Synthesis of Mimosamycin

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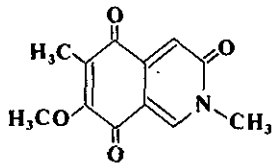
Mimosamycin, which shows an antibiotic activity against mycobacteri including streptomycin-sensitive and resistant strains of human tubercle bacilli, is one of the metabolites isolated from the culture filtrate of Streptomyces sp. No. 314.[1,2]

Structure of mimosamycin was determined as 1 by X-ray analysis.[3]



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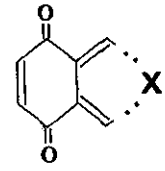
The characteristic feature of the structure (1) is a heterocyclic quinone* consisted of 3,5,8-isoquinolinetrione,

* The term 'heterocyclic quinone' is taken to mean a quinone in which a heterocyclic ring (or rings) is fused directly onto the quinone moiety and it excludes those which contain a heterocyclic ring insulated from the quinone nucleus[4] and those which posses a heterocyclic system as a substituent. In the strict sense of the term, mimosamycin does not enterinto this category, because there is not a quinone moiety,in 1. Some heterocyclic quinones of type (2), in which the double bonds of a heterocyclic ring are fused exo onto the quinone moiety, have been synthesized.[5]



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which has been never found in the literature. Recently renewed interest in heterocyclic quinones has been stimulated by the discovery of a number of antibiotics containing such systems, e.g. bruneomycin,[6] granatacin,[7] the mitomycins,[8] naphthyrinomycin,[9] the naphthocyclinones,[10] phomazarin,[11] porfiromycin[12] and so on.

Synthesis of mimosamycin makes us arise an interest, because it is produced only in a small amount as a so-called 'satelite product' of the metabolite and 3,5,8-isoquinolinequinone is a novel heterocyclic quinone albeit a simple ring system.

(1) T. Arai, K. Yazawa, Y. Mikami, A. Kubo, and K. Takahashi, J. Antibiotics(Tokyo), 29, 398(1976).
(2) Y. Mikami, K. Yokoyama, A. Omi, and T. Arai, ibid., 29, 408(1976).
(3) H. Fukumi et al., in preparation.
(4) I. Baxter and B. A. Davis, Quart. Rev., 25, 239(1971).
(5) For example, D. V. Nightingale and B. Sukornick, J. Org. Chem., 24, 497(1959); D. V. Nightingale and H. L. Needles, J. Heterocyclic Chem., 1, 74(1964); L. A. Cort and P. A. B. Rodriguez, J. Chem. Soc., (C) 949(1967); O. Dischendorfer, K. Lercher, and J. Marek, Monatsh., 80, 333(1949); R. Pummerer and G. Marondel, Chem. Ber., 89, 1454(1956); G. Weisgerber and C. H. Eugster, Helv. Chim. Acta, 49, 1806 (1966); H. Brockmann and T. Reschke, Tetrahedron Letters, 4593(1965); H. Wynberg and H. J. M. Sinnige, Rec. Trav. chim., 88, 1244(1969); S. Ebine, Bull. Chem. Soc. Japan, 38, 2029 (1965); W. Schäfer and H. Schulde, Tetrahedron Letters, 4313 (1967); E. Müller, Synthesis, 761(1974).
(6) L. A. Averbukh, Antibiotiki (USSR), 20, 307(1975).
(7) R. Corbaz, L. Ettlinger, E. Gäumann, J. Kalvoda, W. Keller-Schierlein, F. Kradolfer, B. K. Manukian, L. Neipp, V. Prelog, R. Reusser, and H. Zähner, Helv. Chim. Acta, 40, 1262(1957).
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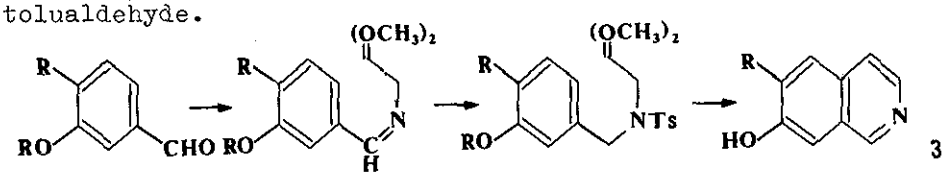
(9) J. Sygusch, F. Brisse, and S. Hanessian, Tetrahedron Letters, 170(1975).
(10) A. Zeck, H. Zähner, and M. Mardin, Ann., 1100(1974).
(11) F. Kögl, G. C. van Wessem, and O. I. Elsbach, Rec. Trav. chim., 64, 23(1945).
(12) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, J. Am. Chem. Soc., 84, 3185, 3187(1962).

In comparison with the quinolinediones the isoquinoline derivatives have received scant attention and the para-quinone forms the only well-characterized group. Oxidation of 5,8-diamino-, 5-amino-8-hydroxy-, and 5,8-dihydroxyisoquinolines has been employed in their synthesis.[13] Phenols are known to undergo ortho-hydroxylation on aerial oxidation in the presence of cupric ion-amine mixtures[14] and this reaction has been employed in the formation of a large number of ortho-trione. Recent extension of syntheses of Tsizin using Cu^{++} catalyzed oxidation of 7-isoquinol in the presence of a variety of secondary amines provided facile entry to the series of 7,8-isoquinolinedione.[15]

7-Methoxy-6-methyl-5,8-isoquinolinedione

Convenient synthesis of 7-isoquinolinol from m-methoxybenzaldehyde was reported by Jackson et al. in 1974.[16] By the application of their procedure, 6-methyl-7-isoquinolinol (3, R=CH_3) was obtained in 80% over-all yield from m-methoxytolualdehyde.



By oxidation of 3 (R=H and R=CH_3) with oxygen in the presence of secondary amine and cupric acetate, 7,8-isoquinolinediones (4, R=H and R=CH_3) were prepared in moderate yields, respectively. Considerable experience with this reaction

(13) P. K. Joseph and M. M. Joullie, J. Med. Chem., 7, 801(1964), and references cited therein.

(14) W. Brockman and E. Havinga, Rec. Trav. chim., 74, 937(1955).

(15) Yu. S. Tsizin, Khim. Geterotsikl. Soedin.(USSR), 1253(1974).

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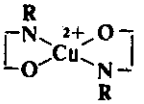
has helped to delineate its scope. No oxidation occurs when an N-alkylated ethanolamine or primary aliphatic amine is used, presumably due to the formation of the cupramine complexes i and ii, respectively, in which the cupric ion is catalytically inert. With secondary amines the formation of cupramine complexes such as ii is apparently less favored and catalytic oxidation uninhibited. But with thiomorpholine as a secondary amine no oxidation occurred.



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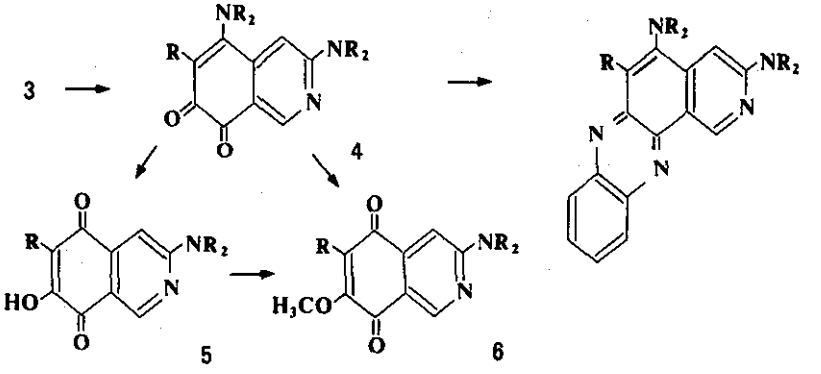
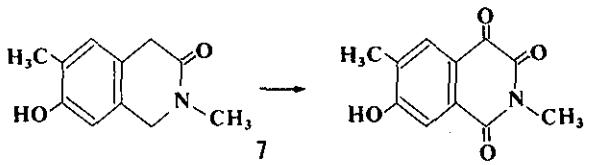
Hydrolysis of 4 (R=H or R=CH_3) by sodium hydroxide gave 5 (R=H or R=CH_3). Acid catalyzed methanolysis of 4 (R=H) gave 6 (R=H) and under the same condition, methanolysis of 4 (R=CH_3) gave 5 (R=CH_3), which was converted to 6 (R=CH_3) by treatment with diazomethane. Treatment of p-quinone (6, R=H) with methyl iodide in the presence of potassium hydride afforded 6 (R=CH_3), which was identified with the compound synthesized, with high yields at all stage, from 6-methyl-7-isoquinolinol (3, R=CH_3).



NR_2 = $N(CH_3)_2$
= Piperidino
= Morpholino

By the aerial oxidation, the necessities of all functional group for synthesis of mimosamycin were provided in one-step at the desired C-3, 5, and 8-positions. However, it may be noteworthy that aerial oxidation of 7 afforded 1,3,4-isoquinolinetrione(8). It has been reported that 2-methyl-1,3,4-isoquinolinetrione is produced by oxidation of 2-methyl-3-isoquinolone with air.[17]



7 8

2,6-Dimethyl-7-methoxy-3,5,8-isoquinolinetrione

Quaternarization of 2-aminopyridine with alkyl halide followed by hydrolysis is a beaten path to N-alky-α-pyridone. Subsequently, methylation of 6 with various methylating agents was attempted but did not produce any quaternary salt even under forced conditions. These fruitless results may be expected deservedly, because the difference in the basic dissociation constants (pKa 5.7 and 2.2) of 5,8-isoquinolindiol and 5,8-isoquinolinedione is about four pK units, the quinone being the weaker base.[18] This problem was circumvented by the reduction of the p-quinone to its hydroquinone.

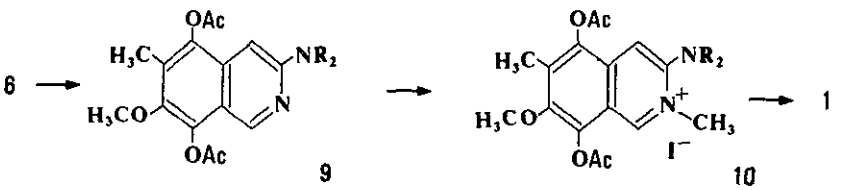
Reductive acetylation of 6 ($R=CH_3$, NR_2=morpholine) with zinc-acetic acid-acetic anhydride gave diacetate(9), which was easily quaternarized at isoquinoline nitrogen with methyl iodide. In this N-methylation reaction, no concurrent

(17) N. J. Mruk and H. Tieckelmann, Tetrahedron Letters, 1209(1970).

(18) N. F. Fieser and E. L. Martin, J. Am. Chem. Soc., 57, 1840(1935).

(19) R. Frampton, C. D. Johnson, and A. R. Katritzky, Ann. Chem., 749, 12(1971).

N-methylation of morpholine nitrogen was observed. It was contrary to the case of 2-dimethylaminopyridine, which forms its methiodide at the exocyclic nitrogen.[19]



In order to convert 10 into mimosamycin, three reactions are still required: i) hydrolysis of the acetoxyl groups, ii) oxidation of the resultant hydroquinone, and iii) substitution of the morpholine group with a hydroxyl group.

Treatment of 10 with silver oxide afforded in one-step 2,6-dimethyl-7-methoxy-3,5,8-isoquinolinetrione, which was identified with a sample of mimosamycin by mixed mp and the comparison of IR, UV, NMR, and MS spectra.

Studies concerning to the chemical properties of 3,5,8-isoquinolinetrione are in progress.

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