more precisely, the structural requirements at C-4 for antibiotic activity.

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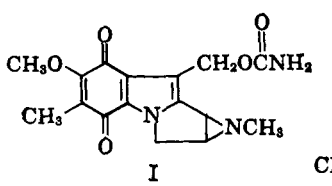
RECEIVED JULY 1, 1964

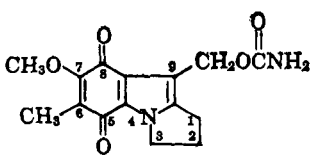
The Mitomycin Antibiotics. Synthetic Studies. II.[1] The Synthesis of 7-Methoxymitosene, an Antibacterial Agent

Sir:

During their research on the structure of the mitomycin class of antibiotics, Patrick, Webb, and coworkers[2] isolated an aziridinopyrrolo[1,2-*a*]indoloquinone which was shown to have structure I and was found to be an orally active antibacterial agent of considerable interest. In the present communication we describe the preparation and antibacterial properties of the related 7-methoxymitosene[3] (II, 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione carbamate).



I



II

4-Nitro-2,5-xylenol[5] was converted *via* the methyl ether [m.p. 91–92°, λ_{max} 312 mμ (ε 7600)][6] by the Reissert technique[7] into 5-methoxy-6-methyl-2-indolecarboxylic acid (III) [m.p. 240–241° (gas), λ_{max} 294 mμ (ε 18,400)]. On treatment with potassium *t*-butoxide and methyl acrylate, the methyl ester of III [m.p. 149–150°, λ_{max} 298 mμ (ε 19,900)] furnished the β-ketoester IV [m.p. 180–182°, λ_{max} 336 mμ (ε 21,800)]. Acid-catalyzed decarbomethoxylation of IV then gave the tricyclic ketone V [m.p. 213–215°, λ_{max} 331 mμ (ε 21,200)].[8] Wolff–Kishner reduction of V gave pyrrolo[1,2-*a*]indole (VI) [m.p. 116–118°, λ_{max} 279 (ε 7930), 295 (ε 6930), and 308 mμ (ε 4530)] which was formylated[9] (Villsmeier–Haack) giving aldehyde VII [m.p. 187–189°, λ_{max} 256 (ε 18,200), 282 (ε 16,800) and 309 mμ (ε 13,500)].

This aldehyde was the key intermediate in the synthesis of II, for in addition to possessing the fundamental pyrrolo[1,2-*a*]indole ring system, the 7-methoxy function represented an entry for the elaboration of the 7-methoxy-5,8-pyrrolo[1,2-*a*]indoloquinone system[1] and the conversion of a β-indolecarboxaldehyde into the corresponding carbinol carbamate had already been demonstrated.[10]

Cleavage of the methoxy group in VII with aluminum chloride in refluxing xylene[11] gave the phenolic aldehyde VIII [m.p. >300°, λ_{max} 256 (ε 15,910), 283 (ε 14,910), and 311 mμ (ε 13,000)] which on oxidation with potassium nitrosodisulfonate[12] afforded the *o*-quinone IX [m.p. 240–248° dec., λ_{max} 225 (ε 86,700), 280 (ε 22,500), and 345 mμ (ε 11,400)]. Thiele acetoxylation of this quinone furnished the triacetate X [m.p. 264–265°, λ_{max} 218 (ε 28,000), 248 (ε 18,300), and 305 mμ (ε 11,200)], which on alkaline hydrolysis followed by air oxidation afforded the 7-hydroxy-5,8-pyrrolo[1,2-*a*]indoloquinone (XI) [m.p. 219–221°; λ_{max} 219 (ε 21,300), 299 (ε 14,450), and 330 mμ (ε 8100); $\lambda_{max}^{0.1\,N\,NaOH}$ 236 (ε 23,800), 299 (shoulder, ε 13,000), and 325 mμ (ε 13,700)]. Methylation (diazomethane) of XI gave methoxyquinone XII [m.p. 224–227°, λ_{max} 216 (ε 25,000), 243 (ε 14,900), 272 (ε 14,250), 289 (ε 13,870), and 332 mμ (ε 7120)].

Elaboration of the carbamate side chain from the quinone aldehyde XII was achieved in the following manner. Reduction of XII with sodium borohydride[13] followed by oxidation of the intermediate hydroquinonecarbinol with acidic ferric chloride[14] afforded the quinonecarbinol XIII [m.p. 180–182°, λ_{max} 230 (ε 17,700), 287 (ε 13,600), 350 (ε 3340), and 460 mμ (ε 1990)].[15] Acylation of this carbinol in pyridine with phenyl chloroformate gave the phenyl carbonate XIV [m.p. 137.5–138.0°, λ_{max} 230 (ε 19,050), 285 (ε 13,900), 345 (ε 3800), and 450 mμ (ε 950)] which on ammonolysis[16] was converted into 7-methoxymitosene (II) [m.p. 206–207°, λ_{max} 230 (ε 19,200), 287 (ε 14,600), 345 (ε 3870), and 460 mμ (ε 1390)].

(1) For paper I see W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963).

(2) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *J. Am. Chem. Soc.*, **86**, 1889 (1964).

(3) Mitosene is the trivial name that has been proposed[4] for the structure 2,3-dihydro-9-hydroxymethyl-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione carbamate.

(4) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962).

(5) K. Auwers and F. Michaelis, *Ber.*, **47**, 1289 (1914).

(6) All compounds, except ketone V, gave satisfactory analyses; infrared spectra were in accord with the assigned structures. Ultraviolet spectra are for methanol solutions, except where otherwise noted.

(7) P. L. Julian, E. W. Meyer, and H. C. Printy in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 18.

(8) For the p.m.r. spectrum of V, see spectrum No. 299 in "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(9) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Am. Chem. Soc.*, in press.

(10) The essential requirement for success in this conversion is the presence of an appropriate electronegative substituent which affords stabilization of the 3-indolylmethanol system and its derivatives (see ref. 15).

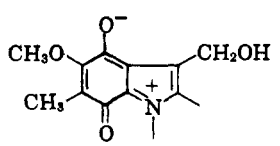
(11) The stability of the 9-formyl group to these cleavage conditions had been demonstrated previously with a model system by Dr. Remers.

(12) H. Teuber and G. Thaler, *Ber.*, **91**, 2253 (1958), and previous papers.

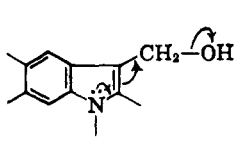
(13) *Cf.* E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959), and references cited therein.

(14) Earlier attempts to regenerate the quinone from this intermediate by air oxidation were not successful (*cf.* the conversion with air of the 9-aldehyde X to XI). We interpret this difference in behavior toward oxygen to be the result of the reduced nucleophilicity of C-9 in the 9-aldehyde series. [The facile reaction of 3-alkylindoles with oxygen is well known (B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951), and previous papers)].

(15) An attempt to develop the 9-carbinol carbamate grouping from the aldehyde group in VII prior to quinone elaboration failed in the preparation of the intermediate alcohol because of diindolylmethane formation (*cf* ref. 10 and 13). We interpret the successful preparation of XIII to be the result of significant intervention of structures such as i in the resonance hybrid of the pyrrolo[1,2-*a*]indoloquinone system, which mitigates against the normal electronic effects of the indole system (ii, arrows) present in the carbinol derived from VII.

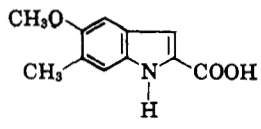


i

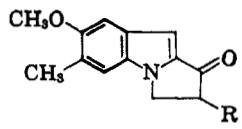


ii

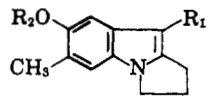
(16) *Cf.* W. M. McLamore, S. Y. P'An, and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).



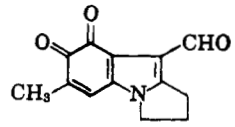
III



IV, R = $COOCH_3$
V, R = H

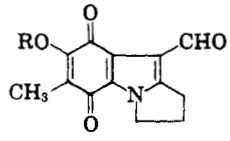


VI, R_1 = H, R_2 = CH_3
VII, R_1 = CHO, R_2 = CH_3
VIII, R_1 = CHO, R_2 = H

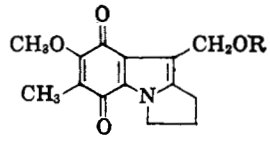


IX

X, R_1 = CHO, R_2 = $COCH_3$, $OOCCH_3$ at C-5 and C-8



XI, R = H
XII, R = CH_3



XIII, R = H
XIV, R = $COOC_6H_5$

7-Methoxymitosene (II) has important antibacterial activity *in vitro* and in mice. *In vitro* this compound shows marked activity against a variety of Gram-positive organisms, including representative tetracycline- and penicillin-resistant species (Table I). However, it has only marginal activity against Gram-negative organisms.

TABLE I

Organism	Minimum inhibitory concn., γ/ml. 7-Methoxymitosene	Tetracycline·HCl
Mycobacterium smegmatis, ATCC 607	62	
Mycobacterium ranae	31	2
Staphylococcus aureus, ATCC 6548P	8	
Staphylococcus aureus, ATCC 6538P	4	4
Staphylococcus aureus, 69	2	>250
Streptococcus faecalis, ATCC 8043	8	4
Streptococcus pyrogenes, C203	1	1
Streptococcus sp., nonhemolytic, 11	4	250
Streptococcus sp., β-hemolytic, 80	4	250
Bacillus subtilis, ATCC 6633	0.5	1
Bacillus cereus, ATCC 10702	0.5	1
Klebsiella pneumoniae, ATCC 10031	4	125
Pseudomonas aeruginosa, ATCC 10145	>250	31
Proteus vulgaris, ATCC 9484	31	15
Escherichia coli, ATCC 9637	>250	15
Escherichia coli, Lederle 22	31	2
Salmonella gallinarum, Lederle 604	>250	15

When administered orally to mice infected with *Staphylococcus aureus* var. Smith, 7-methoxymitosene is about one-third as active as tetracycline hydrochloride. However, despite its marked *in vitro* activity against a tetracycline-resistant *Staphylococcus* species and *Streptococcus pyrogenes* C-203, 7-methoxymitosene is not effective *in vivo* against these organisms. This behavior against the last organism is in direct contrast to that exhibited by 7-methoxy-1,2-(N-methylaziridino)mitosene (I).[2b,17]

(17) Helpful discussions with Dr. W. A. Remers are acknowledged, as are the contributions of the individuals noted in the following paper.

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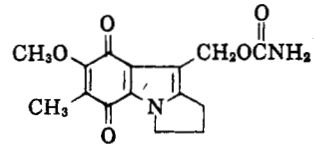
RECEIVED JUNE 20, 1964

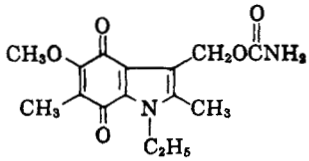
The Mitomycin Antibiotics. Synthetic Studies. III.[1] Related Indoloquinones, Active Antibacterial Agents

Sir:

In an accompanying communication[1] we report the preparation of 7-methoxymitosene (I).[2] In view of the interesting antibacterial properties of this compound, we have sought to define further the minimum structural requirements for antibacterial action in this series and here report the synthesis and antibacterial activity of the related 1,2-dialkylindoloquinone II. In addition, we describe the preparation of certain analogs of the biologically important II and a new procedure for the preparation of the indoloquinone system present in this class of compounds.



I



II

Condensation[3] of *p*-toluquinone with ethyl β-ethylaminocrotonate [b.p. 116–118° (20 mm.), $n^{25}D$ 1.4941, prepared by reaction[4] of ethylamine with ethyl acetoacetate] afforded the indole ester III [m.p. 196–198°, λ_{max} 218, 245, and 298 mμ (ε 38,600, 14,700, and 12,500)].[5] Decarbethoxylation of this compound in constant-boiling hydrochloric acid solution furnished the 5-hydroxy-1,2,6-trialkylindole (IV) [dimorphic, m.p. 90–92° or 120–122°, λ_{max} 280, 297, and 309 mμ (ε 8500, 7000, and 4730)], which on reaction with methyl sulfate gave the corresponding 5-methoxyindole V [m.p. 56–57°; λ_{max} 217, 278, 297, and 307 mμ (ε 31,700, 8340, 7100, and 4560)]. Formylation of V by the Vilsmeier–Haack technique then afforded the 3-carboxaldehyde VI [m.p. 135–137°, λ_{max} 216, 258, 283, and 310 mμ (ε 35,200, 18,300, 15,100, and 12,500)].

Previous methods for the elaboration of the indoloquinone system characteristic of I and II have proceeded *via* the corresponding *o*-quinone.[1,6,7] Application of this method as previously developed for the synthesis of 7-methoxymitosene (I) afforded a satisfactory route from VI to the 3-hydroxymethyl-*p*-quinone (IX). We have also found that this transformation can be achieved by an abbreviated route dependent upon the nitration of the benzenoid nucleus in a 5-methoxy-3-indolecarboxaldehyde. Thus, nitration of VI with sodium nitrate in sulfuric acid, or, preferably, fuming nitric acid in glacial acetic acid,[8] gave the nitro derivative VII [m.p. 157–158°, λ_{max} 218, 247, and 295 mμ (ε 39,900, 16,200, and 12,100)]. Hydrogenation of VII in the presence of 10% palla-

(1) For paper II see G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877 (1964).

(2) For nomenclature see footnote 3, ref. 1.

(3) C. D. Nenitzescu, *Bull. Soc. Chem. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(4) *Cf.* S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(5) All compounds gave satisfactory elemental analyses, and the assigned structures were supported by infrared and p.m.r. spectra. Ultraviolet spectra were taken in methanol solution.

(6) H. Teuber and G. Thaler, *Ber.*, **91**, 2253 (1958).

(7) W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963).

(8) *Cf.* W. E. Noland and R. D. Rieke, *ibid.*, **27**, 2250 (1962), and references cited therein.