

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

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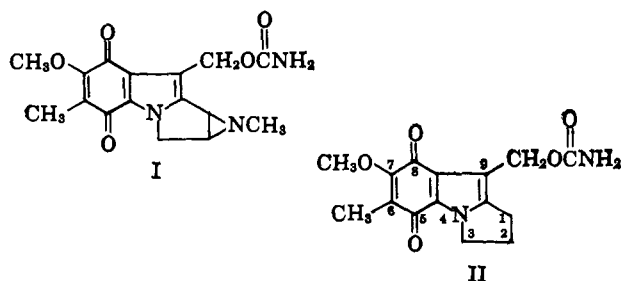
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RECEIVED JULY 1, 1964

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

Sir:

During their research on the structure of the mitomycin class of antibiotics, Patrick, Webb, and co-workers² 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-methoxymitosene³ (II, 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-*a*]indole-5,8-dione carbamate).



4-Nitro-2,5-xyleneol^b was converted *via* the methyl ether [m.p. 91–92°, λ_{\max} 312 m μ (ϵ 7600)]⁸ by the Reissert technique⁷ into 5-methoxy-6-methyl-2-indolecarboxylic acid (III) [m.p. 240–241° (gas), λ_{\max} 294 m μ (ϵ 18,400)]. On treatment with potassium *t*-butoxide and methyl acrylate, the methyl ester of III [m.p. 149–150°, λ_{\max} 298 m μ (ϵ 19,900)] furnished the β -ketoester IV [m.p. 180–182°, λ_{\max} 336 m μ (ϵ 21,800)]. Acid-catalyzed decarbomethoxylation of IV then gave the tricyclic ketone V [m.p. 213–215°, λ_{\max} 331 m μ (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 m μ (ϵ 4530)] which was formylated⁹ (Villsmeier-Haack) giving aldehyde VII [m.p. 187–189°, λ_{\max} 256 (ϵ 18,200), 282 (ϵ 16,800) and 309 m μ (ϵ 13,500)].

(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 proposed⁴ 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.

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 system¹ 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 xylene¹¹ gave the phenolic aldehyde VIII [m.p. >300°, λ_{\max} 256 (ϵ 15,910), 283 (ϵ 14,910), and 311 m μ (ϵ 13,000)] which on oxidation with potassium nitrosodisulfonate¹² afforded the *o*-quinone IX [m.p. 240–248° dec., λ_{\max} 225 (ϵ 86,700), 280 (ϵ 22,500), and 345 m μ (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 m μ (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 m μ (ϵ 8100); $\lambda_{\max}^{0.1N NaOH}$ 236 (ϵ 23,800), 299 (shoulder, ϵ 13,000), and 325 m μ (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 m μ (ϵ 7120)].

Elaboration of the carbamate side chain from the quinone aldehyde XII was achieved in the following manner. Reduction of XII with sodium borohydride¹³ followed by oxidation of the intermediate hydroquinonecarbinol with acidic ferric chloride¹⁴ afforded the quinonecarbinol XIII [m.p. 180–182°, λ_{\max} 230 (ϵ 17,700), 287 (ϵ 13,600), 350 (ϵ 3340), and 460 m μ (ϵ 1990)].¹⁶ 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 m μ (ϵ 950)] which on ammonolysis¹⁶ 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 m μ (ϵ 1390)].

(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).

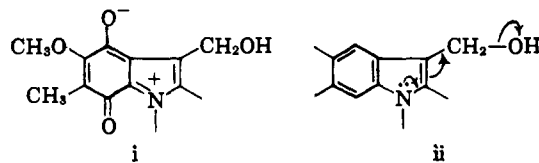
(11) The stability of the 9-formyl group to these cleavage conditions had been demonstrated previously with a model system by Dr. Remers.

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

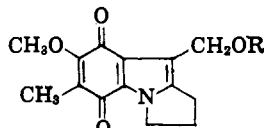
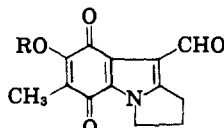
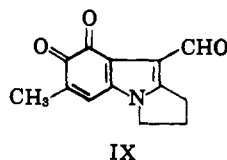
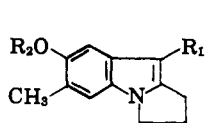
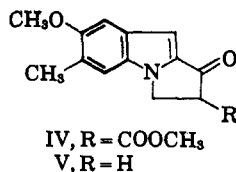
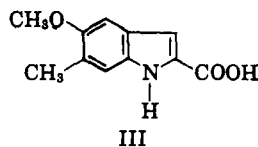
(13) Cf. E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959), and references cited therein.

(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.



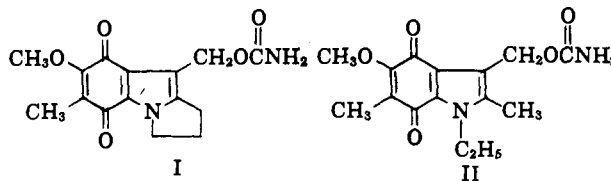
(16) Cf. W. M. McLamore, S. Y. P'An, and A. Bavley, *J. Org. Chem.*, **30**, 1379 (1955).



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

Sir:

In an accompanying communication¹ 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.



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
<i>Mycobacterium smegmatis</i> , ATCC 607	62	
<i>Mycobacterium ranae</i>	31	2
<i>Staphylococcus aureus</i> , ATCC 6548P	8	
<i>Staphylococcus aureus</i> , ATCC 6538P	4	4
<i>Staphylococcus aureus</i> , 69	2	>250
<i>Streptococcus faecalis</i> , ATCC 8043	8	4
<i>Streptococcus pyrogenes</i> , C203	1	1
<i>Streptococcus</i> sp., nonhemolytic, 11	4	250
<i>Streptococcus</i> sp., β -hemolytic, 80	4	250
<i>Bacillus subtilis</i> , ATCC 6633	0.5	1
<i>Bacillus cereus</i> , ATCC 10702	0.5	1
<i>Klebsiella pneumoniae</i> , ATCC 10031	4	125
<i>Pseudomonas aeruginosa</i> , ATCC 10145	>250	31
<i>Proteus vulgaris</i> , ATCC 9484	31	15
<i>Escherichia coli</i> , ATCC 9637	>250	15
<i>Escherichia coli</i> , Lederle 22	31	2
<i>Salmonella gallinarum</i> , 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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Condensation³ of *p*-toluquinone with ethyl β -ethylaminocrotonate [b.p. 116–118° (20 mm.), n_D^{25} 1.4941, prepared by reaction⁴ of ethylamine with ethyl acetoacetate] afforded the indole ester III [m.p. 196–198°, λ_{\max} 218, 245, and 298 $m\mu$ (ϵ 38,600, 14,700, and 12,500)].⁵ Decarboxylation 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 $m\mu$ (ϵ 8500, 7000, and 4730)], which on reaction with methyl sulfite gave the corresponding 5-methoxyindole V [m.p. 56–57°; λ_{\max} 217, 278, 297, and 307 $m\mu$ (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 $m\mu$ (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 $m\mu$ (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. Absir.*, **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.