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The Synthesis of 2-Methoxy-3-methyl-5-(2-carbethoxymethylpyrrolino)-*p*-benzoquinone, I (1)

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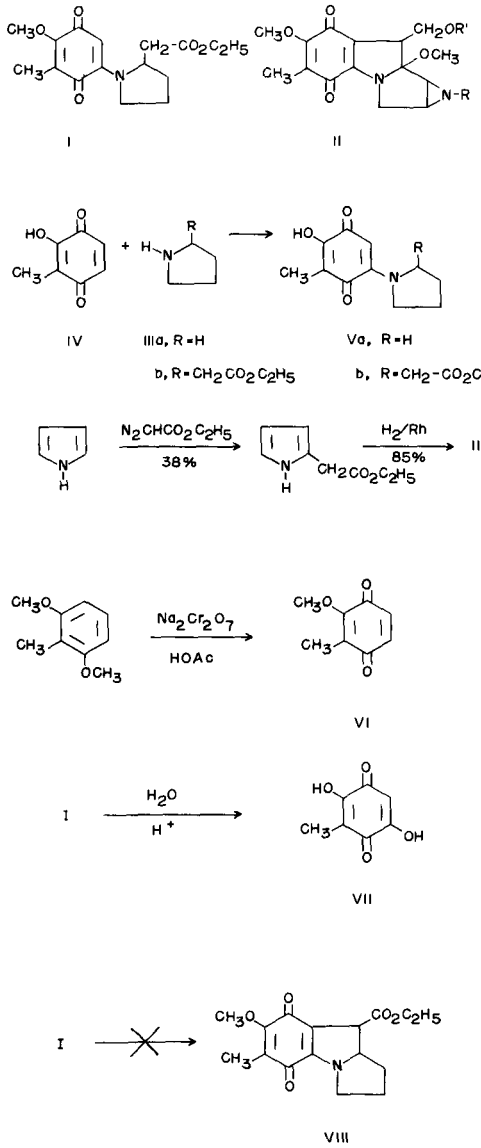
The family of antibiotics known as the mitomycins, typified by the formula II, have become of interest recently (2-7) because of their unusual structural features, especially the aziridine ring, and their physiological activity (8). This work reports the synthesis of 2-methoxy-3-methyl-5-(2-carboxymethylpyrrolidino)-*p*-benzoquinone (I) through which we had hoped to elaborate the mitomycin ring system.

The first route investigated was the addition of ethyl 2-pyrrolidinylacetate (IIIb) to 2-hydroxy-3-methyl-*p*-benzoquinone (IV). Ethyl pyrrolidinylacetate (IIIb) was prepared by the addition of ethyl diazoacetate to pyrrole to yield ethyl 2-pyrrylacetate (9) followed by catalytic hydrogenation over rhodium on alumina to give IIIb in 33% overall yield. The first step represents an improvement in yield from 17% by carrying out the reaction under "wet" conditions. The preparation of 2-hydroxy-3-methyl-*p*-benzoquinone was as described by Flaig and Salfeld (10).

We were not able to effect the addition of IIIb to IV as indicated above to afford Vb; however, in a model study we were able to add pyrrolidine to IV to obtain Va in 7% yield. The structural assignment of Va rests on its n.m.r. spectrum and its characteristic ultraviolet spectrum [typical for a 2-hydroxy-3-methyl-5-amino-*p*-benzoquinone (2)]. The inability to realize the addition of IIIb to IV led us to modify our approach.

2-Methyl-3-methoxy-*p*-benzoquinone (VI) was prepared by the oxidation of the dimethyl ether of 2-methylresorcinol following the procedure of Asano and Yamaguti (11, 12). This is a new method for preparing this known compound (13). The addition of ethyl 2-pyrrolidinylacetate to VI proceeded smoothly to give I in 60-70% yield. The ultraviolet spectrum of I was typical for this system (2) and the n.m.r. spectrum of I provided additional physical evidence for structure I. Chemical confirmation was obtained by hydrolyzing I with 10 *N* sulfuric acid to produce the known dihydroxybenzoquinone (VII).

Extensive investigation (BF_3-etherate, aluminum *t*-butoxide, *p*-toluenesulfonic acid, sodium hydride) was devoted to trying to affect the ring closure of I to VIII, indicated below; however, these efforts were futile.



EXPERIMENTAL (14)

Ethyl 2-pyrrylacetate.

Ethyl diazoacetate (15) (120 g.) was added to 160 g. of pyrrole at 85-90°C in the presence of 6.0 g. of activated copper dust at such a rate to maintain the temperature between 90-100°. The reaction was then held at 100-110° for 2 hours, filtered and distilled to give ethyl 2-pyrrylacetate, 59 g., b.p. 76° (0.2 mm.) (lit. (9) 129°, 15 mm.). Infrared spectrum ($CHCl_3$): 2.87, 3.32, 5.78 μ; n.m.r. spectrum (neat): 7.24 p.p.m. (multiplet, N-H), 6.67 p.p.m. (multiplet, alpha pyrrole H), 6.12 p.p.m. (multiplet, beta pyrrole H), 4.08 p.p.m. (quarter, $-O-CH_2-$), 3.58 p.p.m. (singlet, $-CH_2-C=O$), 1.11 p.p.m. (triplet, $-CH_3$).

Ethyl 2-pyrrolidinylacetate, acetic acid salt.

Ethyl 2-pyrrylacetate (59.0 g.) was hydrogenated in 300 ml. of glacial acetic acid, with 6 g. of 5% rhodium on alumina (16) as the catalyst, at room temperature and a hydrogen pressure of 60 p.s.i. After the hydrogen uptake ceased (2 fillings) the solution was filtered and the solvent removed *in vacuo*. The residue was distilled to yield ethyl 2-pyrrolidinylacetate, acetic acid salt, b.p. 76° (0.2 mm.) to 100° (0.4 mm.); picrolonate, m.p. 145-147° (lit. (17) 146°).

2-Hydroxy-3-methyl-5-pyrrolidine-*p*-benzoquinone (Va).

A solution of 1.0 g. of 2-hydroxy-3-methyl-*p*-benzoquinone (10) (IV) in 150 ml. of ether was added to a solution of 0.5 g. of pyrrolidine in 50 ml. of ether and allowed to stand in the cold for 10 hours. The brown sediment that formed was washed by decantation with ether, filtered and redissolved in ethanol, which solution turned red on exposure to air. The solvent from the decanted washings was removed *in vacuo* and the residue upon solution in ethanol and exposure to air similarly turned red. The combined ethanol solutions were allowed to stand open to air for several hours and the solvent removed *in vacuo* to yield 100 mg. of Va as crimson needles, m.p. 196-197°. Infrared spectrum (CH_2Cl_2): 3.05, 6.06, 6.23, 6.46, 12.30 μ; n.m.r. spectrum ($DCCl_3$): 7.90 p.p.m. (singlet, -O-H), 5.37 p.p.m. (singlet, quinoid H), 3.32 p.p.m. (multiplet, $-CH_2-N=$), 1.97 p.p.m. (multiplet, $-CH_2-$), 1.83 p.p.m. (singlet, quinoid $-CH_3$); U. V. spectrum λ max (EtOH) 218 (20,400), 328 (14,000), 515 mμ (2,500).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.70; H, 6.32; N, 6.56.

2-Methyl-3-methoxy-*p*-benzoquinone, VI.

This material was prepared following the procedure of Asano and Yamaguti (11,12) applied to 2,6-dimethoxytoluene. We give it here as it is in Japanese in the original.

To a solution of 450 g. in 875 ml. of glacial acetic acid at 85-90° was added 22.5 g. of 2,6-dimethoxytoluene (18) in 100 ml. of glacial acetic acid. The vigorous reaction that ensued was moderated using an ice water bath. After 5-7 minutes the reaction was poured on crushed ice. This was repeated a total of four times, the reaction mixtures being poured onto one lot of 3 kg. of ice. This mixture was thoroughly extracted with ether and the ether extract washed with saturated sodium bicarbonate solution and finally water. It was dried over anhydrous sodium sulfate, the solvent removed *in vacuo* and the residue distilled to yield 16.5 g. of 2-methyl-3-methoxy-*p*-benzoquinone, b.p. 73° (0.4 mm.), m.p. 18-30° (lit. (13) 19-30°). The infrared and n.m.r. spectra were in accord with the structure and the ultraviolet spectrum was in accord with that reported (10).

2-Methoxy-3-methyl-5-(2-carbethoxymethylpyrrolidino)-*p*-benzoquinone (I) (19).

To a solution of 24 g. of ethyl 2-pyrrolidinylacetate, acetic acid salt and 13.2 g. of cupric acetate in 300 ml. of methanol was added dropwise with stirring 10 g. of 2-methyl-3-methoxy-*p*-benzoquinone (VI) in 300 ml. of methanol. Before, during, and for 3 hours after the addition, the system was swept with oxygen. The solvent was removed *in vacuo* and the residue taken up in chloroform, filtered, to remove the cupric acetate and concentrated *in vacuo* once again to yield 35 g. of crude purple residue. This material was purified by partition chromatography over 600 g. of basic alumina. The product was placed on the column using a minimum amount of benzene. The column was eluted with 750 ml. of petroleum ether, 500 ml. of 20% ether-petroleum ether, 250 ml. of 30% ether-petroleum ether, 250 ml. of 40% ether-petroleum ether and 250 ml. of 70% ether-petroleum ether. At this point a broad purple band began to elute from the column. Elution was continued with 1 l. of 70% ether-petroleum ether, 500 ml. of 80% ether-petroleum ether and finally 750 ml. ether. These solutions were combined and the solvent removed to give 12.0 g. of a purple oil whose properties demand its structure to be I. Infrared spectrum ($CHCl_3$), 3.34, 3.38, 3.47, 3.49, 5.77, 6.03, 6.21, 6.31, 6.86, 7.10, 7.26, 7.70 and 8.38 μ; n.m.r. spectrum (CCl_4), 5.05 p.p.m. (singlet, quinoid H), 4.03 p.p.m. (quartet, $-CH_2-O$), 3.97 p.p.m. (singlet, $-O-CH_3$), 3.37 p.p.m. (multiplet, $-CH_2-N-CH-$), 1.93 p.p.m. (multiplet, β pyrrolidine (protons), 1.73 p.p.m. (singlet, quinoid CH_3), 1.22 p.p.m. (triplet, CH_3); U. V. λ max (MeOH), 223 (17,500), 314 (9,000), 509 mμ (2,480).

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.25; H, 6.81; N, 4.85.

Further elution of the column with ether/methanol, methanol, methanol/acetone and acetone/chloroform yielded solutions which, from ultraviolet analysis, contained more I with considerable contaminant.

2,5-Dihydroxy-3-methyl-*p*-benzoquinone (VII).

To 7 ml. of 10 *N* sulfuric acid at reflux temperature was added 0.38 g. of I in 3 ml. of benzene. The reaction was allowed to reflux 7 minutes, poured into 20 ml. of chloroform and the layers separated. The aqueous layer was back extracted with more chloroform and the combined chloroform extracts washed with water until neutral. The solvent was removed *in vacuo* and the residue sublimed to yield orange-brown crystals, m.p. 166-171° (lit. 13) 173-175°.

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