also by phenol, through protonation of the nitrogen atom. Although a small amount of II has been shown to form in dimethyl sulfoxide solutions of mitomycin B on several months' standing, the reduction–reoxidation remains the only practical method of preparation.

Bioassays[14] of II *in vitro* showed that it was a potent antibiotic with as broad a spectrum of antibacterial activity as the mitomycins themselves. In mice the compound was active both by oral and subcutaneous routes against infections of *Staphylococcus aureus* (var. Smith) and *Streptococcus pyogenes* C-203; in the latter infection the ED_{50} (subcutaneous) is 0.5 mg./kg., equivalent to the parent antibiotic and 128 times as active as tetracycline under the same conditions.

The oral activity of the mitomycins is surprising in view of their susceptibility to acid degradation. The fact that II is orally active suggests that the biologically active species is really II itself (or its hydroquinone)[15] or a related indolohydroquinone. Inconsistent with this hypothesis, however, is the fact that IV does not show the same high activity as II or III.

(14) We are indebted to A. C. Dornbush and the late M. Hauck for *in vitro* testing, and to G. Redin and E. Ewald for *in vivo* testing.

(15) The recent evidence of Schwartz, *et al.*,[16] that a biological reduction may serve to activate mitomycin C *in vivo* reinforces this concept, inasmuch as II is formed *via* the hydroquinone V. The hydroquinone of II would seem to fit all presently known requirements for the "active species."

(16) H. S. Schwartz, J. E. Sodergren, and F. S. Philips, *Science*, **142**, 1181 (1963). NOTE ADDED IN PROOF.—Prof. W. Szybalski has kindly informed us in advance of p iblication (Iyer and Szybalski, *ibid.*, in press) that he postulates, on the basis of biochemical evidence, substantially the same mechanism of action for the mitomycins as the one we propose here.

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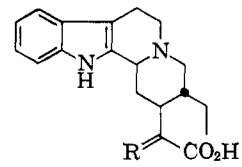
A Novel C–D Ring Cleavage of Dihydrocorynantheine Derivatives[1]

Sir:

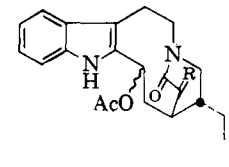
Indole alkaloids bearing an oxygen function at C-3 have been the subjects of several recent investigations. Representatives of this new class of alkaloids include burnamicine,[2] echitamine,[3] and vobasine.[4] We wish to report a novel C–D ring cleavage of dihydrocorynantheine derivatives which simultaneously introduces an acetoxy group at C-3. This reaction may provide a useful synthetic entry to this new group of indole alkaloids oxygenated at C-3.

The action of hot acetic anhydride containing sodium acetate converts the dihydrocorynantheine derivatives Ia and Ib to the corresponding acetoxylactams, IIa, m.p. 176–177°, and IIb, m.p. 194–195°, obtained in approximately 50% yield.

The structures IIa and IIb are supported by the following observations. The ultraviolet spectrum of

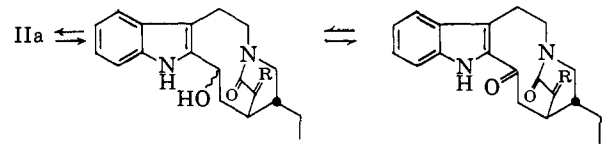


Ia, R = CH_3OCH
b, R = H_2



IIa, R = CH_3OCH
b, R = H_2

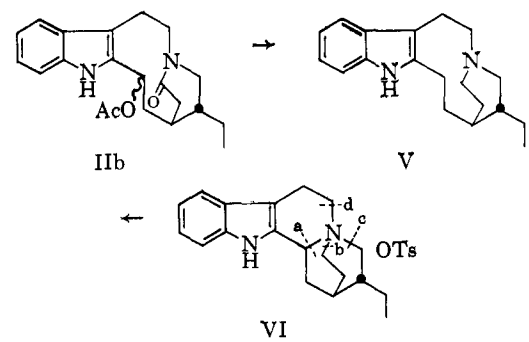
IIa is virtually identical with that of dihydrocorynantheine, whereas IIb shows normal indole absorption. The infrared spectrum of IIa shows absorption at 1720, 1665, and 1608 cm.$^{-1}$ whereas IIb absorbs at 1720 and 1640 cm.$^{-1}$. The n.m.r. spectra of both IIa and IIb indicate an acetate group. Saponification of IIa yielded an alcohol, III, m.p. 149–150°, which was acetylated with acetic acid and sodium acetate to regenerate the acetate IIa. Oxidation of III with manganese dioxide gave in 37% yield the ketone IV, m.p. 240° dec. The ketone IV reverted to the alcohol, III, obtained in 96% yield, by the action of sodium borohydride.



III, R = CH_3OCH IV, R = CH_3OCH

The ultraviolet spectrum of the ketone shows 2-acylindole absorption combined with the α-methoxymethylenecarbonyl chromophore: λ_{max}^{EtOH} 313 mμ (ε 12,700), 238 (25,400), and 217 (26,900). The infrared spectrum shows absorption at 1670, 1640, and 1610 cm.$^{-1}$. Similarly, compound IIb yields a noncrystalline alcohol upon saponification and the alcohol affords a 2-acylindole upon oxidation with manganese dioxide.

Compelling structural evidence was obtained by lithium aluminum hydride reduction of the acetoxylactam, IIb. The product obtained from the acetoxylactam, IIb, by the action of lithium aluminum hydride in refluxing tetrahydrofuran is the oxygen-free base, V, m.p. 178.5–179°. The same compound is obtained from the lithium aluminum hydride reduction of the known quaternary ammonium salt VI.[5] The two samples showed identical infrared spectra, melting points, and mixture melting points.



IIb V VI

In principle, lithium aluminum hydride reduction of the quaternary ammonium salt VI could have broken any one of the four bonds indicated by the dotted lines a, b, c, and d. Cleavage of bond b would have pro-

(1) The authors gratefully acknowledge financial support from the National Science Foundation (Grant GP-252) and the National Institutes of Health (Grant NB 03232-03).

(2) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **85**, 1203 (1963).

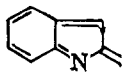
(3) J. A. Hamilton, T. M. Hamor, H. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 5061 (1962).

(4) U. Renner, D. A. Prins, A. L. Burlingame, and K. Bieman, *Helv. Chim. Acta*, **46**, 2186 (1963); M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, and G. O. Dudek, *Tetrahedron Letters*, **No. 2**, 53 (1963).

(5) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959).

duced dihydrocorynantheane, and this possibility is ruled out since the base V differs from an authentic sample of dihydrocorynantheane.[6] Of the three remaining possibilities, rupture of bonds c or d would produce a new C-methyl group while cleavage of bond a is the only pathway that does not result in a new C-methyl group. A clear decision was made from the n.m.r. spectrum of the base V. The spectrum (deuteriochloroform) shows a triplet at τ 9.05 corresponding to three protons using the aromatic proton absorption (four protons) as an internal standard. The presence of two methyl groups in dihydrocorynantheane was readily apparent from its n.m.r. spectrum.

The cyclization reactions and the lithium aluminum hydride reductions of the acetoxylactam IIb, and the quaternary ammonium salt VI, may be examples of elimination–addition reactions involving intermediates of the type shown by structure VII.



VII

It should be pointed out that the conversion of benzylic tertiary amines to the corresponding benzyl esters on treatment with acid anhydrides is a well known reaction[7] and the quinuclidine ring of cinchonamine is cleaved by acetic anhydride to yield an acetylated 2-vinylindole.[8] Intermediates of the type shown by VII are currently under investigation along with the synthetic applications of the ring cleavage reaction.[9]

(6) Prepared by the procedure of M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 588 (1951).

(7) M. Tiffeneau, *ibid.*, [4] **9**, 825 (1911).

(8) R. Goutarel, M. M. Janot, V. Prelog, and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

(9) Satisfactory analytical data were obtained for all new compounds described in this communication.

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RECEIVED FEBRUARY 28, 1964

Sulfines

Sir:

We now report the first examples of a new class of compounds, S-oxides of thioketones, which we designate as "sulfines" (for example fluorenylidene sulfine, **1**).

2 **1**

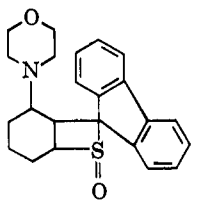
Sulfines, like the S-oxides of thioamides[1] and thioacid chlorides[2] (O=S=C(R)—X, X = NR_2 or Cl) are stable enough to be isolated. In contrast, sulfenes ($R_2C{=}SO_2$) are only proposed as unstable intermediates when nitrogen bases react with alkyl sulfonyl chlorides.[3]

As the route to **1**, sulfur dioxide and 9-lithiofluorene gave the lithium salt of 9-fluorenesulfinic acid, **3**. The unstable sulfinyl chloride **2**, extracted with methylene chloride from the reaction mixture of **3** and thionyl chloride, reacted with triethylamine in ether at room temperature. Triethylamine hydrochloride precipitated immediately and was separated by filtration. The filtrate was concentrated to give fluorenylidene sulfine (**1**, crude yield 75%) as orange crystals, m.p. 103–108°, recrystallized from benzene–hexane, m.p. 111.0–111.8°. *Anal.* Calcd. for $C_{13}H_8OS$: C, 73.6; H, 3.80; S, 15.1, mol. wt., 212. Found: C, 73.6; H, 4.14; S, 15.1, mol. wt., 264 (freezing point in benzene).

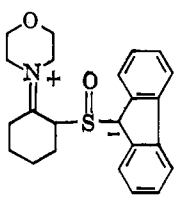
The absence of the 9-hydrogen resonance (in region τ 4.4) in the proton n.m.r. spectrum and the appearance of additional fine structure in the aromatic region[4] confirmed the sulfine structure. The infrared spectrum was extremely simple; in addition to the normal C–H and aromatic absorption bands, strong bands at 1120 and 1019 cm.$^{-1}$ were tentatively assigned to the C=S=O function. A strong absorption at 1087 cm.$^{-1}$ was attributed to the fluorenyl residue since a similar absorption band was found in fluorenone. The ultraviolet spectrum in dioxane was similar to fluorenone but with a hypsochromic shift, λ_{max} in mμ (ϵ): 362 (15,250), 273 (30,000), 265 (26,300), 238 (28,400), 232 (28,400). The orange color was the result of a tail in the visible region.

Compound **1** decomposed slowly on standing at room temperature for several days and rapidly at its melting point, evolving sulfur dioxide. Difluorenylidene, in 48% yield, was extracted from the brown residue; a few per cent of fluorenone was also isolated. Compound **1** was stable at reflux temperature in cyclohexene, benzene, or tetrahydrofuran solutions for several days, but added to a stoichiometric amount of 1-morpholino-1-cyclohexene in tetrahydrofuran to give a white crystalline solid, m.p. 142°. *Anal.* Calcd. for $C_{23}H_{25}NO_2S$: C, 72.8; H, 6.64; N, 3.69; S, 8.45. Found: C, 72.6; H, 6.74; N, 3.62; S, 8.77.

Two structures, **4a** and **4b**, are proposed for this



4a



4b

adduct although several other structures are possible; the polar structure, **4b**, is preferred because of a strong absorption band at 1710 cm.$^{-1}$ in the infrared spectrum.

Aliphatic analogs were also prepared, but were too unstable for isolation or handling at room temperature.[5] For example, isopropyl sulfinyl chloride[6] reacted vigorously with triethylamine in methylene chloride at −20°,

(1) W. Walter and K. D. Bode, *Ann.*, **660**, 74 (1962), and earlier papers of the series cited in this reference.

(2) J. F. King and T. Durst, *Tetrahedron Letters*, 585 (1963).

(3) (a) G. Stork and K. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962); (b) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962); (c) W. E. Truce and J. R. Norell, *J. Am. Chem. Soc.*, **85**, 3231 (1963); (d) J. F. King and T. Durst, *ibid.*, **86**, 287 (1964); (e) W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964).

(4) The CSO group is expected to be bent at an angle of almost 120° like sulfur dioxide. Since the CSO group probably lies in the plane of the fluorene rings, the protons in the two rings experience a different field. *cis–trans* isomers were proposed for the closely related S-oxides of thioacid chlorides.[2]

(5) Reference to an unsuccessful attempt to prepare and trap $CH_2{=}S{=}O$ has been made.[3c] We have similarly found that methanesulfinyl chloride forms a salt with triethylamine and does not lose hydrogen chloride.

(6) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, **22**, 536 (1957); I. B. Douglass and B. S. Farah, *ibid.*, **23**, 330 (1958) [prepared by procedures given in *Org. Syn.*, **40**, 62 (1960)].