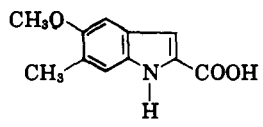
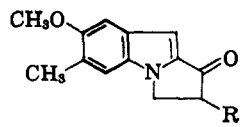
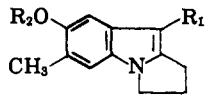


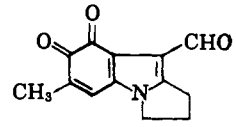
III



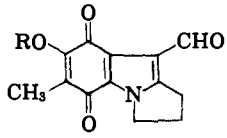
IV, R = $COOCH_3$
V, R = H



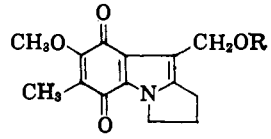
VI, R_1 = H, R_2 = CH_3
VII, R_1 = CHO, R_2 = CH_3
VIII, R_1 = CHO, R_2 = H
X, R_1 = CHO, R_2 = $COCH_3$, $OOCCH_3$ at C-5 and C-8



IX



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.

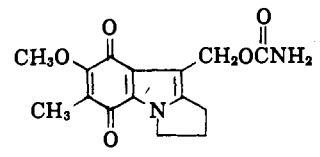
ORGANIC CHEMICAL RESEARCH SECTION GEORGE R. ALLEN, JR.
LEDERLE LABORATORIES DIVISION JOHN F. POLETTO
AMERICAN CYANAMID COMPANY MARTIN J. WEISS
PEARL RIVER, NEW YORK

RECEIVED JUNE 20, 1964

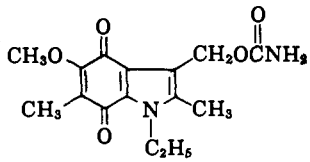
The Mitomycin Antibiotics. Synthetic Studies. III.[1] Related Indoloquinones, Active Antibacterial Agents

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.

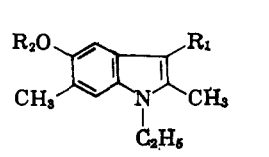
(6) H. Teuber and G. Thaler, *Ber.*, **91**, 2253 (1958).

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

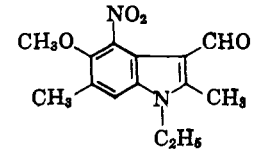
(8) *Cf.* W. E. Noland and R. D. Rieke, *ibid.*, **27**, 2250 (1962), and references cited therein.

dium-on-charcoal catalyst resulted in the uptake of four molar equivalents of gas. Without isolation the presumed 4-amino-3-indolylmethanol (VIII) was treated with potassium nitrosodisulfonate to furnish the desired indoloquinonecarbinol IX [m.p. 85.5–86.5°, λ_{max} 231, 287, 350, and 460 mμ (ε 17,100, 13,900, 3160, and 1300)].[9]

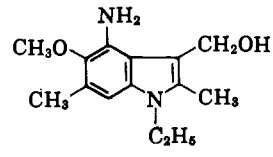
The carbinol IX was converted into the carbamate II [m.p. 202–204°, λ_{max} 231, 286, 345, and 455 mμ (ε 18,400, 13,800, 3520, and 1290)] by ammonolysis of the derived phenylcarbonate X [m.p. 115–117°, λ_{max} 231, 285, 345, and 455 mμ (ε 17,700, 13,800, 3260, and 1150)].



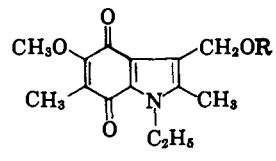
III, $R_1 = COOC_2H_5$, $R_2 = H$
IV, $R_1 = R_2 = H$
V, $R_1 = H$, $R_2 = CH_3$
VI, $R_1 = CHO$, $R_2 = CH_3$



VII



VIII



IX, R = H
X, R = $COOC_6H_5$
XI, R = $CONHCH_3$
XII, R = $CONHCH_2CH{=}CH_2$
XIII, R = $CONHC_3H_7$
XIV, R = $CONHC_4H_9$
XV, R = $CON(CH_3)_2$

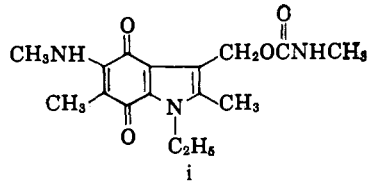
The 1,2-dialkylindoloquinone II has an *in vitro* antibacterial spectrum and *in vivo* activity comparable to that of 7-methoxymitosene (I).[1] It is approximately one-third as active as tetracycline when administered orally to mice infected with *Staphylococcus aureus* var. Smith. However, indoloquinone II is ineffective *in vivo* against *Streptococcus pyrogenes* C-203 and a tetracycline-resistant *Staphylococcus* species, despite its high activity *in vitro* against these organisms.

A variety of analogs of II has been prepared in this laboratory. For example, treatment of carbinol IX with the appropriate isocyanate gave XI–XIV (methyl[10]: m.p. 170–171°; allyl: m.p. 121–122°; propyl: m.p. 129–130°; butyl: m.p. 116–117°).[11] Reaction of phenylcarbonate X with dimethylamine gave XV (m.p. 119–120°).[11]

More extensive reports on our efforts in this area will be published at a later date.

(9) The conversion of certain di- and trisubstituted anilines into the corresponding *p*-benzoquinones by potassium nitrosodisulfonate has been described [H. Teuber and M. Hasselback, *Ber.*, **92**, 674 (1959)].

(10) Treatment of the phenyl carbonate X with methylamine gave i [m.p. 213–215°; λ_{max} 249, 313, 342 (shoulder), and 550 mμ (ε 17,200, 10,800, 5750, and 1600)].



i

(11) The ultraviolet spectra of these compounds were essentially the same as that of the carbamate II.

Acknowledgment.—The *in vivo* assays were carried out by Mr. G. S. Redin and his associates, and the *in vitro* antibacterial spectrum was determined by Mr. A. C. Dornbush and his staff. Microanalyses were furnished by Mr. L. Brancone and his staff, and spectral data were supplied by Mr. W. Fulmor and his associates. We are grateful to these groups for their kind cooperation.

ORGANIC CHEMICAL RESEARCH SECTION GEORGE R. ALLEN, JR.
LEDERLE LABORATORIES DIVISION JOHN F. POLETTO
AMERICAN CYANAMID COMPANY MARTIN J. WEISS
PEARL RIVER, NEW YORK

RECEIVED JULY 27, 1964

Olefin Oxidations with Excited Singlet Molecular Oxygen[1]

Sir:

This communication describes a novel and useful synthetic method for the oxidation of olefins and dienoid compounds to give products identical with those of the well-studied dye-photosensitized autoxidations.[2] The active species appears to be molecular oxygen in an excited singlet state, formed *in situ* by the reaction of sodium hypochlorite and hydrogen peroxide.[3-7]

The significance of this reaction for the mechanism of the photosensitized autoxidations is discussed in the accompanying communication.[8]

The oxidations proceed exceptionally smoothly, and in preparatively useful yields. Examples of the conversions so far carried out are given below. As no attempt at optimization of conditions has been made, the yields given are minimal.

In methanol, 2,5-dimethylfuran (I) is converted to 2,5-dimethyl-2-hydroperoxy-5-methoxydihydrofuran (II) in 84% yield (based on sodium hypochlorite used; in this case, dimethylfuran was in excess). The same product is produced in the photosensitized autoxidation of I in 74% yield, presumably by reaction of methanol with the hypothetical ozonide-like peroxide III.[9]

(1) Supported by N.S.F. Grant G-25086.

(2) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957), and references therein cited; G. O. Schenck and E. Koch, *Z. Elektrochem.*, **64**, 170 (1960); W. Bergmann and M. J. McLean, *Chem. Rev.*, **28**, 367 (1941).

(3) The chemiluminescence[4] of this reaction was originally assigned to emission from the $^1\Sigma_g^+$ state of molecular oxygen[5]; more recent studies, however, have shown that the visible luminescence is more probably derived mainly from a dimer of the $^1\Delta_g$ state[6,7]; infrared emission from the monomeric $^1\Delta_g$ state is also observed.[7]

(4) H. H. Seliger, *Anal. Biochem.*, **1**, 60 (1960); L. Mallet, *Compt. rend.*, **185**, 352 (1927); G. Gattow and A. Schneider, *Naturwiss.*, **41**, 116 (1954).

(5) A. U. Khan and M. Kasha, *J. Chem. Phys.*, **39**, 2105 (1963).

(6) S. J. Arnold, E. A. Ogryzlo, and H. Witzke, *ibid.*, **40**, 1769 (1964).

(7) R. J. Browne and E. A. Ogryzlo, *Proc. Chem. Soc.*, **117** (1964).

(8) C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3880 (1964).

(9) Only polymeric peroxides had been previously isolated from the photosensitized autoxidation.[10] The structure of II (m.p. 75–76°) follows from its chemical and physical properties: *Anal.* Found: C, 52.42; H, 7.45; OCH_3, 18.83; mol. wt., 177.3 (osmometer); infrared (CCl_4, 0.005 *M*) 3512 cm.$^{-1}$ (OOH); n.m.r. ($CDCl_3$) τ 0.78, 3.98, 6.64, 8.42, and 8.47 (all sharp singlets, relative areas 1:2:3:3:3, assigned to OOH, olefinic H, OCH_3, C-CH_3, and C-CH_3, respectively). The *p*-nitrobenzoate (m.p. 91–92°) has an infrared band ($CHCl_3$) at 1775 cm.$^{-1}$ (perester). II gives the bis-2,4-dinitrophenylhydrazone of diacetylethylene, m.p. 286° dec., m.m.p. with a sample (m.p. 284° dec.) prepared by the method of Levisalles[11] (reported m.p. 291–292°) was 284° dec. Schenck has also observed product II.[12] The product formed from photosensitized autoxidation of menthofuran in methanol has an analogous structure (not the one originally assigned[13]).[12]

(10) G. O. Schenck, *Ann.*, **584**, 165 (1953).

(11) J. Levisalles, *Bull. soc. chim. France*, 997 (1957).

(12) G. O. Schenck, private communication.

(13) G. O. Schenck and C. S. Foote, *Angew. Chem.*, **70**, 505 (1958).