New Heterocycles Derived from a Simultaneous Substitution and Reductive Acetylation of 2,5-Dihydroxy-1,4-benzoquinone by *N*-Containing Heterocycles

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Reaction of 2,5-dihydroxy-1,4-benzoquinone with pyridine, 3-picoline and acridine in acetic anhydride lead to the preparation of 3-(4-pyridyl)-1,2,4,5-benzenetetrol tetraacetate, 3-[4-(3-methylpyridyl)]-1,2,4,5-benzenetetrol tetraacetate and 3-(9-acridyl)-1,2,4,5-benzenetetrol tetraacetate, respectively. Moreover, it was possible to isolate the complex derived from the corresponding amines and the quinone. The reaction conditions and the ^{1}H, ^{13}C, ir and mass spectra of the new compounds are discussed.

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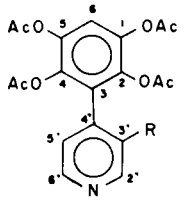
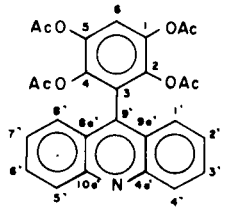
As part of a research program to synthesize new compounds for pharmacological studies, we decided to prepare new derivatives of 2,5-dihydroxy-1,4-benzoquinone with pyridine **1**, 3-picoline **2** and acridine **3**, since it has been reported that structurally related substances show biologically interesting properties [1]. The study also



1 R=H
2 R=CH$_3$



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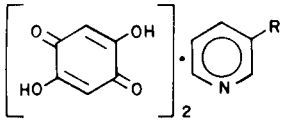
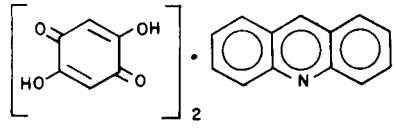
provides additional information concerning the coupling reaction [2] of aromatic heterocycles of nitrogen with 2,5-dihydroxy-1,4-benzoquinone and describes the isolation of complexes formed (**4, 5** and **6**) in the course of the



4 R=H
5 R=CH$_3$



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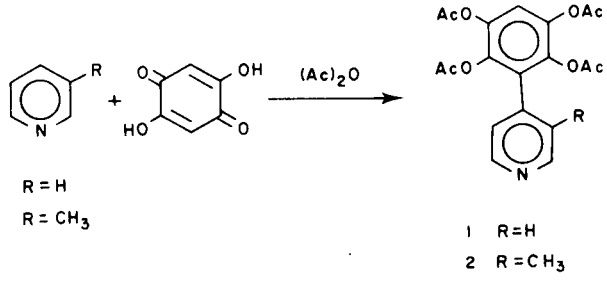
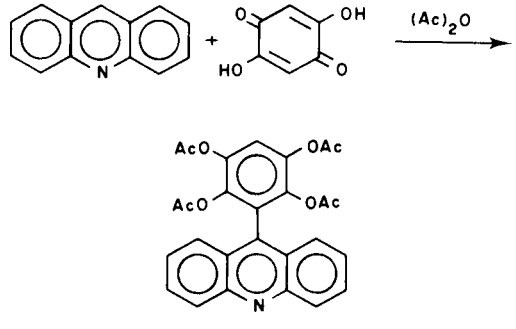
reactions. It was found that heterocycles **1-3** may be easily obtained by reaction of pyridine, 3-picoline or acridine with 2,5-dihydroxy-1,4-benzoquinone in acetic anhydride (Scheme 1). In all cases the 1,2,4,5-benzenetetrol tetraacetate **7** was isolated as a by-product. Moreover, treatment of 4-picoline or 2,6-lutidine under the same reaction conditions failed to afford the corresponding benzenetetrol derivatives.

It was interesting to note that as far as the experimental procedure is concerned, good results are obtained either if pyridine or picoline and the quinone are allowed to be in contact and then acetic anhydride is added or by addition of the quinone to a mixture of equivalent quantities of

Scheme I



1 R=H
2 R=CH$_3$



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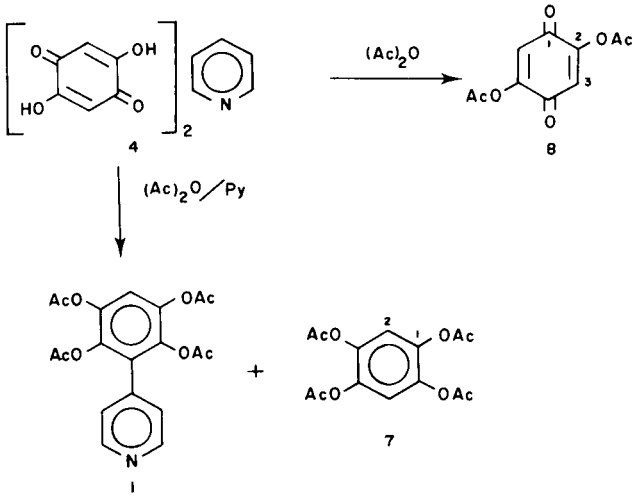
pyridine and acetic anhydride. In contrast, reaction of quinone with acetic anhydride followed by addition of pyridine afforded compound **7** only.

This observation prompted us to investigate the product of the reaction of pyridine with 2,5-dihydroxy-1,4-benzoquinone and found that it lead to complex **4** containing two molecules of the quinone and one of pyridine, as

deduced from spectroscopic data and elemental analysis. This type of complex has been recently described for phenols and amines [3].

To understand the role of a complex formation on the course of this alkylation reaction, complex **4** was allowed to react with acetic anhydride under different reaction conditions. Hence, when **4** was treated with acetic anhydride, the diacetylated quinone **8** was obtained in almost quantitative yield. On the other hand, addition of acetic anhydride and pyridine to **4** gave compound **1** as well as leucotetraacetate **7** (Scheme II). In view of the possibility that formation of a salt could be promoting alkylation, we decided to carry out the transformation using the pyridinium hydrochloride in acetic anhydride and were unable to isolate either **1** or **7** or **8**. The results imply that polarization of acetic anhydride by pyridine plays an important role in the reaction. On the other hand,

Scheme II

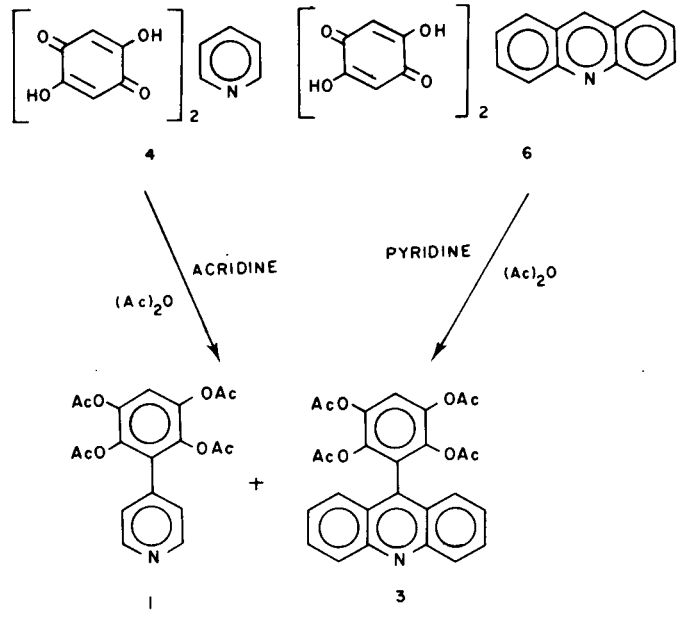


crossed reaction of **4** with acridine or **6** with pyridine gave a mixture of alkylated products resulting from an equilibrium of species, as well as predominant formation of **3**. A faster reaction rate was also observed for acridine.

The structures of all the compounds were assigned based on the spectroscopic data.

The ^{1}H nmr spectrum of compound **1** shows the characteristic AA'BB' system for the 2',6' and 3',5' protons at 8.66 and 7.21 ppm, respectively and a singlet at 7.28 for the proton at position 6. Comparison of the ^{1}H chemical shifts of the acetate group in 3-(4-pyridyl)-1,2,4,5-benzenetetrol tetraacetate (**1**) and the acridine derivative **3** allowed assignment of the acetate groups at positions 1,5 and 2,4 to the signals at 2.28 and 2.01 ppm, respectively, since the first one remains essentially invariant while the latter is further upfield shifted in **3**. The ^{1}H nmr spectrum of **2** shows a singlet at 8.65 ppm for H-2' and the AX system at 8.50 (J_{AX} = 4.5 Hz) and 7.05 (J_{AX} = 4.5 Hz) due to the protons at 6' and 5', respectively. It also shows a singlet at 7.35 ppm due to the proton at the free position of the aromatic ring (H-6) and two singlets at 2.27 and 1.90 for the C-1,5 and C-2,4 methyl groups. Finally, the C-3' methyl group singlet appears at 2.15 ppm. Compound **3** shows a

Scheme III



double doublet at 8.32 ppm (J = 6, 1 Hz) for the protons at the 5' and 4' positions in the ^{1}H nmr spectrum. The protons at C-1', 2', 3', 6', 7' and C-8' appear as a complex multiplet in the range of 7.48 to 7.92 ppm, while the singlet at 7.30 corresponds to H-6. The singlets at 2.28 and 1.50 ppm in **3** correspond to the acetates at C-1,5 and C-2,4, respectively, where the upfield shift of the latter is attributed to the proximity of the acridine ring. The ^{1}H nmr spectrum of **4** shows a broad signal centered at 9.85 ppm due to the protons at the 2', 4' and 6' positions of pyridine, while the protons at 3' and 5' were ascribed to the signal at 8.30 ppm. The quinone proton in **4** gives rise to a singlet at 5.80 ppm while the hydroxyl proton appears at 7.50 ppm.

As far as the ir spectra of compounds **1** to **3** is concerned, all compounds showed the characteristic ester band around 1770 cm^{-1}.

The mass spectra show in all cases the presence of the corresponding molecular ion and four successive losses of $[CH_2CO]^+$ units which gave rise to the base peak.

The ^{13}C nmr spectra of these compounds **1-3** were ascribed using the literature values reported for pyridine [4], 3-picoline [5] and acridine [6] as well as observation of long range coupling constants. In general, it was observed that the ^{13}C chemical shifts of the leucotetraacetate substi-

tuents do not differ considerably on going from compound **1** to **3**. Thus C-6 shows a $\Delta\delta$ (0.1 ppm), C-1,5(0.4), C-4,2(0.7) and C-3(0.8). In contrast to the ^{1}H nmr spectrum of **1**, the ^{13}C spectrum showed nearly identical shifts for the four acetate groups. The singlets at 140.0 ppm and 140.6 ppm in **1** were ascribed to C-4′ and C-1,5, respectively based on long range coupling constants since 4′ gives rise to a triplet in the coupled spectrum while C-1,5 gives a doublet that shows a chemical shift in agreement with that of the same carbons in **7**. On the other hand, C-1,5 and C-2,3 in **1** to **3** were tentatively assigned as shown in the experimental part. In the ^{13}C nmr spectrum of **4**, the signal at 104.9 ppm which is observed as a doublet in the coupled spectrum was assigned to C-3 and C-6 while the quaternary oxycarbons at C-1,2,4 and C-5 give rise to a signal at 171.4 ppm, in accordance with previous reports [7].

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a MX-1-FT Nicolet spectrophotometer. Proton nmr spectra were obtained on a Varian EM390 spectrometer while ^{13}C spectra were determined on Varian XL-100A-12FT-16K, Jeol FX90K-FT and Bruker-WP 200 spectrometers. Mass spectra were obtained on a Hewlett Packard 5985-A spectrometer. Elemental analyses were performed by Butterworth Laboratories Ltd., Middlesex, U. K.

3-(4-Pyridyl)-1,2,4,5-benzenetetrol Tetraacetate (**1**).

A solution of 2,5-dihydroxy-1,4-benzoquinone (1 g) in 5.6 ml of pyridine was stirred at room temperature for 1 hour, followed by addition of acetic anhydride (3.3 ml). The reaction mixture was stirred an additional period of 24 hours followed by removal of unreacted acetic anhydride and pyridine. The residue was chromatographed over silicagel 60 using a 1:1 hexane:dichloromethane mixture affording 0.80 g of **1**, mp 228-230°; ^{1}H-nmr (deuteriochloroform): δ 8.66 (m, 2H, H-2′, 6′), 7.28 (s, 1H, H-6), 7.21 (m, 2H, H-3′, 5′), 2.28 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$); ^{13}C-nmr (deuteriochloroform): δ 167.5 (CO), 167.4 (CO), 149.8 (C-2′, C-6′), 140.6 (C-1, C-5), 140.0 (C-4′), 137.5 (C-2, C-4), 128.8 (C-3), 124 (C-3′,5′), 20.5 (CH_3), 19.9 (CH_3); ir (potassium bromide): 1775, 1765, 1640, 1466, 1371, 1198, 1185 cm^{-1}; ms: m/z 387 (4.4, M$^+$), 388 (1.1, M$^+$ + 1), 345 (20.0), 303 (41.6), 261 (48.4), 219 (100.0, base peak), 218 (44.9), 190 (12.0), 43 (25.0).

Anal. Calcd. for $C_{19}H_{17}O_8N.H_2O$: C, 56.29; H, 4.72; N, 3.45. Found: C, 56.81; H, 4.57; N, 3.34.

3-[4-(3-Methylpyridyl)]-1,2,4,5-benzenetetrol Tetraacetate (**2**).

Compound **2** was prepared from 1 g of 2,5-dihydroxy-1,4-benzoquinone, 3 ml of 3-picoline and 3 ml of acetic anhydride using the procedure described for the preparation of **1**. The product (125 mg) showed mp 186-187°; ^{1}H-nmr (deuteriochloroform): δ 8.65 (s, 1H, H-2′), 8.50 (d, J = 4.5 Hz, 1H, H-6′), 7.35 (s, 1H, H-6), 7.05 (d, J = 4.5 Hz, 1H, H-5′), 2.27 (s, 3H, $COCH_3$), 2.15 (s, 3H, CH_3), 1.90 (s, 3H, $COCH_3$); ^{13}C-nmr (deuteriochloroform): δ 167.4 (CO) 167.1 (CO), 151.0 (C-2′), 146.9 (C-6′), 140.7 (C-5, C-1), 139.5 (C-4′), 137.5 (C-4, C-2), 132.9 (C-3′), 128.6 (C-3), 124.5 (C-5′), 118.1 (C-6), 20.6 (CH_3), 19.8 (CH_3), 16.4 (3′-CH_3); ir (potassium bromide): 1777, 1761, 1465, 1372, 1207, 1177, 1132, 1102, 1021, 903 cm^{-1}; ms: m/z 401 (10.9 M$^+$), 402 (3.3 M$^+$ + 1), 360 (7.0), 359 (30.0), 318 (6.0), 317 (40.0), 276 (10.0), 275 (43.0), 234 (15.0), 233 (100.0, base peak), 232 (47.0), 43 (40.0).

Anal. Calcd. for $C_{20}H_{19}O_8N.H_2O$: C, 57.28; H, 5.04; N, 3.34. Found: C, 57.82; H, 4.98; N, 3.03.

3-(9-Acridyl)-1,2,4,5-benzenetetrol Tetraacetate (**3**).

The title compound was prepared from 1 g of 2,5-dihydroxy-1,4-benzoquinone, 1 g of acridine and 3 ml of acetic anhydride. The solution was stirred at room temperature for 24 hours and the solvent removed. The residue was chromatographed over silica gel 60 using a 1:1 hexane:-dichloromethane solution and afforded 350 mg of **3**, mp 204-208°; ^{1}H-nmr (deuteriochloroform): δ 8.32 (dd, J = 6, 1 Hz, 2H, H-5′, 4′), 7.48-7.92 (m, 6H, H-1′, 2′, 3′, 6′, 7′, 8′), 7.30 (s, 1H, H-6), 2.28 (s, 3H, $COCH_3$), 1.50 (s, 3H, $COCH_3$); ^{13}C-nmr (deuteriochloroform): δ 167.4 (CO), 166.8 (CO), 148.7 (C-10a′, C-4a′), 141.0 (C-1, C-5), 138.7 (C-2, C-4), 136.2 (C-9′), 130.3 (C-1′, C-8′), 129.6 (C-3), 125.8 (C-2′, C-7′), 126.4 (C-9a′, C-8a′), 124.9 (C-4′, C-5′), 119.1 (C-3′, C-6′), 118.1 (C-6), 20.6 (CH_3), 19.5 (CH_3), 19.5 (CH_3); ir (potassium bromide): 1778, 1462, 1178, 1107, 1019, 964, 763 cm^{-1}; ms: m/z 487 (28.6, M$^+$), 488 (8.7, M$^+$ + 1), 445 (16.0), 404 (7.0), 403 (20.0), 362 (10.0), 361 (47.0), 320 (20.0), 319 (100.0 base peak) 318 (53.0), 43 (20.0).

Anal. Calcd. for $C_{20}H_{19}NO_8.H_2O$: C, 64.41; H, 4.20; N, 2.78. Found: C, 64.47; H, 4.54; N, 2.48.

2,5-Dihydroxy-1,4-benzoquinone, Pyridine Complex (**4**).

2,5-Dihydroxy-1,4-benzoquinone (2 g) was dissolved in benzene (20 ml) and pyridine (0.57 ml) was added. The reaction mixture was refluxed for 1 hour giving rise to a red precipitate which was filtered off and washed to yield 2.5 g of **4**, mp 163-164°; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 9.85 (broad, 6H, H-2′, 4′, 6′), 8.30 (broad, 4H, H-3′, 5′), 7.50 (broad, 2H, OH), 5.80 (s, 2H, H-6); ^{13}C-nmr (deuteriodimethylsulfoxide): δ 171.4 (C-1, C-2, C-4 and C-5), 147.5 (C-2′, C-6′), 138.9 (C-4), 124.8 (C-3′, C-5′), 104.9 (C-3, C-6); ir (potassium bromide): 1660, 1632, 1596, 1408, 1294, 1231, 1214, 1167, 823 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}NO_8$: C, 56.81; H, 3.64; N, 3.90. Found: C, 56.61; H, 3.54; N, 3.55.

2,5-Dihydroxy-1,4-benzoquinone, 3-Picoline Complex (**5**).

Compound **5** was prepared using the procedure described for **4**. The reaction gave a red precipitate, mp 180-183°; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 8.50-7.40 (broad, 8H, H-2′, 4′, 5′, 6′), 5.85 (s, 2H, H-3,6), 2.45 (s, 6H, CH_3).

Anal. Calcd. for $C_{18}H_{15}NO_8$: C, 57.91; H, 4.04; N, 3.75. Found: C, 58.33; H, 4.12; N, 3.52.

1,5-Dihydroxy-1,4-benzoquinone, Acridine Complex (**6**).

The title compound was prepared as in the case of **4**, the reaction gave a red precipitate, mp 320-324°; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 8.50-7.40 (broad, 6H, H-4,5,9), 6.60-7.20 (broad, 12H, H-1,2,3,6,7,8), 5.85 (s, 2H, H-3,6).

Anal. Calcd. for $C_{25}H_{17}NO_8$: C, 65.36; H, 3.72; N, 3.04. Found: C, 68.25; H, 3.98; N, 2.59.

1,2,4,5-Benzenetetrol Tetraacetate (**7**).

The title compound was a by-product in the formation of **1** to **3**. It was obtained by chromatography, from the first dichloromethane fractions and recrystallized from acetone, mp 217-220°; ^{1}H-nmr (deuteriochloroform): δ 7.15 (s, 2H, H-2), 2.25 (s, 12H, $COCH_3$); ^{13}C nmr (deuteriochloroform): δ 167.6 ($COCH_3$), 139.6 (C-1), 118.2 (C-2), 20.6 (CH_3); ir (potassium bromide): 2940, 1782, 1766, 1501, 1373, 1210, 1190, 1177, 1160, 1012, 917 cm^{-1}; ms: m/z 310 (M$^+$, 4.4), 311 (M$^+$ + 1, 0.7), 268 (17.9), 226 (55.1), 184 (58.2), 142 (100.0 base peak), 43 (12.0).

Anal. Calcd. for $C_{14}H_{14}O_8$: C, 54.19; H, 4.54. Found: C, 54.26; H, 4.60.

2,5-Acetoxy-1,4-benzoquinone (**8**).

A solution of **4** (0.5 g) in 3 ml of acetic anhydride was stirred at room temperature for 12 hours followed by removal of excess anhydride. The residue was extracted with dichloromethane and the organic phase washed with water, dried (sodium sulfate) and evaporated. Crystallization from chloroform gave 345 mg of **8**, mp 135-137°; ^{1}H nmr (deuteriochloroform): δ 6.65 (s, 2H, H-3), 2.35 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): δ 179.9 (C-1), 167.3 ($COCH_3$), 152.6 (C-2), 122.3 (C-3), 20.5

(CH_3); ir (potassium bromide): 1784, 1771, 1684, 1671, 1624, 1373, 1196, 1129, 917, 908 cm^{-1}; ms: m/z 224 (0.1, M^+), 182 (25.0), 140 (29.0), 69 (30.0), 43 (100.0 base peak).

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.57; H, 3.59. Found: C, 53.49; H, 3.62.

Acknowledgement.

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