[Chem. Pharm. Bull. 12(10)1262~1264(1964)] UDC 547.682.1.07

Synthesis of Methyl 2-Ethyl-6,11-dioxo-5,7,10-trimethoxy-6,11-dihydro-1-naphthacenecarboxylate (η-Pyrromycinone Trimethyl Ether)

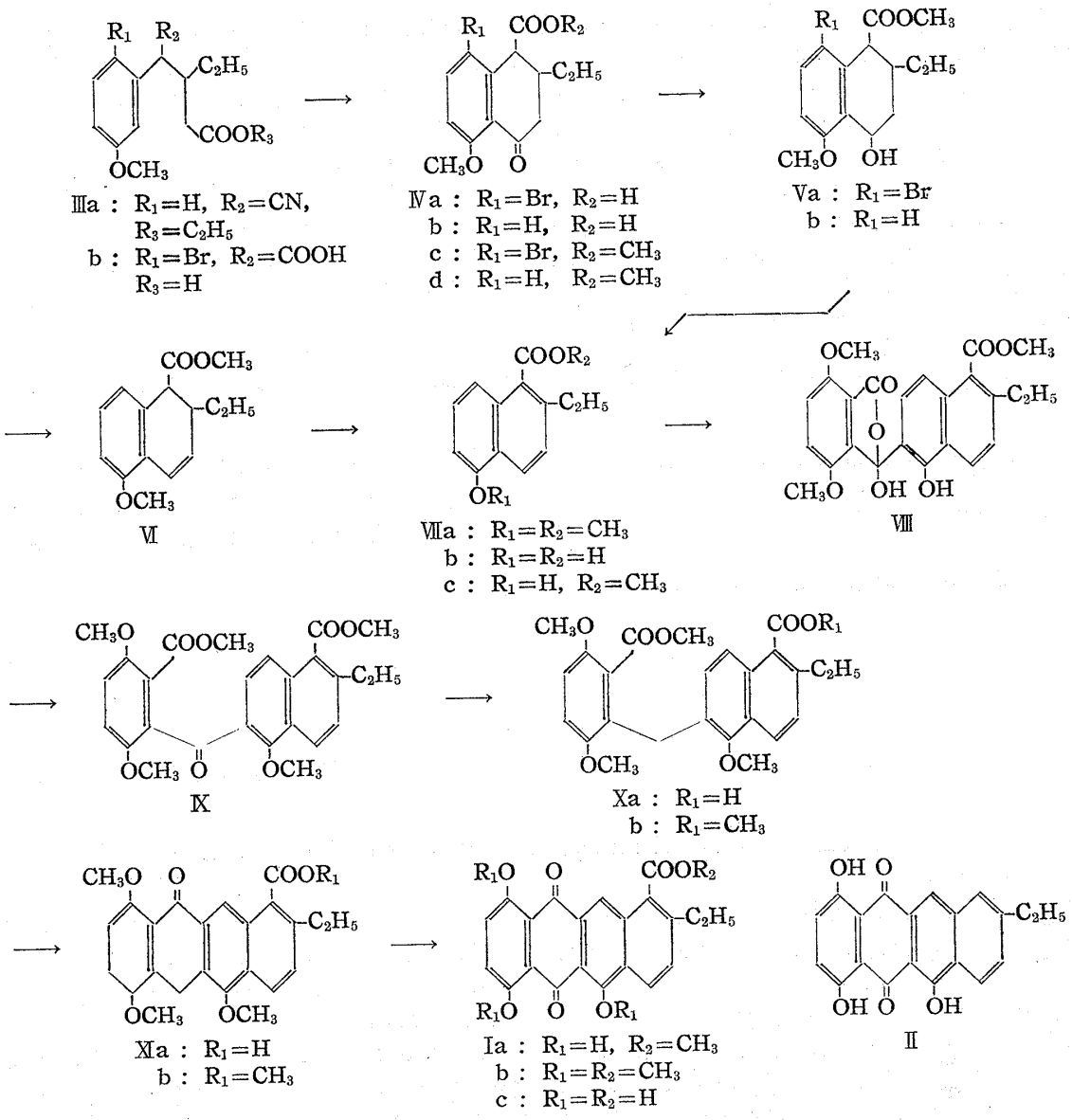
η-Pyrromycinone[1] is one of the metabolites of the Streptomyces and has played an important role in the chemistry of the anthracycline antibiotics. Brockmann, Prelog, Ollis, *et al.*,[2] in 1960, assigned its structure as methyl 2-ethyl-6,11-dioxo-5,7,10-trihydroxy-6,11-dihydro-1-naphthancenecarboxylate (Ia) from the degradative studies. Shortly afterwards, Ollis, *et al.*[3] synthesized demethoxycarbonyl-η-pyrromycinone (II), proving structure Ia except for the position of the methoxycarbonyl group. We have now synthesized the trimethyl ether (Ib) of Ia, and found that demethylation of Ib by means of boron tribromide produces a hydroxy acid whose melting point and infrared spectrum are well in agreements with those reported for η-pyrromycinonic acid, assigned as Ic by Brockmann.[4]

Condensation of (*m*-methoxyphenyl)acetonitrile and ethyl 2-pentenoate[6] in anhydrous ethanol in the presence of sodium ethoxide gave a cyanoester (IIIa), b.$p_{0.1}$ 153° (IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2227 (C≡N), 1724 (C=O)), which was hydrolysed with aqueous potassium hydroxide, followed by bromination with bromine in chloroform to give a bromoacid (IIIb), m.p. 169~170° (IR : ν_{max}^{Nujol} 1701 cm^{-1} (C=O)). The product (IIIa) or (IIIb) is assumed to be a diastereoisomeric mixture and, actually, one pure isomer was separated from IIIb by employing a difference of solubility in chloroform. However, the mixture was carried on in the subsequent reactions because this source of isomerism was going to be removed in the later stages of this synthesis.

Cyclization of IIIb by means of polyphosphoric acid gave a bromotetralonecarboxylic acid (IVa), m.p. 155~161° (IR ν_{max}^{Nujol} cm^{-1} : 1733 (C=O), 1654 (C=O)), which was debrominated by catalytic reduction over Raney nickel in aqueous methanol (1:1) in the presence of potassium hydroxide to a tetralonecarboxylic acid (IVb), m.p. 149~153° (IR ν_{max}^{Nujol} cm^{-1} : 1724 (C=O), 1645 (C=O)). The methyl ester (IVc), b.$p_{0.06}$ 162~163° (IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1732 (C=O), 1686 (C=O)), of IVa and the methyl ester (IVd), b.p_4 192~193° (IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1734 (C=O), 1686 (C=O)), of IVb were reduced with sodium borohydride in methanol to tetralol-esters (Va), m.p. 110~112°*1 (IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3546 (OH), 1724 (C=O)), and (Vb), m.p. 81~82°*1 (IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3534 (OH), 1727 (C=O)), respectively. Dehydration of Vb with *p*-toluenesulfonic acid in methanol and subsequent dehydrogenation of a resulting dihydronaphthalene (VI), b.p_4 158° (IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1735 (C=O), 1633 (C=C)), by heating with sulfur gave methyl 2-ethyl-5-methoxy-1-naphthoate (VIIa), m.p. 69~70° (IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1727 (C=O), 1623, 1599, 1581 (arom.)), which was also obtained directly by dehydrogenation of Va and Vb. Fusion of VIIa with two molecular equivalents of pyridine hydriodide at 230° for 30 minutes gave 2-ethyl-5-hydroxy-1-naphthoic acid (VIIb), m.p. 159~160° (IR ν_{max}^{Nujol} cm^{-1} : 3067 (OH), 1712 (C=O)), which was remethylated with diazomethane in ether at 0~5° to methyl 2-ethyl-5-hydroxy-1-naphthoate (VIIc), m.p. 95~96° (IR ν_{max}^{Nujol} cm^{-1} : 3330 (OH), 1685 (C=O)).

*1 Only a crystalline sample separated from the oily stereoisomeric mixture was analyzed.

1) Dianhydro-ε-pyrromycinone and dianhydrorutilantinone are the same compounds as η-pyrromycinone. For recent reviews on this subject, see H. Brockmann : Fortschr. Chem. org. Naturstoffe, **21**, 121 (1963).
2) H. Brockmann, V. Prelog, W. D. Ollis, *et al.* : Tetrahedron Letters, No. 8, 25 (1960).
3) W. D. Ollis, *et al.* : Proc. Chem. Soc., **1960**, 349.
4) H. Brockmann, W. Lenk : Chem. Ber., **92**, 1880 (1959).
5) J. W. Cornforth, R. Robinson : J. Chem. Soc., **1942**, 684. Cf. H. Tsukamoto, *et al.* : Pharm. Bull. (Tokyo), **3**, 239 (1955).
6) R. Tschesche, *et al.* : Chem. Ber., 88, 1258 (1955).



The hydroxynaphthoate (Ⅶc) was condensed with 3,6-dimethoxyphthalic anhydride[7] in acetylene tetrachloride in the presence of anhydrous aluminum chloride to a hydroxy-lactone form of methyl 2-ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate (Ⅷ), pale yellow prisms, m.p. 188~190° (IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3279 (OH), 1731 (C=O), 1630 (arom.)), which was methylated with methyl iodide in dry acetone in the presence of anhydrous potassium carbonate to methyl 2-ethyl-5-methoxy-6-(2-methoxycarbonyl-3,6-dimethoxybenzoyl)-1-naphthoate (Ⅸ), m.p. 160~162° (IR ν_{max}^{Nujol} cm^{-1} : 1724 (C=O), 1646 (C=O)). Reduction of Ⅸ with zinc powder in aqueous sodium hydroxide solution gave 2-ethyl-5-methoxy-6-(2-methoxycarbonyl-3,6-dimethoxybenzyl)-1-naphthoic acid (Xa), m.p. 130~132° (IR ν_{max}^{Nujol} cm^{-1} : 1721 (C=O), 1672 (C=O)). The diester (Xb), m.p. 126~127° (IR : ν_{max}^{Nujol} 1723 cm^{-1} (C=O)), which was prepared from the half ester (Xa), was cyclised by heating in polyphosphoric acid at 95~100° for 15 minutes to two products, 2-ethyl-5,7,10-trimethoxy-11-oxo-6,11-dihydro-1-naphthacenecarboxylic acid (XIa), m.p. 258~260° (IR ν_{max}^{Nujol} cm^{-1} : 1706 (C=O), 1645 (C=O), 1610, 1589, 1562 (arom.)), and its methyl ester (XIb), m.p.

7) G. D. Graves, R. Adams : J. Am. Chem. Soc., **45**, 2439 (1923). Cf. B. Helferich, H. G. Bodenbender : Ber., **56**, 1113 (1923).

174~176° (IR ν_{max}^{Nujol} cm^{-1} : 1714 (C=O), 1656 (C=O), 1613, 1592, 1560 (arom.)). The methyl ester (XIb) was also obtained by methylation of XIa with diazomethane in ether-tetrahydrofuran. Oxidation of XIb employing a large excess of chromic trioxide in glacial acetic acid at room temperature gave methyl 2-ethyl-6,11-dioxo-5,7,10-trimethoxy-6,11-dihydro-1-naphthacenecarboxylate (Ib) as yellow needles, m.p. 235~237° (*Anal.* Calcd. for $C_{25}H_{22}O_7$: C, 69.11; H, 5.10. Found : C, 68.72; H, 5.06. IR ν_{max}^{KBr} cm^{-1} : 1721 (C=O), 1663 (C=O), 1608, 1586, 1569 (arom.)). Demethylation of Ib with boron tribromide in methylene chloride gave dark red needles as an acidic fraction, m.p. 260~262° (decomp.) (IR ν_{max}^{KBr} cm^{-1} : 1704 (C=O), 1648, 1600, 1587) (lit.,[4] dark red needles, m.p. 263° (decomp.), IR : ν_{max}^{KBr} 1704 cm^{-1} for η-pyrromycinonic acid).

All substances mentioned in this paper gave satisfactory elemental analyses.

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Received August 3, 1964

[Chem. Pharm. Bull. 12(10)1264~1268(1964)]

UDC 615.778 [547.722.5] : 541.69

Electronic Structure and Antibacterial Activity of Nitrofuran Derivatives

Stillman and Dodd[1] reported in 1944 that 5-nitrofurfural semicarbazone (nitrofurazone) and some related compounds possessed notable bacteriostatic and bactericidal activities. On account of their wide antibacterial spectrum and low development of bacterial resistance, attention has been attracted to those compounds from every quarter.

The relationship between the structure of nitrofuran derivatives and the antibacterial activity had been already discussed from the various point of view and the following results had been obtained. The nitro group is indispensable and in its absence there is very little or no activity. The introduction of a conjugated double bond between the nitrofuryl group and the end group of the side chain might result to enhance the activity to some extent.[2] The polarographic reduction half-wave potential of the nitro group is related partially to the activity.[3]

Moreover, many enzymological and bacteriological investigations[4~8] have been made to elucidate the mechanism of the antibacterial action of these compounds.*1 The above-stated empirical rules hold good partially, but they would be of little use for systematic elucidation of the structure-activity relationships.

*1 It may be worthy to note that those compounds inhibit some enzyme system (for example SH-enzyme system) involved in the carbohydrate metabolism of the microörganisms.

1) M.C. Dodd, W.B. Stillman : J. Pharmacol. Exptl. Therap., **82**, 11 (1944).
2) H. Saikachi, *et al.* : Yakugaku Zasshi, **69**, 285 (1949).
3) T. Sasaki : Pharm. Bull. (Tokyo), **2**, 104 (1951).
4) D.L. Cramer, M.C. Dodd : J. Bacteriol., **51**, 119, 293 (1947).
5) R.C. Bender, H.E, Paul : J. Biol. Chem., **191**, 217 (1951).
6) R.E. Asnis, J.S. Gots : Arch. Biochem., **30**, 25 (1951).
7) M.F. Paul, *et al.* : J. Biol. Chem., **206**, 491 (1954).
8) M.N. Green, E.C. Heath, Irving Yall : Proc. Soc. Exptl. Biol. Med., **76**, 152 (1951).