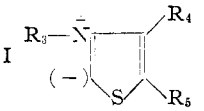
loss of a band at 11.0μ which can be assigned to the out-of-plane bending of the H at C-2.[5] In addition, both substances are free of D_2O (no band at 4.0μ). Thiamine chloride hydrochloride itself incorporates 5.2 atoms of deuterium (including the OH and NH_3^+ groups), and also shows the new band at 4.5μ and the loss of a band at 11μ.

Confirmation of the conclusion that it is the hydrogen at C-2 which exchanges is found in nuclear magnetic resonance studies[6] on (II) in D_2O as solvent. The compound initially shows two small equal peaks, at -108 and -47 cycles/sec., and a larger pair at $+66$ and $+114$ cycles/sec. (Varian V-4012A magnet, 7050 gauss field, 30 megacycles/sec. probe; frequencies referred to benzene capillary and increasing field). These are assigned to the groups at C-2, C-5, N-3, and C-4, respectively. On standing, the peak at -108 cycles/sec. diminishes and disappears because of exchange with the solvent. *The half time for this disappearance is of the order of 20 minutes at 28°;* more accurate studies are in progress.

Thus the hydrogen at C-2 of thiazolium salts exchanges with D_2O more rapidly than almost any other "active" carbon-bound hydrogen so far reported,[7] and this is especially striking since its activity apparently is derived merely from attachment to a doubly-bonded carbon and proximity to two electronegative atoms. Such factors are, of



course, like the ones which stabilize cyanide ion, with its triple bond, but it is apparent that in suitable cases even a double bond is sufficient.[8]

(6) Performed by P. Corio and A. Okaya of this department.

(7) Most such exchanges require base or acid in order to proceed at an observable rate. As one example, it is reported that acetylene does not exchange with neutral D_2O after 36 hours (L. H. Reyerson and S. Yuster, THIS JOURNAL, **56**, 1426 (1934)).

(8) It seems that geometrical considerations rule out the possibility that sulfur assists ionization by valence expansion, as this would require a bent allenic carbon at C-2.

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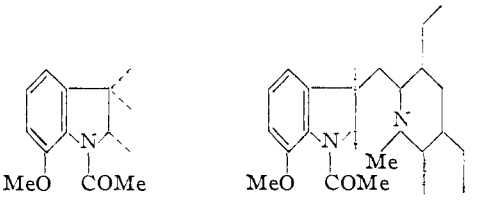
RECEIVED JANUARY 30, 1957

THE STRUCTURE OF ASPIDOSPERMINE

Sir:

Contrary to published reports, the alkaloid aspidospermine,[1] $C_{22}H_{30}O_2N_2$, contains an N-methyl grouping; this is shown by the presence of an intense singlet peak at 1164 cycles[2] in the nuclear magnetic resonance spectra of aspidospermine and of deacetylaspidospermine, and by a direct Herzig–Meyer determination upon aspidosine (calcd. for one N-methyl: 5.04; found: 4.72). Aspidospermine had been shown[1d] to contain the 7-methoxy-1-acetylindoline system (I), to give 3,5-diethylpyridine and, presumably, 3-ethylindole and/or skatole, upon zinc dust distillation[1c] and to contain one additional C-methyl grouping.[1b] The NMR spectra strongly suggest the presence of three aminomethine hydrogen atoms >CHN– and the absence of any methylene groups adjacent to nitrogen[3]; the latter conclusion is consistent with our failure to prepare any corresponding lactam in oxidation experiments. In consideration of the certain relationship to tryptamine we propose the part-structure (II) and from the evidence for the lack of additional unsaturation we note that the two C—C bonds are missing in II; one bond must



I II

join the alpha carbon of the piperidine ring to either the *alpha* or *beta* indolic positions.[4]

The von Braun degradation with aspidospermine leads to a bromocyanamide, m.p. 178° (calcd. for $C_{23}H_{30}O_2N_3Br$: C, 59.98; H, 6.57; N, 9.13; found: C, 59.35, 59.98; H, 6.67, 6.28; N, 8.55, 9.77) and not to loss of methyl bromide or to any other cyanamide; the bromocyanamide is converted to aspidospermine merely by reflux with hot aqueous ethanol or to deacetylaspidospermine by reflux with dilute acid. Clearly N_b is bonded to some center which can undergo displacement with extraordinary ease.[5] Zinc dust in methanolic ammonium chloride gave a cyanamide, m.p. 188° (calcd. for $C_{23}H_{31}O_2N_3$: N, 11.01, found:

(1) (a) A. J. Ewins, *J. Chem. Soc.*, **105**, 2738 (1914); (b) E. Schlittler and M. Rottenburg, *Helv. Chim. Acta*, **31**, 446 (1948); (c) B. Witkop, THIS JOURNAL, **70**, 3712 (1948); (d) B. Witkop and J. B. Patrick, *ibid.*, **76**, 5603 (1954).

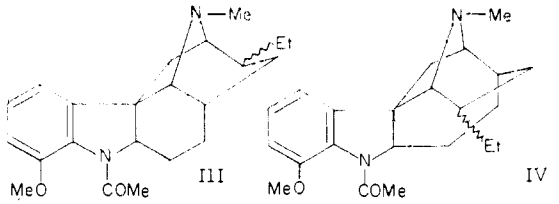
(2) At 40.01 mc./sec. on an arbitrary scale wherein the toluene aromatic proton resonance peak is assigned a value of 1000 cycles and the toluene methyl proton peak assigned 1197 cycles. The proton resonance peak of water on this scale is at 1067 cycles. Spectra were examined in carbon tetrachloride or chloroform solution with an internal toluene reference capillary on a Varian Associates High Resolution Nuclear Magnetic Resonance Spectrometer with Superstabilizer.

(3) In our experience with NMR spectra of a number of compounds containing —CH_2—N< groupings taken in chloroform or carbon tetrachloride solution resonance fell within the range 1115–1150 cycles, usually within the range 1120–1140 cycles. While the NMR curve for aspidospermine showed a weak, broad peak at 1127 cycles, its integrated intensity corresponded to no more than one proton, so that it cannot represent a methylene group. A peak at 1097 cycles corresponding to two protons in area is ascribed to two tertiary hydrogens adjacent to nitrogen and another peak at 1086 cycles is assigned to a single tertiary hydrogen next to the acetylated N_a. Other features were: aromatic protons, 980; methoxyl, 1100; acetyl C-methyl, 1168; ethyl C-methyl, 1227 and miscellaneous methylene and methine protons, 1127–1210 cycles.

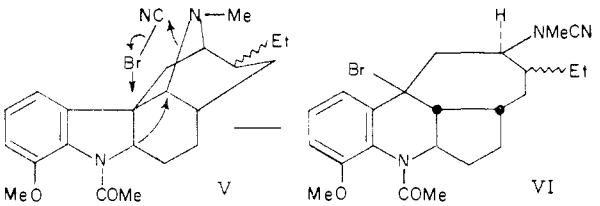
(4) We reject an eserine-like structure: (i) because of the difficulty in rationalization of formation of 3,5-diethylpyridine (ref. 1c), (ii) because aspidospermine methiodide, m.p. 268–272° (calcd. for $C_{23}H_{33}N_2O_2I$: C, 55.63; H, 6.70; N, 5.64; found: C, 55.14; H, 6.84, N, 5.63) gives upon acid hydrolysis a deacetyl methiodide which shows no tendency to revert to the expected indolenine-tertiary amine with alkali and is stable to sodium borohydride, (iii) because although deacetylaspidospermine is slowly degraded by lithium aluminum hydride at higher temperatures the product still contains a tertiary N_b and (iv) the change in pK at N_b upon acetylation at N_a is negligible (ref. 1d).

(5) The methiodide, in contrast, gave upon Hofmann degradation merely a mixture of deacetylaspidospermine and its N_a-methyl derivative substantially identical to that produced in a lithium aluminum hydride reduction of vallesine.

N, 11.27) in which hydrogen replaces bromine; there is no evidence of unsaturation and there is no NH band in the infrared spectrum of the debrominated substance. Structures where the corresponding bromocyanamide contains the grouping Br—CH—CH—N—$COCH_3$ should have allowed β-elimination rather than replacement at this stage; moreover, none of these provides a satisfactory explanation for the course of the von Braun reaction or its easy reversal; we conclude that the piperidine ring must be joined to the beta indolic position. The two possibilities are III and IV



Although we know of no experimental evidence as yet conclusively eliminating either of these, the structure III is preferred for biogenetic reasons.[6] On the basis of III the abnormal von Braun degradation is interpreted in terms of a rearrangement transition state (V) meeting eminently well all stereoelectronic requirements. The bromocyanamide, then formulated as VI, in fact does not appear to contain the CHBr grouping, for no new peak is evident in the region (*ca.* 1090 cycles, as in isopropyl bromide) expected in its NMR spectrum.



Acknowledgment.—We wish to thank Dr. E. Schlittler for a generous gift of aspidospermine, Dr. Aksel Bothner-By for his assistance with the NMR spectrometer and Dr. S. M. Nagy for the analyses. The work is supported by grants from Research Corporation and from the National Institutes of Health.

(6) The expression (III) is sufficiently similar in relevant detail to that proposed by Openshaw (*cf.* "Structural Relations of Natural Products," by R. Robinson, Oxford University Press, Oxford, 1955, p. 117) and by Witkop (ref. 1d) so that Openshaw's biogenesis could be adapted to fit. A simpler, and perhaps preferable, scheme pictures the biogenetic derivation of III with appropriate Mannich/aldol condensations of precursors formed from tryptophan and phenylalanine, where the phenylalanine suffers typical ring cleavage, but between its *ortho* and *meta* positions, to give a *butylidenesuccindialdehyde equivalent.*

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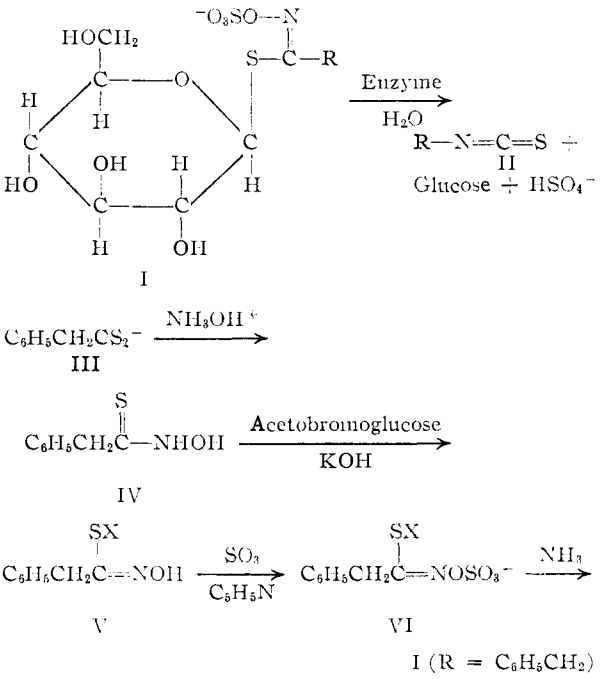
RECEIVED FEBRUARY 5, 1957

FIRST SYNTHESIS OF A MUSTARD OIL GLUCOSIDE; THE ENZYMATIC LOSSEN REARRANGEMENT

Sir:

We have proved analytically that sinigrin is the potassium salt of I (R = H_2C=$CHCH_2$)[1] and rearranges during enzymatic cleavage to allyl isothiocyanate (II, R = H_2C=$CHCH_2$). All the two dozen or more known natural isothiocyanates and thioöxazolidones are believed to arise similarly from precursors of type I, possibly varying in the carbohydrate portion. We have now synthesized the glucotropaeolate ion I (R = $C_6H_5CH_2$), a natural source of benzyl isothiocyanate, and confirmed the new structure of the class.

Ethereal magnesium dithiophenylacetate (III), prepared[2] by addition of benzylmagnesium chloride to carbon disulfide, was treated[3] with aqueous hydroxylamine hydrochloride at 0° to furnish, in 33% over-all yield from benzyl chloride, **phenylacetothiohydroxamic acid**[4] (IV), m.p. 73–74.2°, $\lambda_{max.}$ 267 mμ in methanol (log $\epsilon_{max.}$ *ca.* 3.9).[5] After IV had reacted with 0.9 equivalent each of potassium hydroxide and acetobromoglucose in 1:3 methanol–acetone during 6 hours at room temperature,[3,6] there was obtained, in 47% yield from acetobromoglucose, **S-β-D-1-(tetraacetylglucopyranosyl)-phenylacetothiohydroximic acid**[4] (V), m.p. 163.8–164.1°, $[\alpha]^{32}D$ −9.6° (chloroform), without accessible ultraviolet absorption maximum (in methanol log



(1) M. G. Ettlinger and A. J. Lundeen, THIS JOURNAL, **78**, 4172 (1956). Dr. J. Waser and Mr. W. H. Watson, Jr., are studying sinigrin by X-ray diffraction.

(2) A. Kjaer, *Acta Chem. Scand.*, **6**, 327 (1952).

(3) *Cf.* L. Cambi, *Atti reale accad. Lincei, Rend. classe sci. fis., mat. e nat.*, [5] **18**, I, 687 (1909).

(4) Obtained analytically pure.

(5) The thiohydroxamic acid could be stored below 0°, but decomposed[3] in a few days at 30° and puffed when heated in bulk to *ca.* 100°, giving phenylacetonitrile and sulfur. The substance was tolerably stable in aprotic solvents, but a methanolic solution deposited sulfur quantitatively during 24 hours at room temperature. Solid sodium phenylacetothiohydroxamate kept 10 weeks at room temperature afforded N,N'-dibenzylthiourea in 25% yield by Lossen rearrangement.

(6) *Cf.* C. B. Purves, THIS JOURNAL, **51**, 3619 (1929).