Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.21; OCH_3, 40.14 (three methoxyls); C-CH_3,[22] 6.45; CH_3CO, 18.54. Found: C, 46.33; H, 5.99; OCH_3, 39.34; C-CH_3, 6.57; CH_3CO, 18.82.

Infrared spectrum in chloroform: 2.86 (weak; partly bonded OH), 5.69^s, 6.06^w, 6.95^s, 7.29^s, 7.65^s, 7.93^s, 9.02^s, 9.25^s, 9.78^w, 10.30^w μ.

Compound $C_6H_8O_5$ (XIII).—In a larger scale run, using 6.6 g. of diacetoxymaleic anhydride, diazomethane in large excess was immediately used on the freshly prepared solution of the anhydride in a mixture of methanol–ether. The oily product, obtained after evaporation of the solvents, distilled *in vacuo* over a wide range. A fraction of colorless distillate (bands at 5.64 and 5.75 μ) collected at 69° (0.15 mm.), was analyzed.

Anal. Calcd. for $C_6H_8O_5$: C, 45.00; H, 5.04; OCH_3, mol. wt., 160.2. Found: C, 44.89; H, 4.85; OCH_3, 17.64; mol. wt., 176 (calcd. from methoxyl value).

Dibenzoyloxymaleic Anhydride (XI).—Following Fenton's procedure[6] the compound was prepared in 40% yield, crystallizing from cyclohexane or benzene, silky white needles, m.p. 168–170° (reported 167–168°).

Infrared spectrum in chloroform: no OH, no aliphatic CH, weak duplet at 5.30^w, 5.37^w μ; very strong duplet at 5.55^s, 5.64^s μ; shoulder at 5.84^w, 5.90^w; 6.22^m, 6.87^m, 7.40^m, 7.97^s, 8.50^s, 8.83^s, 9.11^s, 9.63^m, 9.95^s, 10.26^s, 10.72^m μ.

Dimethyl Methoxybenzoyloxymaleate (Presumably XII).—A suspension of dibenzoyloxymaleic anhydride in a small volume of methanol was warmed slightly to effect solution. After cooling an excess of diazomethane in ether solution was added and the reaction mixture allowed to stand overnight. The oily residue obtained after evaporation of the solvents, had a peppermint odor; it was distilled *in vacuo*. A fraction of distillate, b.p. 160° (0.1 mm.), was analyzed.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.43; H, 4.67.

Infrared spectrum in chloroform: 2.78^w, 5.70–5.80^{vs}, 6.23^s, 6.30^m, 6.70^m, 6.88^s, 6.94^s, 9.03^s, 9.37^s, 9.77^s μ.

Dimethyl Diketosuccinate (XIV).—Prepared according to the directions of Anschütz[23] the yellow oily compound was obtained by vacuum distillation, b.p. 102–104° (14 mm.) (reported 102–110° (12–13 mm.)[9]).

The infrared spectrum of several different fractions measured in chloroform still showed OH at 2.85 μ and one single ester CO at 5.70 μ. The very hygroscopic diketosuccinate apparently became hydrated in the process of transfer and solution.

Dimethyl α-Keto-α'-hydroperoxysuccinate (XV).—A solution of 360 mg. (2 mm.) of dimethyl diketosuccinate (XIV) in 1 ml. of dry ether was treated with 0.4 ml. of 4.55 *M* hydrogen peroxide (1.8 mm.) in absolute ether. The initially *yellow* solution became *colorless* immediately after addition of the hydrogen peroxide. Evaporation *in vacuo* yielded a colorless viscous residue, giving a strong peroxide test (iodide–starch paper, lead tetraacetate.)[24] On standing this compound solidified to a new compound[25] which no longer gave peroxide reactions.

Infrared spectrum in Nujol: broad and strong band at 2.95 (bonded O–OH and/or OH); very broad C=O at 5.95–6.00 μ. The viscous material was difficult to mull and gave a poorly resolved spectrum.

(22) The C-methyl determination was carried out, since C-methylation of a related (quinoid) system by diazomethane has been observed by L. F. Fieser and J. Hartwell, THIS JOURNAL, **57**, 1479 (1935). The finding of only one C-methyl group (from the acetoxy group) eliminates the possibility of C-methylation.

(23) R. Anschütz and O. Parlato, *Ber.*, **25**, 1975 (1892).

(24) R. Criegee, H. Pilz and M. Flygare, *ibid.*, **72**, 1799 (1939).

(25) *Cf.* J. E. Leffler, *J. Org. Chem.*, **16**, 1785 (1951).

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Aspidospermine. II

BY BERNHARD WITKOP AND JAMES B. PATRICK

RECEIVED APRIL 3, 1954

The reactions and infrared data of the mono-(VI) and diacetyl (VIII) derivatives of aspidosine (VII) support the same 7-position for the oxygen function in aspidospermine as in vomicine and strychnospermine. The reactions of deacetylaspidospermine (II) with benzoyl chloride, methyl and ethyl iodide are clarified (Chart I). Hypothetical working structures (XVI, XVII) are discussed for aspidospermine.

In continuation of our studies on aspidospermine (I), a new type of dihydroindole alkaloid,[1] it was necessary to establish the position of the methoxy group in the benzene ring. On the basis of spectral comparison Openshaw and Smith[2] favored the position *meta* to N^a (harmine position). We have now found new evidence which allocates the 7-position (*peri* to the (acet)imino group) to the methoxy group (Chart I).

The aluminum chloride-catalyzed ether cleavage of aspidospermine led to phenolic demethylaspidospermine (VI, N-acetylaspidosine) also obtainable from aspidosine (VII) by acetylation or from N,O-diacetylaspidosine (VIII) by treatment with acid or base. The ultraviolet spectrum of demethylaspidospermine is closely related to that of another N-acetyl-*peri*-hydroxydihydroindole, *viz.*, vomicine (Chart I, ref. *d*). Like vomicine, the analogous compound VI shows no band in the OH or NH region as a consequence of strong hydrogen bonding of the cryptophenolic hydroxyl. The same effect is operative in shifting the carbonyl band of the amide group to 6.12 μ (6.12 μ in vomicine) compared with 6.01 μ in the non-bonded diacetyl compound VIII.[3] The acetylation of aspidosine and the failure to obtain O-acetylaspidosine from diacetylaspidosine are reactions which have been encountered similarly in the homologous system, 8-hydroxy-1,2,3,4-tetrahydroquinoline.[4] Table I shows that in a tricyclic system, such as vomicine, the phenolic hydroxyl group is more strongly hydrogen-bonded than in bicyclic or monocyclic systems.

(1) B. Witkop, THIS JOURNAL, **70**, 3712 (1948). ADDED IN PROOF.—A referee directed our attention to an abstract of a recent paper by H. T. Openshaw, G. F. Smith and J. R. Chalmers, presented at the XIIIth International Congress of Pure and Applied Chemistry, Stockholm and Uppsala, 1953, Abstracts p. 223, in which these authors arrive at similar conclusions with regard to the position of the methoxy group on the basis of comparison with the ultraviolet spectra of suitable model compounds.

(2) H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948).

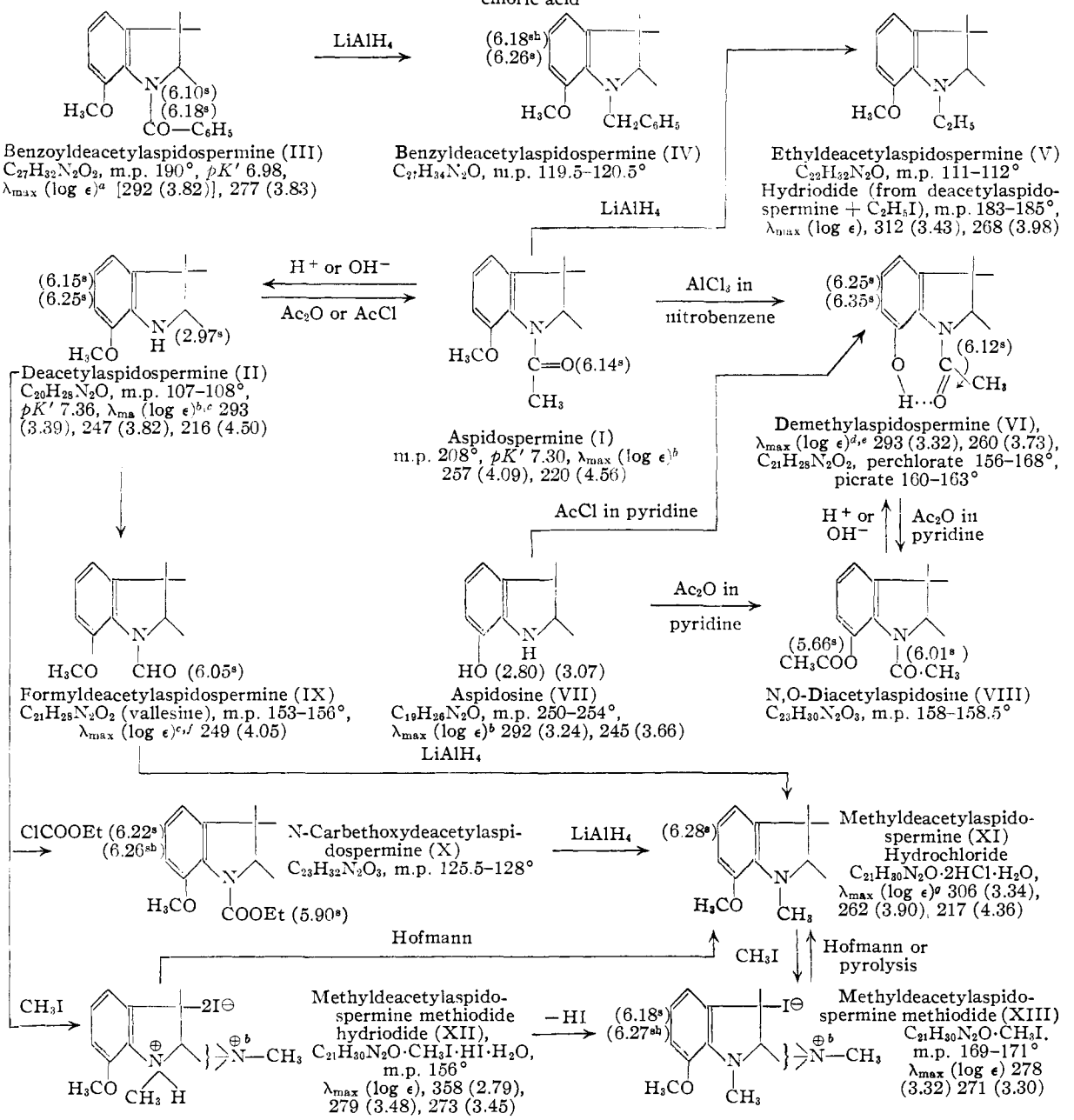
(3) The CO amide band in the diacetyl derivative of diaboline, a dihydroindole alkaloid, is at 6.02 μ (F. E. Bader, E. Schlittler and H. Schwarz, *Helv. Chim. Acta*, **36**, 1257 (1953)), the CO of O-acetyl at 5.73 μ (unconjugated ester, *cf.* J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951)); the position of this ester band does not support a cryptophenolic hydroxyl. Diacetylyohimbine shows bands at 5.76 (strong narrow band, no separate band for the carbomethoxy group) and 5.90 (CO of N-acetylindole).

(4) C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **66**, 1166 (1944); *cf.* A. Ek and B. Witkop, *ibid.*, **76**, 5579 (1954).

CHART I

CORRELATION OF DEGRADATION AND TRANSFORMATION PRODUCTS DERIVED FROM ASPIDOSPERMINE

The pK' values were determined by alkali titration of the bases in 50% ethanol containing a known excess of hydrochloric acid



[a] The hydrochloride (m.p. 205°, Schlittler's compound A) shows λ_{max} (log ϵ) [289–296 (3.71)]; 276 (3.73). [b] *Cf.* H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948). There are two shoulders in aspidospermine, 290 (3.48) and 280 (3.56) which appear as distinct maxima in strychnospermine, λ_{max} (log ϵ) 294 (3.66), 252 (3.93), and in spermostrychnine, 281 (3.67), 252 (4.33); *cf.* ref. 11. [c] *Cf.* E. Schlittler and M. Rottenberg, *Helv. Chim. Acta*, **31**, 452 (1948). Compare also deacetylstrychnospermine, 301 (3.55), 248 (3.57), and deacetylspermostrychnine, 298 (3.54), 245 (3.92); see ref. 11. [d] *Cf.* vomicine, λ_{max} (log ϵ) 291 (3.62), 266 (3.95) [R. Huisgen, H. Eder, L. Blazejewicz and E. Mergenthaler, *Ann.*, **573**, 138 (1951)]. [e] The analogous benzoyl compound (oily) showed λ_{max} (log ϵ) 295 (3.56), 274 (3.72). [f] Compare: N-formyl-*p*-anisidine λ_{max} (log ϵ) 252 (4.15) in ethanol; N-formyl-*o*-anisidine [290 (3.66)], 284 (3.71), [256 (3.91)] 246 (4.07) in ethanol; *o*-anisidine 287 (3.76), 237 (4.18) in ethanol; *p*-anisidine 303 (3.34), 236 (3.96) in ethanol. [g] The free (oily) base shows (in ethanol) λ_{max} (log ϵ) 305 (3.40), 266 (3.87), 220 (4.42). The hydrochloride in 6 *N* aqueous hydrochloric acid has λ_{max} (log ϵ) 278 (2.86), 272 (2.86), 218 (3.47). Compare: *o*-anisidine hydrochloride [287 (2.99)], 277 (3.29), 271 (3.26), 237 (3.39); N-methyl-*o*-anisidine hydrochloride: 286–293 (2.99), 277 (3.26), 271 (3.25), 247 (3.50); *p*-anisidine hydrochloride: 304 (2.29), 282 (3.14), 276 (3.20), 224 (3.91).

The report[5] that the benzoylation of deformylvallesine (identical with II, deacetylaspidospermine) yielded, besides the expected benzoyldeacetylaspidospermine (III), a neutral compound ("Substanz

(5) E. Schlittler and M. Rottenberg, *Helv. Chim. Acta*, **31**, 446 (1948).

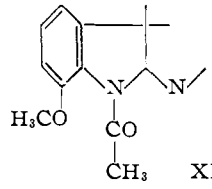
TABLE I

DEGREE OF CHELATION IN MONO-, DI- AND TRICYCLIC STRUCTURES CONTAINING AN *o*-ACYLAMINOPHENOL ARRANGEMENT

Compound	Ferric chloride test	Alkali	Acetylation
o-Acetaminophenol	Green[a]	Soluble	Easy
Demethylaspidospermine (VI)	Green	Soluble	Difficult
Demethylstrychnospermine[b]	Not reptd.	Soluble	Not obsd.
N-Benzoyl-1,2,3,4-tetrahydro-8-quinolinol[c]	Green	Soluble	Reported
Vomicine	Negative[d]	Insoluble	Difficult[e]

[a] E. Bamberger, *Ber.*, **36**, 2050 (1903). [b] See ref. 11. The use of water in working up the product resulting from the reaction of acetic anhydride on demethyldeacetylstrychnospermine could well have hydrolyzed an initial N,O-diacetyl compound (*cf.* preparation of VIII). [c] See ref. 4. [d] H. Wieland and F. Calvet, *Ann.*, **491**, 117 (1931). [e] H. Wieland and M. Thiel, *ibid.*, **550**, 287 (1942).

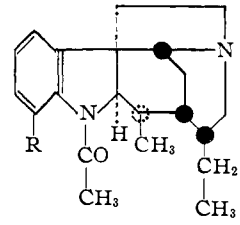
A''), initially seemed to point to ring cleavage on acylation (Bamberger–Berlé cleavage) and to an eserine-like arrangement XIV of the two nitrogens.[6] However, we found that the "neutral com-



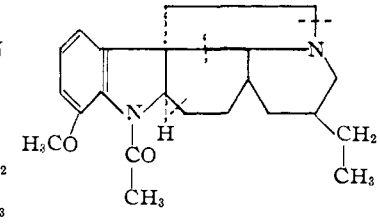
XIV

pound" or "dihydrate" was in reality the chloroform-soluble *hydrochloride* of benzoyldeacetylaspidospermine (III) convertible to the latter by base and yielding the same benzyldeacetylaspidospermine (IV) on reduction with lithium aluminum hydride as III itself. Reaction of II with ethyl chlorocarbonate gave N-carbethoxydeacetylaspidospermine (X) with no sign of cleavage of the Tiffeneau type.[7]

We failed to find any evidence in support of the assumption of a relationship of N^a to N^b as expressed in XIV.[8] The increase in basicity observed in the conversion of aspidospermine (I, pK' 7.30) to deacetylaspidospermine (II, pK' 7.36) is too small to substantiate such an assumption, nor is such a structure borne out by the somewhat involved reactions of II and its N^a-methyl derivative (XI) with methyl and ethyl iodide (summarized in Table I). The so-called "deacetylaspidospermine bismethiodide"[9] actually is N^a-methyldeacetylaspidospermine N^b-methiodide hydriodide (XII), yielding with base the same methiodide (XIII) as is obtained in the reaction of XI with methyl iodide. The ultraviolet data given for various ammonium bases (Chart I) are only of limited help in the location of the charge at N^a or N^b, respectively. Ethyl iodide alkylates N^b (II with EtI → V·HI) but fails to quaternize N^b probably because of steric hindrance.



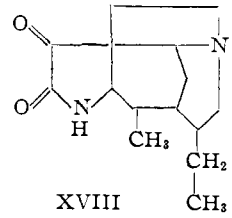
XV, R = H; XVI, R = OCH_3



XVII

As a working hypothesis for aspidospermine one might consider a structure such as XVI which would be the unknown dihydrodeoxystrychnospermine.[10,11] The methoxy free compound XV has been obtained from spermostrychnine, as well as from strychnine *via* sodium borohydride reduction of the Wieland–Gumlich aldehyde.[11] The hypothetical structure XVII would provide an easier explanation for the cleavage, on dehydrogenation with zinc dust, yielding 3,5-diethylpyridine and (presumably) 3-ethylindole (dotted lines) and for the fact that deacetylaspidospermine (II) in the Kuhn–Roth determination indicates *one* C-methyl group,[5] whereas dihydrodeoxyspermostrychnine contains *three* C-methyl groups,[11] as formula XVI would require. However, XVII is difficult to reconcile with Woodward's well-accepted biogenetic scheme.[12]

We are now exploring the suitability of aspidospermine N^b-oxide, prepared with peracetic acid rather than by ozonization,[1] as well as of apoaspidospermine ($C_{14}H_{22(24)}N_2O_2$, m.p. 193°),[9] possibly related to the unknown apodihydrodeoxyspermostrychnine (XVIII), for further degradation.



XVIII

Experimental[13]

Attempted Bamberger Cleavage of Deacetylaspidospermine (II). A. With Acetyl Chloride.—A solution of 500 mg. of deacetylaspidospermine in 16 cc. of benzene was treated with 0.91 cc. of acetyl chloride and set aside for 24 hours. The clear benzene solution was extracted with 30 cc. of 2 *N* alkali and then with 30 cc. of 2 *N* hydrochloric acid. On standing, the alkaline extract deposited crystals which, after filtration, washing and vacuum drying over phosphorus pentoxide, amounted to 90 mg. of aspidospermine, m.p. 206–209°. The acid extract was made basic with concentrated alkali solution and filtered. The precipitate, after drying *in vacuo* over phosphorus pentoxide, amounted to 465 mg. of aspidospermine (I), m.p. 205.5–208.5°, identified by mixed melting point and infrared spectrum.

(6) Benzoyl chloride cleaves eserine to the N^b-benzoyleserethole-methine according to M. and M. Polonovski, *Bull. soc. chim.*, [4] **35**, 1492 (1924).

(7) *Cf.* cleavage of boldine, E. Schlittler, *Ber.*, **66**, 988 (1933).

(8) The influence of the acetyl at N^a on the ease of quaternization of N^b—aspidospermine does not react with methyl iodide under conditions which easily lead from II to XII—does not necessarily support XIV, since vomicine in which N^a and N^b are separated, is very difficult to quaternize in contrast to vomicidine derivatives (H. Wieland and O. Müller, *Ann.*, **545**, 59 (1940)).

(9) A. J. Ewins, *J. Chem. Soc.*, **105**, 2738 (1914).

(10) F. A. L. Anet, G. K. Hughes and E. Ritchie, *Nature*, **166**, 476 (1950).

(11) F. A. L. Anet, "The Chemistry of Some Alkaloids of the Indole Group," Thesis, Oxford, 1952.

(12) R. B. Woodward, *Nature*, **162**, 155 (1948).

(13) All melting points are corrected (Kofler hot-stage). The analyses were performed by Dr. W. C. Alford and his associates, Analytical Service Laboratory of the National Institutes of Health.

B. With Benzoyl Chloride. Benzoyldeacetylaspidospermine Hydrochloride (III, Schlittler's Compound A) by Schotten–Baumann.—Five hundred milligrams of deacetylaspidospermine in 3 cc. of chloroform was benzoylated with 0.2 cc. of benzoyl chloride and excess of 2 *N* potassium hydroxide, according to the Schotten–Baumann technique. The chloroform solution was then washed with water, *2 N hydrochloric acid*, water, and saturated sodium chloride solution. The chloroform solution was then shaken with anhydrous magnesium sulfate, filtered and concentrated, after which dilution of the remaining oil with two volumes of carbon tetrachloride and scratching caused formation of a copious white crystalline precipitate; yield 661 mg. (91.3%), m.p. 191–201°. After one recrystallization from ethyl acetate–methanol, the crystals melted at 197–260°. A second crystallization from chloroform–carbon tetrachloride gave crystals, m.p. 184–189°. A third crystallization from ethyl acetate–methanol furnished two different types of crystals: A, large prisms, m.p. 184–196°, and B, fine needles, m.p. 194–203.5°. A, on recrystallization from ethyl acetate–methanol, gave crystals, m.p. 197°, resolidifying and melting a second time between 235 and 261°. B, on recrystallization from ethyl acetate–methanol, showed m.p. 194.5–197° and no depression on admixture with "Compound A" (m.p. 203–205°) prepared by Schlittler's original method, and gave the following analytical figures.

Anal. Calcd. for $C_{26}H_{30}N_2O_2 \cdot HCl \cdot 1H_2O$: C, 68.20; H, 7.28; Cl, 7.75. Found: C, 67.84; H, 7.41; Cl, 7.35 (ionic chlorine), 7.41 (total chlorine).

C. With Chlorocarbonate: N-Carbethoxydeacetylaspidospermine (X). Method I.—One hundred milligrams of deacetylaspidospermine in 3 cc. of ether, containing suspended potassium carbonate, was treated with ten drops of ethyl chlorocarbonate. A creamy precipitate formed almost immediately. After two days the mixture was treated with two volumes of 2 *N* potassium hydroxide and extracted with ether. The ether solution was extracted with 2 *N* hydrochloric acid; the residual ether solution left no residue. The aqueous acid solution was made basic with 2 *N* potassium hydroxide and extracted with ether. After drying the ether extract with magnesium sulfate, filtration, and evaporation, there remained 105 mg. of an olive-colored oil, which was dissolved in pentane and decolorized with diatomaceous earth. Slow crystallization from pentane yielded crystals which were dissolved in ether and treated with charcoal. A second recrystallization from pentane furnished rhombic colorless crystals, m.p. 125.5–128° (clear colorless melt).

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.83; H, 8.46; N, 7.24.

Method II.—Deacetylaspidospermine (600 mg.) in 15 cc. of benzene was treated with 1 cc. of ethyl chlorocarbonate and the mixture set aside. No heat effect was noted. After twelve days the reaction mixture was filtered and evaporated. The residue was extracted with ether (which dissolved only a negligible amount), taken up in water, and the solution filtered, made basic with 2 *N* potassium hydroxide, and extracted with ether. The extract was dried over magnesium sulfate, filtered and evaporated to leave 654 mg. (88.5%) of a colorless sirup which crystallized on standing. Recrystallization from hexane left 440 mg. of large colorless, birefringent prisms, m.p. 127–129°, undepressed on admixture with material obtained by method I.

Ethyldeacetylaspidospermine (V). A. By Reduction of Aspidospermine with $LiAlH_4$.—Five hundred milligrams of aspidospermine was added slowly to a suspension of 500 mg. of lithium aluminum hydride in 10 cc. of tetrahydrofuran, with ice cooling. There was no observable reaction. The mixture was then refluxed for one hour, cooled, decomposed with ice and extracted with ether. After drying over magnesium sulfate and filtration, the ether extract was evaporated to leave a light yellow oil which was freed of traces of tetrahydrofuran by vacuum degassing. The remaining oil (388 mg.) resisted crystallization. It was converted to its hydrochloride by hydrogen chloride in ether, and the hydrochloride was recrystallized, with difficulty, from ethyl acetate–ethanol; colorless crystals, m.p. 173–179°. The free base was then recovered by solution of the hydrochloride in water, treatment with 2 *N* alkali and ether extraction. After drying over magnesium sulfate, filtration and evaporation, the ether extract left a colorless oil which readily crystallized on scratching; colorless needles, m.p. 111–112°.

Anal. Calcd. for $C_{22}H_{32}N_2O \cdot {}^1/_4H_2O$: C, 76.58; H, 9.48; N, 8.12. Found: C, 76.26; H, 8.99; N, 8.45.

The catalytic hydrogenation of ethyldeacetylaspidospermine in 2 *N* sulfuric acid in the presence of an excess of platinum oxide led to the slow uptake of close to one mole of hydrogen. The reduction was stopped at this point. The acetylation of the ether-soluble reduction product in pyridine with acetic anhydride yielded aspidospermine (mixed m.p., infrared spectrum). We have no explanation yet for this apparent loss of an N-ethyl group in the process of reduction.

Pharmacological Activity.[14]—The compound produced immediate as well as gradual drop in blood pressure at 0.7 mg./kg. (anesthetized dog); fatal dose >17.5 mg./kg. Aspidospermine in similar doses causes a slight rise in blood pressure and then a marked fall; higher doses (19.2 mg./kg.) produce marked convulsions; 31.96 mg./kg. is the fatal dose.

B. By the Reaction of Deacetylaspidospermine (II) with Ethyl Iodide.—A solution of deacetylaspidospermine in excess ethyl iodide was left at room temperature for two days. After evaporation of the ethyl iodide the viscous yellow residue was dissolved in a little warm acetone. On standing there appeared glass-hard, polyhedric, colorless crystals which, after several washings with acetone, showed m.p. 183–185° (colorless melt).

Anal. Calcd. for $C_{22}H_{32}N_2O \cdot HI \cdot {}^1/_2H_2O$: C, 56.57; H, 7.33; N, 5.99; I, 27.17. Found: C, 56.67; H, 7.23; N, 6.05; I, 25.57 (total iodine).

The addition of alkali or ammonia to a solution of the hydriodide in water gave a colorless precipitate of a tertiary base extractable with ether, identical (infrared spectrum) with the compound V obtained by method A.

Infrared spectrum in chloroform: no bands in the NH or OH region; 6.29^s, 6.74^s, 6.87^s, 7.26^s, 7.38^w, 7.51^s, 7.57^w, 7.70^w, 7.82^s, 7.94^s, 8.52^s, 8.70^w, 8.86^{sh}, 8.98^m, 9.15^m, 9.28^m, 9.51^m, 9.70^m, 9.63^{sh}, 10.09^w, 10.42^w, 11.00^m, 11.10^w, 11.21^m.

Benzyldeacetylaspidospermine (IV).—Benzoyldeacetylaspidospermine (m.p. 190–192.5°, 100 mg.) was added to a suspension of 50 mg. of lithium aluminum hydride in 15 cc. of ether. After refluxing for an hour, the cooled solution was decomposed with saturated sodium potassium tartrate solution. The ether layer was dried over magnesium sulfate, filtered and evaporated to leave 96 mg. of a colorless oil. The oil was crystallized from pentane to yield birefringent neeedles, m.p. 119.5–120.5° (clear colorless melt).

Anal. Calcd. for $C_{27}H_{34}N_2O$: C, 80.55; H, 8.51; N, 6.96. Found: C, 80.47; H, 8.50; N, 6.96.

The same compound was obtained when 25 mg. of the above-mentioned benzoyldeacetylaspidospermine *hydrochloride* was reduced with 25 mg. of lithium aluminum hydride: birefringent needles, m.p. 119–120° after one crystallization from pentane.

Methyldeacetylaspidospermine (XI). A. From Formyldeacetylaspidospermine (IX).—Formyldeacetylaspidospermine (3.90 g., m.p. 152–154°) was reduced with 500 mg. of lithium aluminum hydride in 50 cc. of ether. After refluxing for 30 minutes the mixture was decomposed with ice and extracted with ether. The ether extract was dried over magnesium sulfate, filtered and evaporated to leave a clear-yellow sirup which, after 36 hours in a vacuum desiccator, weighed 3.71 g. The substance resisted all attempts at crystallization. The hydrochloride, formed in ether, could not be recrystallized and was submitted for analysis after drying in a vacuum desiccator.

Anal. Calcd. for $C_{21}H_{30}N_2O \cdot 2HCl \cdot H_2O$: C, 60.44; H, 8.21; N, 6.71. Found: C, 61.03; H, 8.16; N, 6.45.

B. From N-Carbethoxydeacetylaspidospermine (X).—Lithium aluminum hydride reduction of 100 mg. of N-carbethoxydeacetylaspidospermine (X, m.p. 128°) in ether in the usual fashion gave amorphous N-methyldeacetylaspidospermine, in good yield. The infrared spectra of the free bases prepared by methods A and B were identical. A small amount of the free base was converted into the perchlorate, which after recrystallization from ethanol showed m.p. 192–204°.

(14) Tested by Dr. N. C. Moran in Dr. A. P. Richardson's Department of Pharmacology, Emory University, Georgia.

Methiodide (XIII). Method I. By the Reaction of Methyldeacetylaspidospermine (XI) with Methyl Iodide.—Two grams of methyl deacetylaspidospermine was refluxed 2 hours with 20 cc. of methanol and 1.8 cc. of methyl iodide. After standing overnight the solution was evaporated to leave a crystalline mass which was washed with acetone; yield 1.587 g. of fairly pure methiodide. This was crystallized three times from methyl ethyl ketone–ethyl acetate to yield colorless birefringent flat plates, m.p. 169.5–171°. It was necessary to dry the compound 9 hours at 100° in high vacuum to obtain consistent analytical results.

Anal. Calcd. for $C_{21}H_{30}N_2O\cdot CH_3I$: C, 56.41; H, 7.10; N, 5.98. Found: C, 56.67; H, 7.27; N, 5.91.

The dipicrate, prepared in methanol, crystallized in fine yellow needles, m.p. 220–222°.

Anal. Calcd. for $C_{22}H_{33}N_2O\cdot 2C_6H_3N_3O_7$: N, 13.88. Found: N, 13.61.

From acetone the dipicrate crystallized as an *acetone adduct* in rhombic yellow plates, frothing at 105°, resolidifying at 130°, m.p. 225–229°.

Anal. Calcd. for $C_{22}H_{33}N_2O\cdot 2C_6H_3N_3O_7\cdot CH_3COCH_3$: C, 51.86; H, 5.3. Found: C, 51.82; H, 5.09.

Method II. *Via* Methyldeacetylaspidospermine Methiodide Hydriodide (XII, the former "Deacetylaspidospermine Bismethiodide").—Deacetylaspidospermine (1.766 g.) was dissolved in 4 cc. of methyl iodide, with ice cooling and the solution was set aside for 4 days. The crystals (3.3 g.) were then collected and recrystallized from methanol. A second crystallization from ethanol yielded birefringent prisms of the hydriodide of methyldeacetylaspidospermine methiodide, m.p. 156–158° (bubbly melt).

Anal. Calcd. for $C_{21}H_{30}N_2O\cdot CH_3I\cdot HI\cdot H_2O$: C, 43.01; H, 5.91; N, 4.56; I, 42.57. Found: C, 42.94; H, 6.05; N, 4.59; I, 42.43 (total iodine; ionic iodine, 26.2, using the method of Volhard); the fact that not all ionizable iodine is found by titration is unexpected and may need further investigation.

The infrared spectrum (mulled in Nujol) showed the following major bands: 2.95^w, 3.03^w, 3.70^m (quaternary N), 6.17^s, 6.26^m, 6.72^s, 6.85–6.90^s, 7.15^w, 7.26^s, 7.73^s, 7.85^s, 8.16^w, 8.28^w, 8.55^w, 8.60^w, 8.67^w, 8.75^w, 8.89^w, 9.06^m, 9.22^m, 9.39^m, 9.64^m, 9.84^w, 10.10^w, 10.32^w, 10.50^w, 10.66^m, 10.83^m, 11.50^m, 11.97^w, 12.63^s.

Dipicrate.—From an aqueous solution of the methiodide hydriodide, the water-insoluble dipicrate formed, after recrystallization from methanol, light yellow plates, m.p. 230–232° dec., undepressed on admixture with the dipicrate of methyldeacetylaspidospermine methiodide XIII.

Anal. Calcd. for $C_{22}H_{33}N_2O\cdot 2C_6H_3N_3O_7\cdot {}^1/_2H_2O$: C, 50.47; H, 4.98; N, 13.84. Found: C, 50.52; H, 4.90; N, 13.73.

On recrystallization from acetone one obtained an *acetone adduct*, rhombic transparent plates of a deeper yellow shade than the crystals from methanol, becoming opaque at 110°, frothing at 124°, resolidifying at 140°, m.p. 233–235° dec., undepressed on admixture with the acetone adduct of the dipicrate of XIII.

Anal. Calcd. for $C_{22}H_{33}N_2O\cdot 2C_6H_3N_3O_7\cdot CH_3COCH_3$: C, 51.86; H, 5.3; N, 13.07. Found: C, 52.19; H, 5.67; N, 12.65.

The methiodide hydriodide was dissolved in hot water and ammonia added. On cooling there appeared well-formed, glass-clear, rhombohedric prisms of XIII, m.p. 160–182°.

Anal. Calcd. for $C_{21}H_{30}N_2O\cdot CH_3I\cdot {}^1/_2H_2O$: C, 55.38; H, 7.18; I, 26.62. Found: C, 55.15; H, 7.17; I, 26.67.

The infrared spectrum (in Nujol) showed: 2.89^m, 2.95^m, 6.16^s, 6.27^m, 6.70^s, 6.87^s (Nujol), 7.27^s (Nujol), 7.47^w, 7.55^w, 7.75^s, 7.85^w, 8.17^w, 8.25^w, 8.48^m, 8.69^w, 8.81^m, 8.95^m, 9.14^m, 9.42^m, 9.69^m, 9.85^m, 10.63^m, 10.86^m, 12.64^s, 13.40^m. The spectrum of the methiodide prepared by method I was almost identical; some minor differences observed are probably due to crystalline modifications. The ultraviolet spectra were identical.

The dipicrate, recrystallized from acetone, m.p. 234–235°, was identical with the acetone adducts of dipicrates above.

Methyldeacetylaspidospermine (XI). C. By Attempted Hofmann Degradation of Methyldeacetylaspidospermine Methohydroxide.—Two hundred milligrams of methyldeacetylaspidospermine methiodide in 10 cc. of methanol was boiled with silver oxide freshly prepared from 150 mg. of silver nitrate. The mixture was centrifuged and the supernatant was evaporated. The residue, 159 mg. of an oil, was distilled in a sublimation apparatus at 0.2 mm. and 130°. The temperature was finally raised to 150°. The clear colorless oil was washed off the cold finger with ether and the ether solution evaporated. The residual cloudy oil had an infrared spectrum identical with that of methyldeacetylaspidospermine. The methiodide was prepared with methyl iodide in ether. After recrystallization from ethyl acetate–acetone it formed colorless birefringent plates, m.p. 166–174.5° (colorless melt with bubbles). The infrared spectrum was identical with that of methyl deacetylaspidospermine methiodide.

D. By Pyrolysis of Methyldeacetylaspidospermine Methiodide (XIII).—Methyl deacetylaspidospermine methiodide (XIII, 65 mg.) in a vacuum sublimation apparatus was heated slowly to 220° (bath temp.) at 0.3 mm. The colorless sublimate was washed off the cold finger with ether, and the ether solution evaporated to leave 55 mg. of a colorless oil whose infrared and ultraviolet spectra were identical with those of methyldeacetylaspidospermine. The methiodide, prepared in ether, was recrystallized from ethyl acetate–acetone to yield colorless birefringent plates, m.p. 168–170.5° (colorless melt with bubbles); the infrared spectrum was identical with that of methyldeacetylaspidospermine methiodide.

Aspidosine (VII, Hydrobromic Acid Method).—One gram of aspidospermine (I) was refluxed for two hours with 20 cc. of 48% hydrobromic acid. The mixture was evaporated to dryness at reduced pressure, the residue taken up in warm water, charcoaled and filtered. The filtrate was then poured into excess concentrated ammonium hydroxide. The mixture was filtered and the precipitate, after thorough washing with water, was dried in a vacuum desiccator. The residue, 710 mg. (84.3%), was extracted with 25 cc. of boiling ethanol in three portions; the extract was filtered hot and set aside to crystallize. There was obtained 213 mg. (25.3%) of brownish, birefringent plates, m.p. 245–254° (brown viscous melt). After two recrystallizations from ethanol the compound melted at 250–254°, undepressed on admixture with aspidosine prepared by the action of hydriodic acid on aspidospermine.

The infrared spectrum in chloroform showed: 2.80^{vw}, 3.07^s (broad band), 6.18^m, 6.25^s, 6.82^s, 6.93^{sh}, 7.24^m, 7.80^m, 8.70^w, 8.92^w, 9.16^w, 9.23^w, 9.96^w, 11.16^m, 11.70^m.

N,O-Diacetylaspidosine (VIII).—Aspidosine (VII, 130 mg.) was dissolved in 1 cc. of pyridine and treated with 0.5 cc. of acetic anhydride; the mixture was heated 10 minutes on the steam-bath and then left overnight in a vacuum desiccator over sulfuric acid. The remaining red oil was taken up in 1.5 cc. of ether and extracted into 12 drops of 2 *N* hydrochloric acid. The greenish acid extract was made basic with 2 *N* potassium hydroxide and extracted with ether. After drying over magnesium sulfate the ether extract was filtered, whereupon large colorless crystals were deposited in the filtrate. These were washed twice with ether and dried. The yield at this stage averaged 50–70% in various runs. After two recrystallizations from ligroin the clusters of colorless, birefringent prisms melted at 158–158.5° (clear colorless melt).

Anal. Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.21; H, 7.90; N, 7.32; O-acetyl, 11.26; total acetyl, 22.51. Found: C, 71.95; H, 7.91; N, 7.40; O-acetyl, 12.15, total acetyl, 23.27.

The infrared spectrum in chloroform showed: no bands in the OH or NH region; 5.66^s (carbonyl of O-acetyl), 6.01 (amide carbonyl of N-acetyl), 6.21^m, 6.76^m, 6.85^s, 7.16^s, 7.33^w, 7.51^m, 7.75^m, 8.48^s, 8.87^w, 9.05^w, 9.44^w, 9.56^w, 9.80^w, 9.92^w, 10.40^w, 10.78^w, 10.93^w, 11.87^w.

The reduction of N,O-diacetylaspidosine with lithium aluminum hydride yielded oily N-ethylaspidosine (infrared spectrum in chloroform: no CO, no NH).

When, after acetylation in pyridine, the mixture was decomposed with water instead of being evaporated, the product had lost its O-acetyl group and was identical with N-acetylaspidosine (VI, demethylaspidospermine) described below.

On warming diacetylaspidosine in methanol saturated with hydrogen chloride aspidosine but not O-acetylaspidosine was obtained.

N-Acetylaspidosine (VI, O-Demethylaspidospermine). A. By Aluminum Chloride-catalyzed Cleavage of Aspidospermine (I).—Two grams of aspidospermine and 10 g. of anhydrous aluminum chloride in 60 cc. of nitrobenzene[15] were kept at 140° for 30 minutes, with stirring. The black mixture was then cooled, decomposed with ice and dilute hydrochloric acid, mixed with ether, treated with Filter-aid and filtered. After the filter cake was washed with dilute hydrochloric acid and ether, the filtrate and washings were transferred to a separatory funnel and the layers separated. The organic layer was extracted thoroughly with dilute hydrochloric acid and the extracts were added to the aqueous layer. The total aqueous phase was then washed thoroughly with ether, made basic with solid sodium bicarbonate followed by 2 *N* potassium hydroxide, and thoroughly extracted with ether. The ether solution was then extracted with dilute hydrochloric acid, and the acid extract charcoaled and filtered. The acidic filtrate was made basic in the same fashion as before, extracted with ether and the ether extract dried over magnesium sulfate, filtered and evaporated. There remained 1.037 g. of a dark yellow oil which was taken up in approximately 6 cc. of ethanol and converted to the perchlorate with 70% perchloric acid. After two recrystallizations from methanol the *perchlorate* formed beautiful, colorless, birefringent crystals which showed no distinct melting point, but slowly softened and melted at 156–168°.

Anal. Calcd. for $C_{21}H_{28}N_2O_2 \cdot HClO_4 \cdot CH_3OH \cdot {}^1/_2H_2O$: C, 56.69; H, 7.35; N, 6.01. Found: C, 56.69; H, 7.12; N, 5.73, 5.83.

Picrate: Flat diamond-shaped, yellow, birefringent plates, m.p. 160–163° after two recrystallizations from methanol.

Anal. Calcd. for $C_{21}H_{28}N_2O_2 \cdot C_6H_3N_3O_7$: C, 56.93; H, 5.49; N, 12.30. Found: C, 57.24; H, 5.63; N, 12.14.

The free base was recovered from a portion of the perchlorate, using saturated lithium hydroxide. The substance, which was *soluble in excess alkali*, was a colorless oil. The infrared spectrum (chloroform) was identical with that of material obtained from aspidosine or diacetylaspidosine (see below) and showed the following bands: no bands in the OH or NH region; 6.12^s (bonded carbonyl of N-acetyl), 6.23^s, 6.34^s, 6.80^s, 6.93^s, 7.27^s, 7.37^m, 7.52^s, 7.74^w, 7.95^s, 8.54^w, 8.68^w, 8.87^s, 9.04^m, 9.46^m, 9.94^w, 10.41^w, 10.75^m.

B. From Diacetylaspidosine (VIII).—N,O-Diacetylaspidosine (100 mg.) was refluxed for one-half hour with 20 cc. of 2 *N* potassium hydroxide; 10 cc. of methanol was then added and the refluxing continued for another 30 minutes. The *p*H was adjusted to 7 with 2 *N* hydrochloric acid (the precipitate which formed was soluble in excess acid) and the solution was extracted with ether. The orange extract was dried over magnesium sulfate, filtered and evaporated, leaving 65 mg. of reddish crystalline material whose infrared spectrum showed no absorption in the range of 5.5–6.1 μ and was different from that of aspidosine. The substance was charcoaled in ether and converted to the *hydrochloride* with ethereal hydrogen chloride; colorless microcrystals, m.p. 165–172°, very difficult to recrystallize.

Anal. Calcd. for $C_{21}H_{28}N_2O_2 \cdot HCl \cdot H_2O$: C, 63.85; H, 7.18; N, 7.08; acetyl, 10.88. Found: C, 63.61; H, 7.17; N, 7.23; acetyl, 11.5.

Ferric Chloride Reaction.—The hydrochloride or perchlorate of demethylaspidospermine in methanolic solution on addition of a drop of methanolic ferric chloride solution gave a striking green color turning to rust red on addition of a drop of pyridine.

Conversion of Demethylaspidospermine (VI) to N,O-Diacetylaspidosine (VIII).—When 50 mg. of demethylaspidospermine perchlorate was refluxed in 1 cc. of pyridine and 0.5 cc. of acetic anhydride for 10 minutes the isolation procedure described in the preparation of diacetylaspidosine (see above) gave a yellow viscous oil, the infrared spectrum of which showed it to be a mixture of about $^1/_3$ unchanged starting material (bonded carbonyl at 6.13 μ) and $^2/_3$ of N,O-diacetylaspidosine (strong phenyl acetate carbonyl at 5.67 and lactam carbonyl at 6.02).

The attempted methylation of demethylaspidospermine perchlorate under mild conditions (refluxing with methyl iodode in methanol in the presence of 2 moles of sodium hydride) gave no aspidospermine but mainly unchanged starting material.

Aspidospermine N-Oxide (*gen*-Aspidospermine).—A mixture of 300 mg. of aspidospermine, 1.0 cc. of glacial acetic acid, and 0.4 cc. of 30% hydrogen peroxide was heated 90 minutes on the steam-bath, then evaporated to dryness in a vacuum desiccator. The residual yellow glass was taken up in chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution; the bicarbonate solution was, in turn, well washed with chloroform; and the combined chloroform solutions were dried over anhydrous potassium carbonate. The dry chloroform solution was treated with decolorizing carbon and diatomaceous earth, filtered and evaporated. The residue, after drying *in vacuo*, amounted to 269 mg. Recrystallization was difficult, but was finally effected by concentration of a chloroform–carbon tetrachloride solution on the steam-bath. There was obtained 160 mg. (51%) of slightly yellow crystals, m.p. 216–220°. The infrared spectrum (in chloroform) was identical with that of *gen*-aspidospermine obtained by ozonization[1]: 2.71^{vw}, 4.03 (quaternary N), 6.03^{vs}, 6.20^s, 6.72^s, 6.84^s, 6.94^s, 7.25^{vs}, 7.40^s, 7.59^s, 7.85^s, 8.49^{sh}, 8.65^w, 8.94^w, 9.02^w, 9.13^w, 9.38^w, 9.55^w, 9.71^w, 10.36^w, 10.50^w, 10.95^w, 11.27^w. Crude samples obtained in other runs showed a strong CO band at 5.86^s, presumably due to the presence of CH_3COO; on treatment with base and recrystallization the amine oxide was obtained with the same spectrum.

On refluxing with 2 *N* hydrochloric acid, basification and extraction with ether an oily fraction was obtained whose infrared spectrum was practically identical with that of deacetylaspidospermine.

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(15) Treatment of aspidospermine with aluminum chloride in hexane (P. L. Julian and J. Pikl, THIS JOURNAL, **57**, 755 (1935)) gave starting material back in good yield.