treated with 3.3 ml. of 0.1 *M* periodic acid solution, and drops of bicarbonate solution were then added to restore the faint basicity of the mixture. After 10 minutes the solution was brought to *p*H 4 with acetic acid and 67 mg. of potassium permanganate in 6.7 ml. of water added. The solution was decolorized with solid sodium bisulfite after one-half hour, the manganese dioxide centrifuged and the supernatant lyophilized. The residual solid was taken up in 1 ml. of lower phase from equilibration of equal volumes of 1-butanol and 1% acetic acid and extracted with six 1-ml. portions of upper phase. The latter yielded 67 mg. of colorless gum which was put on a solvent-partition column[7] prepared from 1 g. of Supercel. Early fractions gave crystalline material which was combined and recrystallized from 1 ml. of 8 *N* hydrochloric acid. A yield of 24 mg. of 9-guanidinonanoic acid hydrochloride, m.p. 164–165° dec., was obtained. The material was identified by melting point and infrared comparisons with an authentic sample.

Periodate Treatment of Eulicin.—Under the conditions described above for the oxidation of eulamine and eulicinine with periodate, eulicin was resistant to attack. A 30-mg. (0.05 millimole) sample of the acetate salt, treated with two equivalents of periodate at *p*H 7.7, consumed 0.11 equivalent in 3 minutes and 0.38 equivalent in 126 minutes. Eulicin hydrochloride behaved similarly. No odor developed during the oxidations. At the end of 5 minutes, papergram analysis of the reaction mixture showed only unchanged eulicin at R_f 0.70.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BRANDEIS UNIVERSITY]

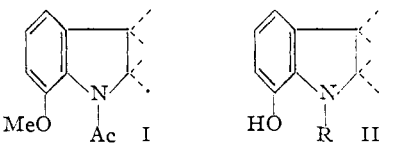
Aspidospermine. II. Nuclear Magnetic Resonance Spectra and Classical Degradations[1]

BY HAROLD CONROY, PETER R. BROOK, MAHENDRA K. ROUT AND NORMAN SILVERMAN

RECEIVED MARCH 8, 1958

Nuclear magnetic resonance spectra of the alkaloid aspidospermine and a number of its degradation products are recorded and their structural implications discussed. The Hofmann, Emde and von Braun degradations have been carried out. An N-methyl group, thought previously to be present on the basis of n.m.r. spectra and direct Herzig–Meyer determinations, has been excluded by these classical methods and by the fact that inactive aspidospermine can be recovered by decomposition of its radioactive N-methyl-C-14 methiodide. Evidence obtained leads to the formulation of the environment at N_b.

Aspidospermine, $C_{22}H_{30}O_2N_2$, one of the alkaloids of *Aspidosperma quebracho blanco* and of *Vallesia glabra*, was first studied from a chemical viewpoint by Ewins[2]; he found it to contain a methoxylated aromatic ring, an acetamido grouping and a tertiary, basic nitrogen atom. Spectral comparisons of aspidospermine and derivatives with model substances allowed Openshaw,[3] Witkop[4] and their coworkers to conclude that a 7-methoxy-1-acetylindoline system (I) is present. Deacetylaspidospermine, obtained by acid hydrolysis of aspidospermine, or alternatively from the corresponding formamide (vallesine), contains one C-methyl grouping[5]; the isolation of propionic acid in the Kuhn–Roth determination[3d,6] indicates that this is actually a C-ethyl grouping. The molecule apparently contains no additional centers of unsaturation, so its composition taken together with I implies a pentacyclic structure.



The proton magnetic resonance spectra of aspidospermine (curves A and B) show peaks at 980 c.p.s.[7] for the aromatic hydrogen atoms, at 1100 c.p.s. for the O-methyl, 1168 c.p.s. for the acetyl C-methyl and 1227 c.p.s. for the ethyl C-methyl; the multiplets near 1200 c.p.s. are due to the various C-methylenes. The spectrum (curve C) of N-acetylaspidosine (II, R = Ac) does not contain the O-methyl peak while the curve (D) for deacetylaspidospermine does not contain the intense 1168 c.p.s. maximum. The presence of the strong resonance at 1164 c.p.s., midway between the peaks due to the O-methyl and the C-methyl suggested the possibility of an N-methyl.[1,8] It has been stated,[2,5] that the alkaloid contains no N-methyl group; although Djerassi, *et al.*, have recently reported low N-methyl values for aspidospermine (calcd. for one N-methyl, 4.22; found,[9] 1.83, 0.50),

(1) Part I of this series appears as a preliminary Communication, H. Conroy, P. R. Brook, M. K. Rout and N. Silverman, THIS JOURNAL, **79**, 1763 (1957).

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

(3) (a) H. T. Openshaw, G. F. Smith and J. R. Chalmers, XIIIth International Congress of Pure and Applied Chemistry, Stockholm and Uppsala, 1953, Abstracts p. 223; (b) H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948); (c) J. R. Chalmers, H. T. Openshaw and G. F. Smith, *J. Chem. Soc.*, 1115 (1957); (d) A. J. Everett, H. T. Openshaw and G. F. Smith, *ibid.*, 1120 (1957).

(4) (a) B. Witkop, THIS JOURNAL, **70**, 3712 (1948); (b) B. Witkop and J. B. Patrick, *ibid.*, **76**, 5603 (1954).

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

(6) W. I. Taylor, THIS JOURNAL, **79**, 3298 (1957); M. F. Bartlett, D. F. Dickel and W. I. Taylor, *ibid.*, **80**, 126 (1958).

(7) At 40.01 mc./sec. on an arbitrary scale wherein the toluene aromatic resonance peak is assigned a value of 1000 c.p.s. and the toluene methyl proton peak assigned 1197 c.p.s. Spectra, except for curve B, were examined in chloroform solution with a toluene capillary for external reference on a Varian Associates high resolution nuclear magnetic resonance spectrometer with superstabilizer.

(8) N-Methyl resonance would be expected to occur in this vicinity on the basis that chemical shifts are dependent upon the electronegativity of adjacent atoms. Empirical observations with compounds known to contain that system, with the exception of cases wherein the nitrogen is conjugated with electron-withdrawing groups as in amides, have generally supported the plausibility of the assignment. In carbon tetrachloride or chloroform solution these N-methyl peaks were observed: β-dimethylaminoethyl alcohol, 1169, and dimethylaniline, 1139 (A. A. Bothner-By, private communication); dimethylformamide, 1141, 1148; dimethylformamide neat, 1155, 1162; and dimethylcyanamide neat, 1153 (B. Bonne, M. A. Thesis, Brandeis University, 1957); thebaine, 1160; gelsemine, 1164 c.p.s.

(9) O. O. Orazi, R. A. Corral, J. S. E. Holker and C. Djerassi, *J. Org. Chem.*, **21**, 979 (1956).

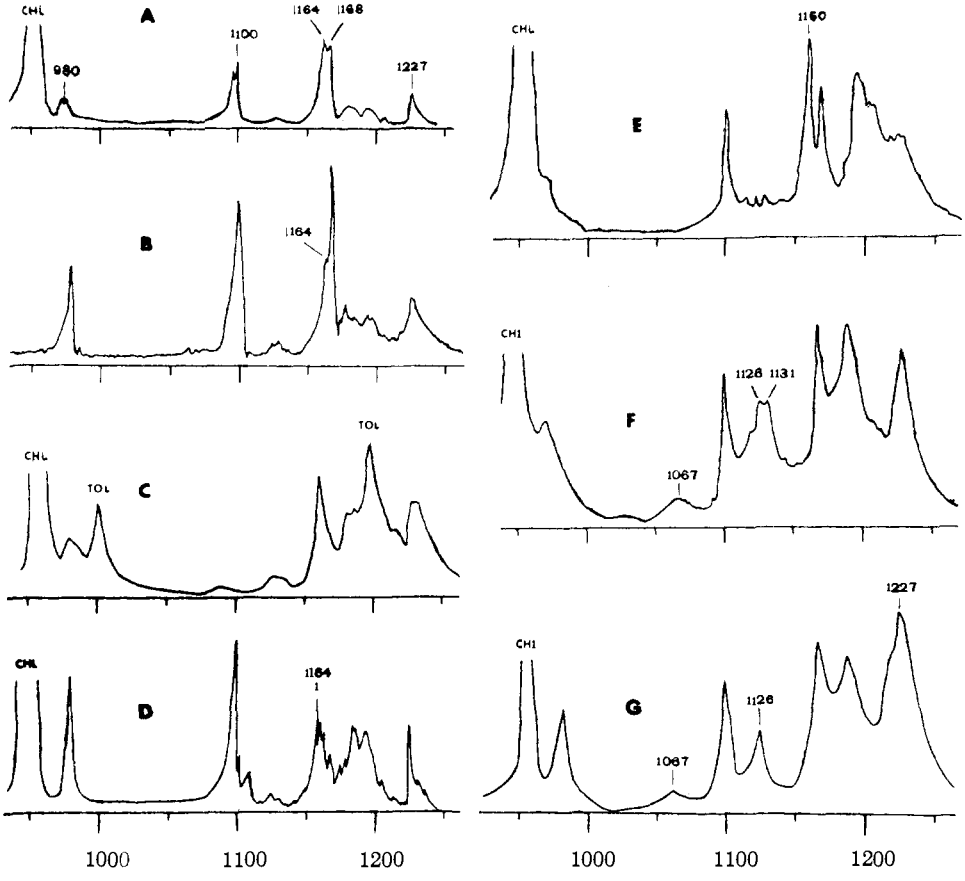


Fig. 1.—Nuclear magnetic resonance spectra: curve A, aspidospermine; curve B, aspidospermine in carbon tetrachloride; curve C, N-acetylaspidosine; curve D, deacetylaspidospermine; curve E, aspidospermine dihydromethine; curve F, aspidospermine bromocyanamide; curve G, aspidospermine cyanamide.

these could not be regarded as significant since Witkop[10] has shown that other materials, *e.g.*, yohimbol, which certainly do not contain this grouping give similar low "blank" values in the Herzig–Meyer determination. Otherwise, it seemed possible that these results might be ascribed to incomplete removal of the O-methyl prior to the N-methyl determination proper; nevertheless a sample of our aspidosine[2] (II, R = H), containing no methoxyl, gave an exceedingly high value corresponding to 94% of theory for one N-methyl[1] with the standard procedure. The presence of an N-methyl was hardly supported by the alkaloid's behavior in the von Braun degradation (*vide infra*); we have therefore devised a more absolute method for detection of the controversial function.

Although Ewins[2] reported that aspidospermine does not react with methyl iodide except at higher temperatures to give what was described by him as a complex mixture, we experienced no difficulty in the preparation of aspidospermine N_b-methiodide[1] by the prolonged action of methyl iodide on the base in a sealed tube at 100°.[11] Since the pK_a (7.30)[4b] is not abnormal, this low reactivity does indicate an exceptional steric block at the tertiary nitrogen; still the quaternary salt can be obtained nearly quantitatively under the conditions used. The salt is smoothly converted back to the free tertiary base on pyrolysis[11] (dry distillation *in vacuo*). In the event that aspidospermine contains an N-methyl, it should have been possible to prepare a radioactive specimen by pyrolytic decomposition of the labeled salt formed by combination of the alkaloid with C-14 tagged methyl iodide.

The aspidospermine preparation resulting from distillation of the labeled methiodide was carefully purified by chromatography to eliminate any trace of unchanged precursor and then recrystallized to a constant specific count rate of the barium carbonate resulting from its combustion. *The free base so obtained was nearly completely inactive*, with less than 3% of the C-14 originally incorporated having been recovered. While the two methyl groups in the supposed dimethylammonium cation need not be equivalent, it is very difficult to believe that the ejection process could be so selective; indeed such stereoselectivity was sought for and found to be quite absent in a recent study of the formation and decomposition of C-14 labeled tropine methochloride.[12] The retention of a small trace of radioactivity could find explanation in the

(10) B. Witkop, THIS JOURNAL, **71**, 2559 (1949).

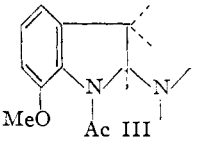
(11) The English group (ref. 3d) recently and independently found similar conditions for the preparation of aspidospermine N_b-methiodide and as well for its pyrolytic decomposition.

(12) K. Schmid, W. von Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **39**, 394 (1956).

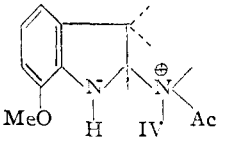
possibility of some O-methyl exchange at the high temperature of the decomposition. This result then undermines the earlier conclusion; other evidence obtained will, in the sequel, fully retire the N-methyl hypothesis.

A positive result in the Herzig–Meyer N-methyl determination is virtually meaningless in this series, even when, as in the case mentioned, a full equivalent of volatile alkyl iodide is generated. But the n.m.r. data must be reckoned with. If the intense 1164 c.p.s. peak (curves A, B and D) is not associated with an N-methyl group then its position is still indicative of protons in proximity to nitrogen and its strength suggests at least two, or probably four, such species, as in $-CH_2N<$ or $-CH_2NCH_2-$. That the latter idea is actually correct was shown ultimately by chemical work; nevertheless the observed peak location is somewhat atypical, the N-methylene resonance exhibited by a number of model compounds falling within the range 1115–1150 c.p.s.[13]

Witkop[4b] rejected the possibility that aspidospermine contains an eserine-like unit (III) on grounds, (i) that the increase in basicity attending

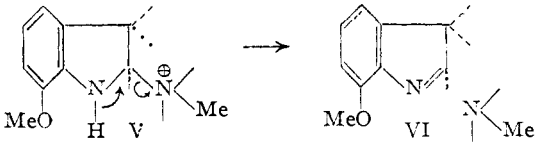


III



IV

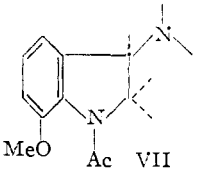
the conversion of aspidospermine (pK' 7.30) to deacetylaspidospermine (pK' 7.36) was too small for such close juxtaposition of nitrogens and (ii) because treatment of deacetylaspidospermine with acylating agents did not result in ring cleavage but merely in acylation at N_a. Ground (i) appears reasonable, but (ii) could perhaps be discounted. With sufficient steric hindrance at N_b the N_b acylammonium ion (IV) required for cleavage might form at a rate negligible in comparison to that of simple acylation at N_a. We have adduced some further evidence on the point. Acid hydrolysis of aspidospermine N_b-methiodide yields the deacetyl methiodide,[1,3d] which on the assumption of III would be V, and which must certainly be expected



V VI

to cleave to VI as shown, at least reversibly, with alkali. But deacetylaspidospermine N_b-methiodide is stable to alkali, and to alkaline sodium borohydride solution, which should have removed any VI from equilibrium. Furthermore compounds containing the N–C–N linkage are ordinarily sensitive to lithium aluminum hydride reduction, but deacetylaspidospermine is stable to this reagent under the usual conditions and only very slowly at higher temperatures is degraded to a poorly characterized material which, as it was shown, still contains a tertiary N_b.

A similar objection applies to the part structure VII in which N_b is directly connected to the β-indolinic position. As a benzylamine type, VII would be expected to suffer cleavage of the C–N bond by catalytic hydrogenolysis; this reaction does



VII

not proceed. Especially with the modification of VII containing hydrogen at the α-indolinic carbon, Hofmann elimination of the N_b-methiodide would be expected to be facile and to result in an indole; again this is not observed (*vide infra*). Clearly N_b is not directly substituted on the (benzo)pyrroline nucleus.

When aspidospermine N_b-methiodide was heated with potassium hydroxide in a sublimation apparatus *in vacuo* a colorless, viscous, oily base was obtained as distillate. Unfortunately this is no tetracyclic unsaturated amine formed in a normal Hofmann elimination but a mixture of deacetylaspidospermine with N_a-methyldeacetylaspidospermine.[4b] The composition of material produced in one experiment was such that the infrared spectrum was found to be superimposable in every detail with the spectrum of the total crude product of lithium aluminum hydride reduction of vallesine (formyldeacetylaspidospermine).[14] Aspidospermine methosulfate is formed when the alkaloid and excess methyl sulfate are kept together at room temperature for a week or more; both the methosulfate and the methiodide could be converted to the same (N_b) methoperchlorate. Hofmann degradation of the methosulfate failed similarly, although in one experiment the oily base obtained was shown to be the N_a-methyldeacetylaspidospermine in essentially pure condition. The situation finds a parallel in the degradation of gelsemine methiodide, where N_a-methylgelsemine is formed and elimination does not occur.[15] It is at odds with the statement of Openshaw, *et al.*,[3d] that their preliminary observations indicate that aspidospermine methiodide is susceptible to Hofmann degradation. Acting on the chance that the discrepancy might have resulted from the presence of inorganic salts with our pro-

(13) In carbon tetrachloride or chloroform solution, not including derivatives wherein the nitrogen is conjugated with an electron-withdrawing group, where a somewhat lower range would apply. The following compounds containing the group $-CH_2N$ showed strong maxima as given: ibogamine, 1125, 1134; thebaine, 1115; dihydroquinone, 1145; ethylamine, 1150 (quartet center); piperidine, 1147 (B. Bonne, M. A. Thesis, Brandeis University, 1957). These other compounds examined neat or in *t*-butylamine showed maxima 15–20 c.p.s. higher because of the solvent bulk susceptibility difference: ethylamine, 1165 (quartet center); *n*-butylamine, 1156; di-*n*-propylamine, 1158; triethylamine, 1163; tri-*n*-propylamine, 1167 (A. A. Bothner-By, private communication).

(14) The lithium aluminum hydride reduction of vallesine to the oily N_a-methyldeacetylaspidospermine, characterized by a crystalline hydrochloride, is reported by Witkop (ref. 4b); although he did not mention the presence of deacetylaspidospermine in the crude reduction product, the spectra of our samples leave little doubt of the concomitant formation of that substance. Similarly, reduction of aspidospermine itself leads to a mixture of N_a-ethyldeacetylaspidospermine with some deacetyl compound as first pointed out by Prof. Carl Djerassi (private communication).

(15) 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).

cedures, we adopted the method involving pyrolysis of the methohydroxide prepared from the methiodide with silver oxide, but this led again to deacetylaspidospermine as the only product identified. In the absence of the hoped for elimination reaction[16] we conclude only that the environment at N_b lacks any hydrogen atoms *trans*, *beta* and *accessible*.

Sodium–liquid ammonia reduction of aspidospermine for a short time (five minutes) gave largely unchanged material, but reaction for a longer time (twenty minutes) gave some deacetylaspidospermine by ammonolysis or reduction of the amide grouping. Deacetylaspidospermine was quite unchanged by excess sodium in liquid ammonia after 2.5 hours. In contrast to these results and to the results of Hofmann elimination attempts, sodium–liquid ammonia reduction (Emde degradation) of aspidospermine N_b-methiodide was successful and led smoothly to the desired base, *aspidospermine dihydromethine*. This was acccompanied by a small amount of demethylated material, *i.e.*, aspidospermine. The dihydromethine was characterized by its perchlorate, its methiodide and its methoperchlorate; acid hydrolysis gave the deacetyl derivative characterized as the N_a-benzoyldeacetylaspidospermine dihydromethine. The ultraviolet spectrum of the Emde base is very similar to that of aspidospermine itself, while the infrared spectrum confirms survival of the acetyl group; as expected, the infrared and ultraviolet spectra of the deacetylated derivative are comparable to those of deacetylaspidospermine. The n.m.r. spectrum (curve E) of aspidospermine dihydromethine contains an "N-methyl" peak at 1160 c.p.s. of twice the intensity[17] of the neighboring acetyl C-methyl peak at 1167 c.p.s. and a somewhat stronger resonance near 1190 c.p.s. (methylene region); there is no increase in relative area in the C-methyl region (1225–1230 c.p.s.). That the number of C-methyl groups is no larger in the Emde base was confirmed by Kuhn–Roth determinations, so it is clear that the course of Emde reduction has not involved fission at any N-methylene group which might be present. Of the remaining possibilities, *viz.*, separation of N_b from a tertiary or from a secondary position, we favor the latter somewhat on the basis of additional information contained in the n.m.r. curves.[18]

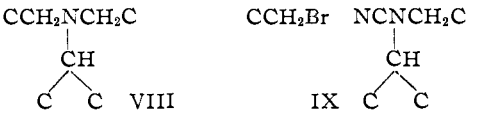
(16) In a letter dated May 15, 1957, Dr. G. F. Smith very kindly mentioned that while no *des*-base had been isolated as yet, the reason for believing that some degradation had occurred was that the derived base gave a poor yield of aspidospermine even after acetylation. At least that result is accounted for by the presence of the N_a-methylated derivative; we concede that our observations do not exclude the possibility that a small trace of *des*-base might have formed.

(17) The high intensity of the 1160 c.p.s. peak is believed due to the fact that it is composed of lines associated with one N-methyl and two N-methylene functions which, most remarkably, appear at very nearly the same chemical shift in this example.

(18) Proton resonance in the system >CH-N< is expected close to 1100 c.p.s., assigned in curve A to the separate maximum at 1097 c.p.s. In curves B and D it is not resolved from the 1100 c.p.s. peak but is apparent as a slight broadening at the left base and in the increase in relative area at 1100 c.p.s. beyond that expected for the three protons of the O-methyl group. In curve C (N-acetylaspidosine-, no methoxyl) the >CH-N< resonance stands alone as a small maximum *ca.* 1090 c.p.s. Both this set of assignments and the preferred formulation of the Emde reduction are supported by the fact that in curve E (aspidospermine dihydromethine) the C-methylene region has increased in area at the expense of the 1100 c.p.s. peak, the latter being sharp and of normal size for an O-methyl.

The von Braun cyanogen bromide degradation of aspidospermine was successful, although it took a course unexpected on the basis that the alkaloid contains an N-methyl group. In the case of simple trialkyl amines the smallest group, usually that most susceptible to bimolecular displacement, is lost as alkyl bromide[19]; tropane,[20] for example, is demethylated quantitatively (except for quaternary bromide). A crystalline bromocyanamide, $C_{23}H_{30}O_2N_3Br$, corresponding simply to the addition of cyanogen bromide, was obtained from aspidospermine. The substance is not a salt-like quaternary cyanoammonium bromide, since its solution in ethanol gives no immediate precipitate with silver nitrate; its infrared spectrum shows an intense sharp peak at 2198 cm.$^{-1}$ (4.55 μ), typical of the cyanamide grouping, and its ultraviolet spectrum is similar to that of aspidospermine. The n.m.r. spectrum (curve F) is particularly instructive. In addition to resonance at 1100 c.p.s. (methoxyl), 1167 (acetyl C-methyl), 1187 (various C-methylenes) and 1227 (ethyl C-methyl) the curve shows a new doublet (area $\cong$ 4 protons) at 1126 and 1131 c.p.s. and a new, weaker band (area $\cong$ 1 proton) near 1067 c.p.s. The peak at 1164 c.p.s. observed in previous spectra is absent.

The grouping >CH–Br might be expected to contribute a band near 1091 c.p.s. as it does in the case of isopropyl bromide; this resonance is not observed. We now propose that von Braun cleavage involves the change VIII→IX, and consider the following assignment: (i) The 1131 c.p.s. peak is



due to the CCH_2Br grouping. A $-CH_2Br$ resonance multiplet is observed near 1125 c.p.s. in the n.m.r. spectra of ethyl, *n*-propyl and *n*-butyl bromides. (ii) The 1126 c.p.s. peak is due to the CCH_2NCN grouping. If the two N-methylene functions of aspidospermine appear in the n.m.r. at 1164 c.p.s. then it is reasonable to suppose that the substitution of the electron-withdrawing cyano group upon N_b in IX will cause a shift (−38 c.p.s.) of the remaining N-methylene resonance to a lower field (*cf.* the case of dimethylformamide ($\sim$ −25 c.p.s.).[8] (iii) The 1067 c.p.s. peak is due to the C>CHNCN grouping. The peak at 1097 c.p.s. in the spectrum of aspidospermine (curve A) is then assigned to the single proton (in C>CHN<)[18] and in the cyanamide is shifted downscale by very nearly the same amount ($\sim$ −30 c.p.s.)

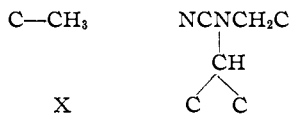
These conclusions must be confirmed by the chemical evidence. The first-order solvolysis rate constant for this bromocyanamide (IX) was found to be $k_1 = 7.0 \times 10^{-6}$ sec.$^{-1}$ (80% aqueous ethanol at 58°) of the same order as observed with other

(19) *Cf.* H. A. Hageman in "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 198ff.

(20) J. von Braun, *Ber.*, **44**, 1252 (1911).

primary alkyl bromides.[21] The product of this solvolysis is aspidospermine, not the ethyl ether which might have been expected. Similarly an attempt at mild acidic hydrolysis of the bromocyanamide yielded deacetylaspidospermine, and aspidospermine was formed even upon attempted vacuum distillation of the bromocyanamide. So far as we are aware this is the first example of facile reclosure of a von Braun bromocyanamide under conditions mild enough to exclude hydrolysis of the cyanamido group *per se* as a separate mechanistic step; a normal cyanamide is quite unaffected by ethanol and ordinarily required drastic conditions for hydrolysis to the corresponding secondary amine.[22] The relative ease of ring closure here apparently reflects a lowered entropy requirement for cyclization, as has been observed often with complex, highly substituted molecular systems, and suggests that the bromine-bearing chain has few degrees of freedom in which it becomes removed in space from N_b.

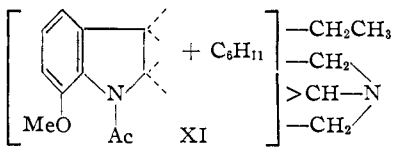
With zinc dust in methanolic ammonium chloride solution the bromocyanamide was debrominated to a cyanamide, $C_{23}H_{31}O_2N_3$, whose infrared and ultraviolet spectra are consistent with the formulation X, wherein the only change is represented to have been simple replacement of bromine by hydrogen. The n.m.r. spectrum (curve G) of the debrominated cyanamide no longer exhibits the



peak at 1131 c.p.s. assigned to the grouping CCH_2Br in IX, but retains the maxima at 1126 c.p.s. (area $\cong$ 2 protons) and at 1067 c.p.s. (area $\cong$ 1 proton) associated with the system $-CH_2-NCH<$, as required. The area under the peak at

1227 c.p.s. is relatively much larger in curve G. This indication that an *additional C-methyl* has been generated in the zinc reduction was fully confirmed by Kuhn–Roth determinations upon the debrominated product (calcd. for two C-methyls, 7.89; calcd. for three C-methyls, 11.82; found, 10.35, 10.3).

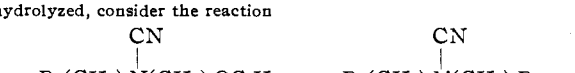
In summary, we represent the structure of aspidospermine at this stage by the expression XI.



Acknowledgment.—This work was supported by a research grant (RG-4852) from the National Institutes of Health and by a Frederick Gardner Cottrell grant from Research Corporation. We wish to thank Dr. E. Schlittler and Dr. B. Witkop for making available supplies of the alkaloid. It is a pleasure to acknowledge the kind assistance of Dr. A. A. Bothner-By in the use of the n.m.r. spectrometer and in connection with some of the measurements on model substances.

(21) Thus ethyl bromide in 80% aqueous ethanol at 55° gave a first-order rate constant of 1.39×10^{-6} sec.$^{-1}$ [L. C. Bateman, K. A. Cooper, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 925 (1940)].

(22) As an illustration of the difficulty with which cyanamides are hydrolyzed, consider the reaction



carried out by von Braun [*Ber.*, **42**, 2035 (1909)] in a sealed tube with a fivefold excess of fuming hydrobromic acid for 10 hr. at 105–107°.

Experimental

All melting points are corrected. Analyses were carried out by Dr. S. M. Nagy and associates at M.I.T. and by W. Manser, E.T.H., Zurich.

Aspidospermine.—The sample had m.p. 208–209°; infrared spectrum (chloroform): 2915s, 2780m, 1630s, 1592m, 1486m, 1460s, 1385s, 1335m, 1319m, 1290m, 1269m, 1171w, 1117w, 1103w, 1073w, 909w.

Deacetylaspidospermine.—Samples had the m.p. 107–109°; infrared spectrum (chloroform): 3356w, 2907s, 2778m, 2717m, 2667w-sh, 2475w, 1621m, 1595m, 1488s, 1462s, 1443m-sh, 1389m, 1376m, 1332m, 1325m, 1302m, 1282s, 1263s, 1175m, 1131m, 1112m, 1085s, 1053m, 1033m, 1016m, 965w, 931w, 901m, 867w.

Aspidosine.—The sample had the m.p. 255.5–257.5° (evacuated tube); infrared spectrum (potassium bromide): 3436w, 3300w, 3049m, 2941s, 2786m, 2717m, 1626w, 1603m, 1504w, 1481s, 1447m, 1376s, 1333m, 1321m, 1304m, 1287m, 1271m, 1261m, 1241m, 1225w, 1199w, 1181s, 1142m, 1114m, 1053w, 1032w, 1013w, 1003m, 971w, 960w, 943w, 925m, 913m, 880m, 857w, 792m, 764s, 722w. *Anal.* Calcd. for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39; O–Me, 0.00; 1 N-Me, 5.04. Found: C, 76.25; H, 8.94; N, 9.20; O–Me, 0.00; N–Me, 4.72.

Aspidospermine N_b-Methiodide.—Aspidospermine (895 mg.) was heated with 6 ml. of methyl iodide in a sealed glass tube at 100° for 34 hr. The crystalline precipitate of aspidospermine methiodide was removed by filtration, washed with benzene and dried *in vacuo*. The crude product (1.214 g.) had a m.p. of 268–272° (rapid heating). For analysis a sample was recrystallized from absolute ethanol as needles, m.p. 277–278° (rapid heating); ultraviolet spectrum (methanol): λ_{max} 255 mμ (10,600); 285 mμ (2960); infrared spectrum (potassium bromide): 2924m, 1647s, 1605m, 1595m, 1486s, 1460, 1441m, 1433m, 1374s, 1355m, 1319m, 1295m, 1271m, 1244m, 1204m, 1179m, 1157w, 1133w, 1107m, 1070m, 1033w, 1013m, 984w, 971w, 951m, 925m, 895w, 877w, 850w, 831w, 808w, 791m, 776m, 744m, 724w, 698w, 678w. *Anal.* Calcd. for $C_{23}H_{33}O_2N_2I$: C, 55.65; H, 6.70; N, 5.65. Found: C, 55.14; H, 6.84; N, 5.63.

Aspidospermine N_b-Methoperchlorate. (A) From the Methiodide.—Treatment of a strong aqueous solution of the methiodide with sodium perchlorate solution yielded the methoperchlorate, which crystallized from water in needles, m.p. 320–323°; infrared spectrum (potassium bromide): 2950m, 1650s, 1608w, 1597w, 1490m, 1462m, 1443m, 1377m, 1355m-sh, 1323m, 1299m, 1274m, 1250m, 1208w, 1178w, 1134w, 1120m-sh, 1096s, 1067s-sh, 1033m, 1010m, 952w, 922w, 893w, 877w, 849w, 829w, 808w, 797w, 776m, 743m. *Anal.* Calcd. for $C_{23}H_{33}O_6N_2Cl$: C, 58.88; H, 7.09. Found: C, 58.35; H, 6.88.

(B) From the Methosulfate.—Aspidospermine (300 mg.) was allowed to stand with dimethyl sulfate (3 ml.) in a stoppered flask. After seven days the solid material had dissolved completely. The excess methyl sulfate was removed under reduced pressure; the residue was taken up in excess of sodium carbonate solution and benzene. The benzene layer yielded some aspidospermine, identified by its infrared spectrum. The aqueous solution was evaporated to dryness and the organic material separated from the inorganic by extraction with methanol; evaporation gave the crude methosulfate still containing some inorganic material. A portion was treated with a concentrated aqueous solution of sodium perchlorate, when a gummy solid separated; this was recrystallized twice from water and twice from acetone. The methoperchlorate had the m.p. 265–270° (slow heating) or 320–323° (rapid heating). The infrared spectrum was identical with that of material prepared above with method A.

Aspidospermine N_b-^{14}C-Methiodide.—In the preparation of the radioactive sample, aspidospermine (700 mg.) was

heated with methyl iodide (2 ml., 4.56 g.) containing 50 microcuries of ^{14}C; the product was worked up as given above. After recrystallization from absolute ethanol the yield was 782 mg., m.p. 277–278°.

Pyrolysis of Aspidospermine N_b-^{14}C-Methiodide.—In a typical experiment, the methiodide (51 mg.) was heated at 280–290° for one hour at 0.01 mm. pressure in a vacuum sublimation apparatus. Aspidospermine (32 mg.) sublimed and was collected on the cold finger. The sample (not completely soluble in benzene) was chromatographed on a basic alumina column (8 × 120 mm.) to remove any contaminating methiodide. The chromatographed product had the m.p. 200°, raised to 207–208° after three recrystallizations. The infrared spectrum was identical with that of an authentic sample of aspidospermine.

Radiochemical Assay.—The Van Slyke wet combustion[23] was carried out with approximately 3 mg. of material (methiodide or base); the barium carbonate disks were counted in a windowless flow counter. After correction for background and self absorption a typical sample of the methiodide was found to have an activity of 780 c.p.m./micromole. A similar determination upon the aspidospermine, m.p. 207–208°, above, gave 22 c.p.m./micromole; after one more recrystallization from methanol the m.p. was unchanged and the corrected count was 21 c.p.m./micromole; still another recrystallization from methanol gave material with 25 c.p.m./micromole. The activity of the recovered aspidospermine, averaging 23 c.p.m./micromole, is therefore 2.9% of that of the precursor methiodide.

Deacetylation of Aspidospermine N_b-Methiodide.—Aspidospermine methiodide (300 mg.) was heated at 80° with dilute hydriodic acid (1:10) for 1.5 hr. The volatile material was removed under reduced pressure, the residue was dissolved in water, neutralized with sodium bicarbonate and extracted with chloroform (3 × 10 ml.). The extract gave a yellow gum upon removal of the solvent. The infrared spectrum in potassium bromide indicated approximately 50% hydrolysis of the acetyl so the gum was heated for an additional three hours at 80° with the same amount of hydriodic acid and the isolation procedure was repeated. The product showed no carbonyl in the infrared and hydrolysis was judged to be complete. The compound did not crystallize from ethanol, acetone or methyl ethyl ketone and was precipitated from these solvents by ether as a yellow gum which was dried *in vacuo*. The yield was 208 mg.; infrared spectrum (potassium bromide): 3270m, 2915m, 1618m, 1595m, 1488s, 1462s, 1395w, 1339w, 1309w, 1279m, 1250m, 1215w-sh, 1202m, 1174w, 1153w, 1120w, 1093w, 1070m, 1026w, 1008m, 988w, 967w, 953w, 923w, 893w, 847w, 826w, 776m, 740s, 693m, 658m.

Attempted Sodium Borohydride Cleavage of Deacetylaspidospermine N_b-Methiodide.—The gum (208 mg.) was dissolved in methanol (4 ml.) and sodium borohydride (53 mg.) was added. After ten minutes the mixture had the *p*H of 10; sodium hydroxide (2 *N*, 3 ml.) was added and the mixture was allowed to stand for a further 3 hr. Extraction with chloroform yielded a gum whose infrared spectrum was identical with that of the starting material.

Lithium Aluminum Hydride Reduction of Deacetylaspidospermine.—Deacetylaspidospermine (100 mg.) in tetrahydrofuran (3 ml.) was heated under reflux with lithium aluminum hydride (200 mg.) for two days. After decomposition of the salt by dropwise addition of water the mixture was extracted with ether; evaporation of the extracts gave material whose infrared spectrum showed that very little change had occurred. In another run, 100 mg. of deacetylaspidospermine in 4 ml. of xylene mixed with 3 ml. of tetrahydrofuran and 200 mg. of lithium aluminum hydride was heated at reflux for seven days, with a mercury sealed nitrogen atmosphere. The product was isolated in the same manner as given above, and the infrared spectrum of the gum so obtained indicated the absence of any unchanged deacetylaspidospermine as well as the absence of any aspidosine. The crude material was acetylated by overnight treatment with 1 ml. of pyridine and 0.5 ml. of acetic anhydride; the reagents were evaporated and the residue taken up in ether and 2 *N* hydrochloric acid. Only a trace of non-basic material was obtained, but the aqueous acidic extract on basification with sodium carbonate yielded a gum whose spectrum contained a medium band at 1754 cm.$^{-1}$ ascribed to a phenolic acetate, and a strong band at 1641 cm.$^{-1}$ due to an N_a-acetyl group and no NH band. The spectrum indicated furthermore that aspidospermine was not a component of this material.

Hofmann Degradation with Aspidospermine N_b-Methohydroxide.—The aspidospermine N_b-methiodide (154 mg.) was dissolved in methanol and shaken with an excess of freshly prepared silver oxide. The slurry was filtered and the precipitate washed with methanol. The filtrate yielded an oily residue after removal of methanol. This was heated in a vacuum sublimation apparatus; at 170–180° at *ca.* 0.01 mm. a colorless gum distilled and was collected on the cold finger. This was redistilled *in vacuo* to ensure complete removal of quaternary hydroxide. The yield was 84 mg. of material whose infrared spectrum was virtually superimposable with that of deacetylaspidospermine. The compound was heated with acetic anhydride for one hour at 80°, whence 67 mg. of aspidospermine, m.p. 206–208°, was obtained after recrystallization from aqueous acetone.

Hofmann Degradation with Aspidospermine N_b-Methiodide.—The methiodide (50 mg.) was treated with five drops of a concentrated aqueous solution of potassium hydroxide. After removal of the water, the mixture was distilled at 290° *in vacuo*, otherwise as given above. The infrared spectrum of the distillate was superimposable with that of a mixture of deacetylaspidospermine and N_a-methyldeacetylaspidospermine as produced in the lithium aluminum hydride reduction of vallesine (*vide infra*).

Hofmann Degradation with Aspidospermine N_b-Methosulfate.—The crude methosulfate (*vide supra*) equivalent to 70–80 mg. of aspidospermine was refluxed with excess potassium hydroxide in aqueous methanol for three hours. The solution was taken to dryness and the residue heated in the vacuum sublimation apparatus as given above. The infrared spectrum, containing an intense singlet peak at 1592 cm.$^{-1}$ and no NH band, was otherwise identical with that of an authentic sample of N_a-methyldeacetylaspidospermine.

Formyldeacetylaspidospermine (Vallesine).—Deacetylaspidospermine (300 mg.) was allowed to stand with a mixture of formic acid (98%, 1 ml.) and acetic anhydride (0.5 ml.) overnight. The excess formic acid and acetic acid were removed and the product, obtained in good yield, was recrystallized from ethyl acetate, m.p. 152–154°.

Lithium Aluminum Hydride Reduction of Vallesine.—Vallesine (200 mg.) in tetrahydrofuran (2 ml.) was treated with excess lithium aluminum hydride and the mixture was allowed to stand for 10 min.; water was added dropwise and the organic product was extracted with ether. The gum obtained on removal of the ether gave an infrared spectrum containing an NH band at 3344 cm.$^{-1}$ and otherwise very similar to that of deacetylaspidospermine but containing as well the peaks due to N_a-methyldeacetylaspidospermine.

Sodium–Liquid Ammonia (Emde) Reduction of Aspidospermine N_b-Methiodide. Preparation of Aspidospermine Dihydromethine.—Aspidospermine methiodide (2.000 g.) was added to liquid ammonia (200 ml.); excess sodium was added, sufficient to maintain a blue color for seven minutes. After this time the sodium and sodamide were destroyed by addition of ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in a mixture of water (10 ml.) and ether (150 ml.) and the ether layer was dried over sodium sulfate and evaporated. The residual pale brown gum was heated with acetic anhydride (4 ml.) for 1.5 hr. at 100°. The volatile matter was removed under reduced pressure and the residue was dissolved in benzene (100 ml.). This solution was washed twice with 10 ml. of 2 *N* sodium hydroxide and once with water. The benzene solution after drying and removal of solvent gave a colorless gum (1.235 g.). The crude Emde base so obtained contained a small amount of aspidospermine, which could be largely removed by dissolving the substance in a small amount of ether and allowing the solution to stand overnight, when the aspidospermine, m.p. 198°, crystallized out. The purification of other samples of the Emde base was carried out *via* the crystalline perchlorate, *vide infra*.

Aspidospermine Dihydromethine Perchlorate.—The perchlorate was formed by treatment of the Emde base with perchloric acid in ethanol to *p*H 3. The solution was diluted with water and the ethanol evaporated in a stream of nitrogen, when the product perchlorate crystallized. For analysis this was recrystallized from water; prisms, m.p. 170–173° with sintering at 155°; infrared spectrum (potas-

(23) "Isotopic Carbon," by M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. F. Yankwich, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 93.

ium bromide): 3390w, 3096w, 2915m, 1639s, 1595w, 1484s, 1462s, 1383m, 1323m, 1304m, 1271m, 1105s, 1080s, 969w, 948w, 919w, 870w. *Anal.* Calcd. for $C_{23}H_{35}O_6N_2Cl$: C, 58.64; H, 7.49; OMe, 6.59; 1 N-Me, 3.19. Found: C, 58.18; H, 7.31; O-Me, 6.79; N-Me, 2.86.

The Emde base regenerated from its perchlorate was obtained as a colorless glass which still stubbornly resisted attempts to induce crystallization. It was distilled for analysis at 105° (10^{-4} mm.); ultraviolet spectrum (ethanol): λ_{max} 217 mμ (31,900); 257 mμ (11,100); $\lambda_{infl.}$ 285 mμ (3200); infrared spectrum (chloroform): 3378w, 2899m, 2762w, 1631s, 1592w, 1486m-sh, 1462s, 1381s, 1355w, 1323m, 1309w-sh, 1271m, 1149w, 1124w, 1111w, 1037m, 990w, 975w, 942w, 871w. *Anal.* Calcd. for $C_{23}H_{34}O_2N_2$: C, 74.53; H, 9.25; two C-Me, 8.12. Found: C, 73.99; H, 9.53; C-Me, 6.70.

Aspidospermine Dihydromethine Methiodide.—The crude dihydromethine base above (1.235 g.) was allowed to stand overnight at room temperature with a mixture of methyl iodide (4 ml.) and benzene (12 ml.), when pale yellow crystals together with some yellow, gummy material separated. This was removed and recrystallized from methyl ethyl ketone as colorless microcrystalline needles, m.p. 280°, with evolution of gas at 214°. The yield was 1.063 g. (first crop) plus 71 mg. (second crop). The benzene–methyl iodide solution, upon being taken to dryness, gave a gum which was chromatographed to give pale yellow needles (110 mg.) of impure aspidospermine. For analysis the methiodide was recrystallized from methyl ethyl ketone; another sample from isopropyl alcohol; infrared spectrum (potassium bromide): 2941m, 1656s, 1616w-sh, 1493s, 1468s, 1389s, 1325w, 1309w, 1276m, 1235w, 1215w, 1182w, 1053m, 1038w, 1013w, 966w, 939w, 912w, 889w, 784w, 761w, 741w. *Anal.* Calcd. for $C_{24}H_{36}O_2N_2I$: C, 56.35; H, 7.10; N, 5.48. Found: C, 54.77, 54.83; H, 7.32, 7.34; N, 5.36. Calcd. for $C_{24}H_{36}O_2N_2I\cdot H_2O$: C, 54.44; H, 7.24; N, 5.29.

Aspidospermine Dihydromethine Methoperchlorate.—The above methiodide, when dissolved in water and treated with a concentrated solution of sodium perchlorate, yielded a precipitate of the methoperchlorate. This was washed twice with a very small amount of water and then crystallized from absolute ethanol as clusters of prismatic needles, m.p. 264° with sintering above 150°.

Anal. Calcd. for $C_{24}H_{37}O_6N_2Cl$: C, 59.44; H, 7.69. Found: C, 59.18; H, 7.85.

Deacetylaspidospermine Dihydromethine.—Aspidospermine N_b-methiodide (795 mg.) was reduced with sodium and liquid ammonia as given above; purification of the reduction product was accomplished by filtration through alumina with benzene as eluent. This product was heated with 10 ml. of *N* hydrochloric acid at 100° for 3 hr. The hydrochloric acid was removed under reduced pressure, leaving a pink gum, which was dissolved in water, basified with 2 *N* sodium hydroxide and extracted with ether (3 × 15 ml.). The extracts yielded 254 mg. of deacetylated Emde base, characterized as N_a-benzoyldeacetylaspidospermine, prepared with benzoyl chloride–pyridine at room temperature overnight. The N_a-benzoyl derivative purified by chromatography on alumina with ether as eluent was crystallized from aqueous acetone as needles, m.p. 163–164°. *Anal.* Calcd. for $C_{25}H_{36}O_2N_2$: C, 77.74; H, 8.39; N, 6.48; 1 C-Me, 3.47; 2 C-Me, 6.95. Found: C, 77.85; H, 8.36; N, 6.55; C-Me, 4.30. A sample of benzoic acid, submitted for C-methyl determination under the same conditions showed "C-Me," 2.28. Subtraction of the indicated blank value (0.64) gives a corrected C-methyl figure of 3.66, in better agreement with expectation for one C-methyl. Infrared spectrum (chloroform): 2915s, 2849w-sh, 2793m, 1961w, 1905w, 1818w, 1721w, 1634s, 1595w, 1582m, 1490s, 1462s, 1389s, 1357w-sh, 1330m, 1276m, 1190w, 1147w, 1124w, 1105w, 1091w, 1078w, 1040w, 993w, 946w, 920w, 908w.

Treatment of Aspidospermine with Sodium–Liquid Ammonia.—Aspidospermine (100 mg.), tetrahydrofuran (10 ml.), ammonia (20 ml.) and sufficient sodium to give a permanent blue color were allowed to stand for 20 minutes. Ammonium chloride was added, the ammonia allowed to evaporate and the tetrahydrofuran was removed in a stream of nitrogen. The residue was extracted with benzene (10 ml.) and the extract gave upon evaporation a brown gum (84.5 mg.) (theory, for loss of acetyl, 88 mg.). The infrared spectrum showed no carbonyl and was very similar to that of deacetylaspidospermine. The compound was acetylated with acetic anhydride (0.5 ml.) for two hours at 100°; the acetic anhydride was removed by evaporation and the product kept over sodium hydroxide *in vacuo* for 12 hours. Chromatography on basic alumina with chloroform as eluent gave as the main fraction, aspidospermine (60.1 mg.) contaminated with material giving rise to weak absorption in the carbonyl region at 1761 (phenolic acetate) and 1712 cm.$^{-1}$.

von Braun Degradation with Aspidospermine. Bromocyanoaspidospermine.—Aspidospermine (350 mg.) in chloroform (5 ml.) with 450 mg. of cyanogen bromide was heated under reflux for 21 hours. The chloroform and excess of cyanogen bromide were removed under reduced pressure at 100° and the residual yellow gum was triturated with ethyl acetate; a pale yellow crystalline material did not dissolve (aspidospermine hydrobromide, m.p. 269.5°, 46.7 mg.) and was recrystallized from chloroform–ethyl acetate to give material with m.p. 269–271°.

Anal. Calcd. for $C_{22}H_{30}O_2N_2\cdot HBr$: C, 60.67; H, 7.18. Found: C, 60.33; H, 7.11.

The ethyl acetate extract, upon removal of solvent, gave a residue (414 mg.) which was recrystallized from 95% ethanol and gave 162 mg. of bromocyanamide, m.p. 177.5–178.5°. Some additional material was obtained as a second crop, m.p. 162–165°. For analysis a sample was recrystallized from ethanol and had the m.p. 177.5–178.5°; ultraviolet spectrum (ethanol): λ_{max} 220 mμ (31,000), λ_{max} 255 mμ (12,400), plateau 286 mμ (4000); infrared spectrum (chloroform): 2924m, 2198s, 1653s, 1605m, 1592m, 1486s, 1458s, 1381s, 1355m, 1348m, 1337m-sh, 1318m, 1285m, 1272m, 1143w, 1062m, 1021w, 951w, 899w. *Anal.* Calcd. for $C_{23}H_{30}O_2N_2Br$: C, 59.98; H, 6.58; N, 9.13. Found: C, 59.35, 59.98; H, 6.67, 6.28; N, 8.55, 9.77.

In a subsequent preparation the aspidospermine hydrobromide was removed by filtration through a short alumina column with chloroform as solvent and the bromocyanamide was crystallized from chloroform–ether; it had the m.p. 187–189°.

Ethanolysis of Bromocyanoaspidospermine.—The bromocyanoaspidospermine (22.5 mg.) in 3 ml. of ethanol containing 0.15 ml. of water was refluxed for two hours. The solution was evaporated to dryness under nitrogen. The residue was made basic with 2 *N* sodium hydroxide, extracted with benzene and the benzene solution was extracted with aqueous acid. When the acidic solution was basified with 2 *N* sodium hydroxide crystallization occurred; 6.1 mg. (35%) of aspidospermine, m.p. 208°, was obtained.

Ethanolysis of Bromocyanoaspidospermine. Kinetic Run.—Bromocyanoaspidospermine was dissolved in 80% aqueous ethanol in a sealed tube at a concentration of 0.0234 g./ml.; this was placed in refluxing acetone (58°). At the end of reaction time, the tube was cooled in ice to quench the reaction. The contents were diluted to 4 ml. with 80% aqueous ethanol. Dextrin (*ca.* 15 mg.) was added together with a few drops of tetrabromofluorescein indicator and the mixture titrated against 0.0106 *N* silver nitrate solution. Two values of the first-order rate constant were determined, *viz.*, $k_1 = 6.7 \times 10^{-6}$ and $k_1 = 7.2 \times 10^{-6}$ sec.$^{-1}$ after reaction times of 21 and 26 hours, respectively.

N_a-Benzoyldeacetylbromocyanoaspidospermine.—N_a-Benzoyldeacetylaspidospermine,[4b] m.p. 185–187° (189.3 mg.), was refluxed in chloroform (5 ml.) with 266 mg. of cyanogen bromide. After 26 hr. the solvent was removed and the yellow residue was chromatographed on acidic alumina with benzene as eluent. The main fraction amounted to 209 mg. from which by crystallization from ethyl acetate 136.4 mg. of material with the m.p. 155–160° was obtained. For analysis this was recrystallized three times from ethyl acetate when it had the m.p. 166.5–168°; infrared spectrum (chloroform): 2907s, 2208s, 1953w, 1905w, 1812w, 1658m-sh, 1639vs, 1629vs, 1613m-sh, 1590m, 1580m, 1488s, 1458s, 1441m-sh, 1381s, 1362m-sh, 1333m, 1277m, 1143s, 1109m, 1093m, 1064s, 1047m-sh, 1019m, 1002w-sh, 982w, 952w, 913w, 895m, 870w, 859w, 844w. *Anal.* Calcd. for $C_{28}H_{32}O_2N_3Br$: C, 64.36; H, 6.18; N, 8.04. Found: C, 64.49; H, 6.25; N, 7.89.

Aspidospermine Cyanamide: Zinc Dust Debromination of the Bromocyanamide.—Bromocyanoaspidospermine (135 mg.) in methanol (8 ml.) was heated under reflux with zinc dust (1 g.) and ammonium chloride (10 mg.) for 10 hours. The zinc was separated and washed with methanol and the combined filtrate evaporated. The residue was treated with water and then extracted with chloroform. The chloro-

form extract was washed, dried, and evaporated to give 129 mg. of crude product. Chromatography on acidic alumina with chloroform as eluent gave a main fraction yielding crystals of m.p. 174° (187–188° after drying) from ethanol. Recrystallization from benzene–ether gave product with m.p. 176°, but two more recrystallizations from ethanol raised this to 188°; ultraviolet spectrum (methanol): λ_{max} 217 mμ (34,800), 257 mμ (12,400), plateau 282 mμ (4000); infrared spectrum (chloroform): 2907s, 2198s, 1656s, 1605m, 1590m, 1484s, 1456s, 1379s, 1350m, 1316m, 1269s, 1143w, 1117w, 1087w, 1066m, 1047m, 967w, 945w, 897w, 860w. *Anal.* Calcd. for $C_{23}H_{31}O_2N_3$: C, 72.40; H, 8.19; N, 11.01; 2 C-Me, 7.89; 3 C-Me, 11.82. Found: C, 71.82; H, 8.41; N, 11.27; C-Me, 10.35, 10.3 (distilled sample).

WALTHAM 54, MASS.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Study of Oxazolidine Ring Isomerization in Models of the Diterpenoid Alkaloids[1]

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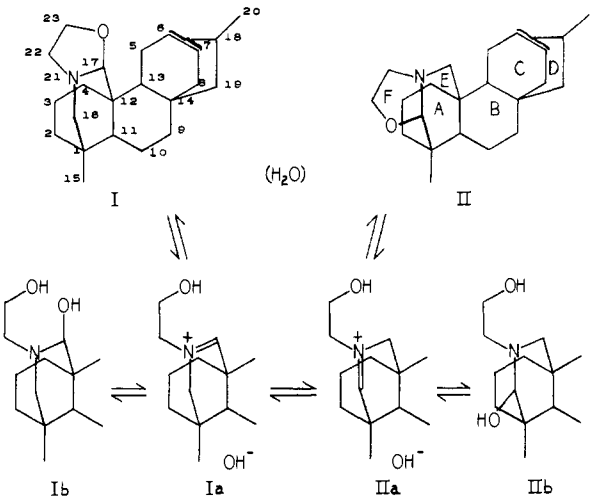
A tricyclic oxazolidine model of the A,E,F-ring system of the hexacyclic diterpenoid alkaloids has been constructed, namely, 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]dodecane (III), in which there is no steric driving force to rearrangement of the oxazolidine ring. Isomerization of this model, which was found to require more strenuous conditions than the alkaloids (veatchine, atisine, cuauchichicine and garryfoline), was followed by means of deuterium incorporation (in deuterated solvents) and by loss of optical activity (using the resolved model). In another model system, of the arylaralkyloxazolidine type, in which there was no steric differentiation between the two α_N-carbons but in which the protons on these carbons were relatively more acidic than in the diterpenoid alkaloids and in the tricyclic oxazolidine, no isomerization occurred under the mild conditions which lead to the formation of the "iso" alkaloids. The original postulates of Wiesner relating to the basicity and isomerization of the diterpenoid alkaloids are supported by our findings. Incidental to these studies, we have found novelty of method in oxazolidine ring formation by means of mercuric acetate, and we have examined, in preliminary manner, the ring closure and ring opening of several oxazolinium compounds.

The alkaloids veatchine[5–10] (pK_a' 11.5),[11] atisine[10,12–20] (pK_a' 12.2),[11] cuauchichicine[21,22] (pK_a' 11.15) and garryfoline[21–23] (pK_a' 11.8) have in common the hexacyclic ring system I and differ only in the points of attachment of ring D and in the substituents on ring D. These alkaloids are readily isomerized, respectively, to garryine (pK_a' 8.7),[5] isoatisine (pK_a' 10.0[13] or 10.35[19]), isocuauchichicine (pK_a' 8.1)[22] and isogarryfoline (pK_a' 8.6),[22,23] represented by the isomeric oxazolidine II.



The conditions used for the isomerization are refluxing methanol (24 hours)[22,24] or refluxing 5% methanolic potassium hydroxide.[6,10] The greater basicity of the normal alkaloids compared with the "iso" alkaloids has been ascribed by Wiesner and Edwards,[10] in the former, to the higher proportion of the ternary iminium form Ia (quaternary Schiff base form) present in a possible equilibrium between the oxazolidine, ternary iminium form and pseudo base (I⇄Ia⇄Ib), and in the latter, to the higher proportion (in II⇄IIa⇄IIb) of the oxazolidine and pseudo base forms. The fundamental reason for the preponderance of form Ia in solution and for the isomerization within each alkaloid pair, proceeding through the ternary iminium form by prototropy (Ia→IIa), has been recognized as the steric inter-

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(2) Monsanto Chemical Co. Fellow, 1956–1957; Ph.D. thesis, 1957.

(3) National Science Foundation Fellow, 1954–1955.

(4) Standard Oil Foundation Inc. (Indiana) Fellow, 1955–1956; Ph.D. thesis, 1956.

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