N-aqueous-alcoholic sulphuric acid. Gelsemicine was recovered unaltered after boiling for 4 hours with hydroxylamine hydrochloride in pyridine, and no 2 : 4-dinitrophenylhydrazone could be prepared. A solution of gelsemicine and methyl iodide in chloroform slowly deposited a solid which crystallised from alcohol in glistening plates, m. p. 227°, evidently a ***methylgelsemicine hydriodide***, since they yielded on treatment with ammonia an oily base giving an uncrystallisable picrate. Analytical data on gelsemicine derivatives are tabulated below, with calculated values based on the formulæ (*a*) $C_{20}H_{24}O_4N_2$ and (*b*) $C_{20}H_{26}O_4N_2$ for the alkaloid.

	Gelsemicine.		Gelsemicine monopicrate.			Benzoyl-gelsemicine.			Methylgelsemicine hydriodide.		
	C.	H.	C.	H.	N.	C.	H.	N.	C.	H.	N.
Found, %	67·3	6·9	53·5	4·7	11·8	70·4	6·3	6·1	51·0	5·6	5·4
(*a*) Calc., %	67·4	6·7	53·3	4·6	12·0	70·4	6·1	6·1	50·6	5·4	5·6
(*b*) Calc., %	67·0	7·3	53·1	4·9	11·9	70·1	6·5	6·1	50·4	5·8	5·6

The authors' thanks are due to the Carnegie Trustees for a Scholarship (S. F. M.), to the Scottish Education Department for a State Research Grant (W. G. C. F.), to the Chemical Society for a grant from the Research Fund, and to Mr. J. M. L. Cameron for the micro-analyses.

UNIVERSITY OF GLASGOW. [*Received, April 20th*, 1945.]