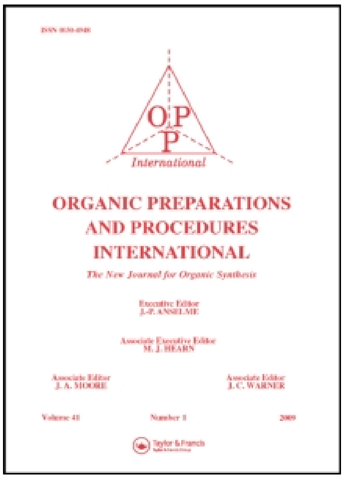

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OXIDATIVE DEMETHYLATION OF 4,7-DIMETHOXYINDOLES. SYNTHESIS OF 4,7-INDOLOQUINONES FROM 4,7-DIMETHOXYINDOLES

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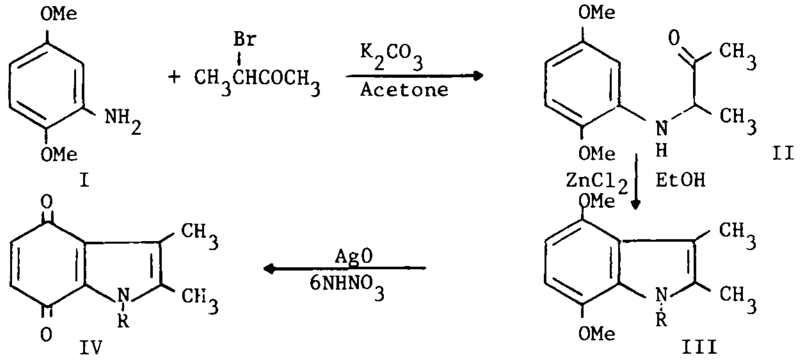
In connection with studies on the synthesis of mitomycin-C analogs and on the mode of action[1] of the mitomycin antibiotics,[2] we became interested in the conversion of 4,7-dimethoxyindoles into 4,7-indoloquinones to gain facile access to mitomycin model compounds. Synthetic procedures for the synthesis of indoloquinones include the Fremy's salt oxidation method[3] which has been used extensively in the preparation of mitomycin analogs,[4] as well as the conversion of 4,7-dimethoxyindoles into 4,7-indoloquinones by a two-step procedure involving demethylation with $AlCl_3$ in refluxing benzene for 12 hours followed by oxidation with $K_2Cr_2O_7/H_2SO_4$.[5] The Fremy's salt method is relatively costly and the



a) R=H b) R=CH_3

method by Blackhall and Thomson, which has recently been studied by several authors,[6,7] employs rather drastic conditions.

We found that a novel oxidative demethylation method developed by Snyder and Rapoport[8] for the preparation of substituted 1,4-benzoquinones from the corresponding 1,4-dimethoxybenzenes using argentic oxide and 6N nitric acid as oxidants can also be used satisfactorily for the preparation of indoloquinones from corresponding 4,7-dimethoxyindoles. Thus, 2,3-dimethyl-4,7-dimethoxyindole (IIIa) was oxidized to the known 2,3-dimethyl-4,7-indoloquinone (IVa) at 0° in 30% yield and 1,2,3-trimethyl-4,7-dimethoxyindole (IIIb) was converted into the novel 1,2,3-trimethyl-4,7-indoloquinone (IVb) in 50% yield.

The higher yield obtained in the second reaction indicates that N-substituted indole is slightly more stable towards the oxidants than the unsubstituted congeners. IIIa was prepared from 2,5-dimethoxyaniline and 3-bromobutanone by way of the previously unknown 3-(2',5'-dimethoxyanilino)butanone (II) and IIIa was used to prepare IIIb a previously unknown compound, by methylation with methyl iodide/sodium amide.

EXPERIMENTAL

3-(2',5'-Dimethoxyanilino)butanone (II).— 2,5-Dimethoxyaniline (I) (0.02 mole) was refluxed with 3-bromobutanone (0.01 mole) in acetone for 12 hours in the presence of freshly heated K_2CO_3. The reaction mixture was filtered and the solvent was evaporated on a rotary evaporator. The residue was taken up in ether and treated with 10% hydrochloric acid. The aqueous layer was separated and made alkaline with sodium hydroxide solution. The separated product was ether extracted with ether and dried over anhydrous sodium sulfate. Evaporation of ether gave II in 65% yield. It was recrystallized from pet ether, mp. 74°; nmr (CCl_4)

δ ppm. 1.2 (3H, d, J = 7 cps, -CH-$\underline{CH}_3$), 1.9 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 3.5 (3H, s, -$OCH_3$ at 5'), 3.6 (1H, q, J = 7 cps, -$\underline{CH}$-CH_3), 3.7 (3H, s, -OCH_3 at 2'), 3.75 (1H, s, -NH), 5.8 (1H, s, aromatic proton at 6'), 6.0 (1H, d, J = 10 cps, aromatic proton), 6.7 (1H, d, J = 10 cps, aromatic proton). Anal. Calcd for $C_{12}H_{16}O_3N$: C, 64.83; H, 7.25; N, 6.30. found: C, 64.44; H, 7.13; N, 6.28.

2,3-Dimethyl-4,7-dimethoxyindole (IIIa).- II (0.01 mole) was refluxed for 5 hrs with fused zinc chloride (0.05 mole) in absolute ethanol (30 ml) under a nitrogen atmosphere to give IIIa in 62% yield according to the procedure of Brown and Mann;[9] mp. 102°, lit.[5] mp. 103-4°; nmr (CCl_4) δ ppm. 2.1 (3H, s, -CH_3 at 2 or 3), 2.3 (3H, s, -CH_3 at 2 or 3), 3.65 (3H, s, -OCH_3 at 4), 3.78 (3H, s, -OCH_3 at 7), 6.0 (1H, d, J = 10 cps, aromatic proton), 6.2 (1H, d, J = 10 cps, aromatic proton, 7.7 (1H, s, broad, -NH); MW (mass spec.), calcd for $C_{12}H_{15}O_2N$, 205.110; found, 205.110.

2,3-Dimethyl-4,7-indoloquinone (IVa).- IIIa (0.001 mole) was treated with argentic oxide (0.003 mole) for 3 minutes in tetrahydrofuran at 0° and then 6N nitric acid (1.3 ml) was added dropwise, over a period of 3 to 5 minutes. The reaction mixture was separated on a preparative TLC plate on silica gel in benzene/chloroform/methanol 80:20:10. IV was isolated from an orange zone at RF = 0.33 in 30% yield; mp. 185-195° (dec.), lit.[5] 215-217° (dec.), ms m/e 175 ($M^{+\cdot}$) besides another orange compound (RF = 0.13) of unknown structure which was formed in small amounts. IVa which is stable at room temperature in the dark, was identical to the material prepared by the Fremy's salt oxidation procedure,[3] starting with 2,3-dimethyl-7-methoxyindole, which itself was obtained from o-anisidine and 3-bromobutanone by a literature procedure.[10]

1,2,3-Trimethyl-4,7-dimethoxyindole (IIIb).–IIIa (0.01 mole) was methylated with methyl iodide (0.011 mole) in the presence of sodium amide (0.01 mole) in anhydrous ether[11] to give IIIb in quantitative yield; mp. 96°, nmr (acetone - d_6), δ ppm. 1.7 (3H, s, $-CH_3$ at 2 or 3), 1.8 (3H, s, $-CH_3$ at 2 or 3), 3.3 (3H, s, $-N-CH_3$), 3.35 (3H, s, $-OCH_3$ at 4), 3.41 (3H, s, $-OCH_3$ at 7), 5.7 (1H, d, J = 10 cps, aromatic proton), 5.9 (1H, d, J = 10 cps, aromatic proton); MW (mass spec.), calcd for $C_{13}H_{17}O_3N$, 219.126; Found, 219.128.

Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.80; N, 6.38. Found: C, 71.46; H, 7.84; N, 6.30.

1,2,3-Trimethyl-4,7-indoloquinone (IVb).– IIIb (0.001 mole) on oxidative demethylation with $AgO-HNO_3$ as described in IIIa, gave IVb as an orange compound in 40-50% yield, from an orange zone at RF = 0.80. It recrystallized from pet ether on standing for several hours in refrigerator; mp. 140-145° (dec.) and showed a single component to tlc in foregoing solvent system. Two additional recrystallization from pet ether gave analytical sample; nmr (acetone-d_6), δ ppm. 1.6 (3H, s, $-CH_3$ at 2 or 3), 2.25 (3H, s, $-CH_3$ at 2 or 3), 3.2 (3H, s, $-N-CH_3$), 5.8 (2H, s, quinonoid protons); ms m/e 189 ($M^{+\cdot}$). The infrared showed strong absorption at 1690 and 1640 cm^{-1} (quinone >C=O).

Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.81; N, 7.40. Found: C, 69.79; H, 5.61; N, 7.30.

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REFERENCES

1. U. Hornemann, Y. Ho, J. Mackey and S. Srivastava, J. Am. Chem. Soc., 98, (22) 7069 (1976).

2. J. Webb, D. Cosulich, J. Mowat, J. Patrick, R. Broschard, W. Meyer, R. Williams, C. Wolf, W. Fulmore, C. Pidacks and J. Lancaster, ibid., 84, 3185-3186 (1962).

3. H. Teuber and K. Thaller, Chem. Ber., 91, 2253 (1958).

4. G. Allen, J. Poletto and M. Weiss, J. Am. Chem. Soc., 86, 3878 (1964).

5. A. Blackhall and R. Thomson, J. Chem. Soc., 3916 (1954).

6. G. Malesani and G. Rigatti, Z. Naturforsch., 30b, 954 (1975).

7. J. Berger, Tetrahedron Lett., 393 (1972).

8. C. Snyder and H. Rapoport, J. Am. Chem. Soc., 94, 227 (1972).

9. F. Brown and F. Mann, J. Chem. Soc., 855 (1948).

10. M. Clerk-Bory, Bull. Soc. Chem. Fr., 88 (1955).

11. K. Potts and J. Sexton, J. Chem. Soc., 2641 (1954).

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