

Angular Heterocycles. A Convenient Synthesis of 6-*N*-(Acetylanilino)-5*H*-benzo[*a*]phenothiazin-5-one, 6-*N*-(Acetylanilino)-5*H*-benzo[*a*]phenoxazin-5-ones and Their Derivatives

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Received May 27, 1983

The reaction of 2-*N*-(acetylanilino)-3-chloro-1,4-naphthoquinone (**2**) with bifunctional aromatic amines afforded angular heterocycles **6** and **7**. Reductive acetylation of **7** provided *o*-acyl **9** and *O,N*-diacyl **10** derivatives depending upon the reaction conditions. The ir, uv, pmr and mass spectral data are also presented.

J. Heterocyclic Chem., **21**, 509 (1984).

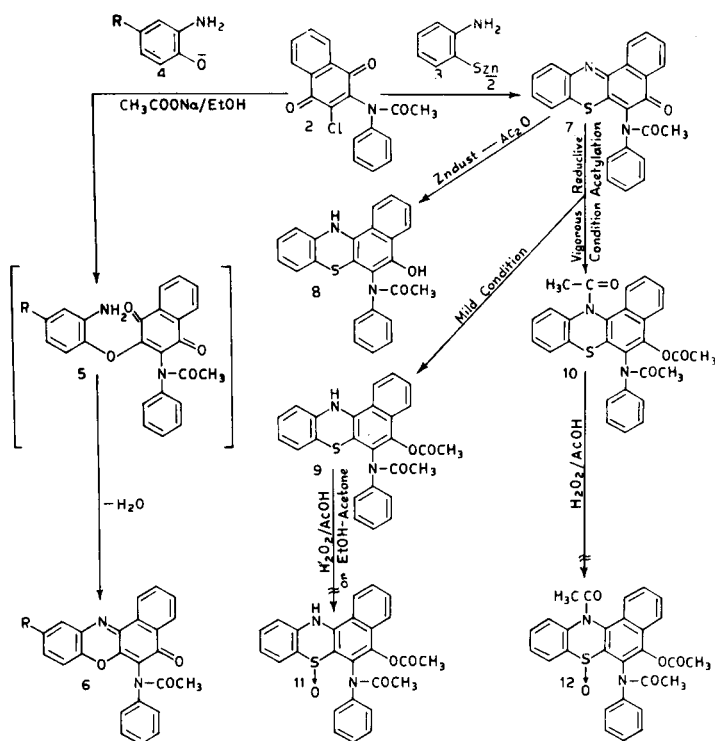
The phenothiazine and phenoxazine ring systems have been extensively studied and many such compounds have now become commercially available which are widely used in medical practice [1-4] and in the dye industry [5,6]. Many structural changes in these heterocycles have been made [6-13] with the view to obtaining new compounds which may also have the biological and coloring properties. A number of interesting changes in properties of these heterocycles have been observed by changing varied nuclear substituents [6-13], synthesising analog new tricyclic compounds [6,11-13] and fused ring derivatives [12,14-20]. To date, however, no reports have appeared in the literature which have described synthesis of any acetylanilino-phenothiazines and acetylanilino-phenoxazines. As a part of our studies [16-20] on the chemistry and spectroscopic properties of new angular heterocycles using 1,4-naphthoquinones as starting material, we now report a convenient single step high yield synthesis of acetylanilino-5*H*-benzo[*a*]phenothiazin-5-one (**7**), acetylanilino-5*H*-benzo[*a*]phenoxazin-5-one (**6**) and their derivatives.

In the previous paper [21] in this series we reported that 2-anilino-3-chloro-1,4-naphthoquinone (**1**) has no reaction with the difunctional nucleophiles *e.g.* *o*-aminophenols, *o*-phenylenediamines *etc.* We were unable to synthesize [21] anilino-5*H*-benzo[*a*]phenoxazines and anilino-5*H*-benzo[*a*]phenothiazines using anilino-1,4-naphthoquinone as starting material. Acetylation of **1** with acetic anhydride in the presence of acid as a catalyst afforded a quantitative yield of **2** in which the chlorine can be easily displaced by nucleophiles [24]. The reactivity of chlorine in **2** is enhanced due to the electron withdrawing nature of the acetyl group attached to nitrogen.

Thus when **2** was condensed with the zinc mercaptide of 2-aminothiophenol (**3**) in ethanol it afforded red colored **7** in excellent yield. Elemental analysis, proton magnetic resonance, infrared and mass spectral data are in close agreement with the assigned structure. A band characteristic 348 nm of benzophenothiazine system [23] was observed in the uv spectrum. Reduction of **2** with zinc dust in

acetic acid and careful work up of the reaction mixture gave the light yellow colored **8**.

Scheme 1



4a. R = H. 4b. R = NO₂. 4c. 2-AMINO-3-HYDROXY PYRIDINE

Reductive acetylation of **7** gave two series of benzo[*a*]phenothiazine derivatives, in which the degree of acetylation depends upon the reaction condition. Under milder condition the acetylation occurred selectively on the oxygen to give a light yellow colored compound melting at 224°. The ir shows the absorption at 1765 cm^{-1} (aromatic acetate) and at 3250 cm^{-1} (NH). Elemental analysis and mass spectroscopy are in agreement with the molecular formula $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$. These results are in perfect agreement with the structure **9**. Further confirmative evidence

Table 1

Reaction of 2-*N*-(Acetylanilino)-3-chloro-1,4-naphthoquinone (**2**) with the *o*-Aminophenols **4a-c**

Reactants	1	Products Yield (%)	Mp °C	Molecular Formula	Data for 6		
					Elemental Analysis (Calcd. %)		
		6a-e			C	H	N
2 + 4a	10	58	235	C ₂₄ H ₁₆ N ₂ O ₃	75.79	4.23	7.37
					(75.40)	(4.45)	(7.80)
2 + 4b	8	70	310	C ₂₄ H ₁₅ N ₃ O ₅	66.77	3.55	9.87
					(66.87)	(3.50)	(9.78)
2 + 4c	7	45	228	C ₂₃ H ₁₅ N ₃ O ₃	72.44	3.96	11.02
					(72.08)	(3.78)	(11.40)

Table 2

Spectroscopic Data of 6-*N*-(Acetylanilino)-5*H*-benzo[*a*]phenoxazin-5-ones **6a-c**

Compound	UV spectrum λ max (nm)	Infrared Spectrum cm ⁻¹	¹ H NMR Spectrum (deuteriochloroform) ppm	Mass Spectral Data m/e (relative intensity)
6a	354, 440	1675 s (COCH ₃), 1602 (C=O), 1602 m, 1580 s, 1560 m, 1510 m	2.17 (s, 3H, COCH ₃), 7.1-8.63 (m, 13H, aromatic protons)	380 (M ⁺ , 6.6), 340 (3.3), 339 (20.4), 338 (79.1), 337 (6.9), 322 (2.1), 321 (8.6), 310 (7.0), 309 (28.1), 308 (7.0), 307 (3.2), 294 (3.8), 293 (12.4), 292 (6.6), 291 (2.7), 282 (3.8), 281 (8.2), 280 (6.9), 279 (9.1), 278 (2.7), 273 (4.3), 272 (8.7), 236 (4.9), 235 (29.7), 234 (100), 233 (3.9), 232 (3.2), 231 (3.1), 229 (2.3), 190 (3.5), 178 (2.8), 177 (4.9), 152 (2.0), 151 (4.9), 118 (2.7), 105 (3.2), 104 (7.2), 103 (3.9), 102 (9.7), 101 (2.3), 100 (3.0), 98 (2.5), 93 (4.4), 92 (2.2), 91 (2.2), 88 (2.7), 77 (7.7), 76 (3.3), 63 (3.6), 62 (8.8), 59 (7.7), 52 (3.7), 51 (50), 50 (27.1)
6b	296, 344, 415	1670 m (COCH ₃), 1630 m (C=O), 1585 s, 1560 sh, 1530 sh, 1490 m	2.13 (s, 3H, COCH ₃), 7.1-8.5 (m, 12H, aromatic protons)	425 (M ⁺ , 3.2), 385 (4.2), 384 (25.4), 383 (100), 353 (2.7), 338 (5.2), 337 (20), 336 (2.7), 320 (2.0), 283 (2.5), 280 (2.9), 279 (8.0), 248 (2.5), 234 (2.0), 233 (9.1), 203 (2.2), 178 (2.3), 177 (7.6), 176 (2.5), 151 (2.9), 150 (2.5), 118 (2.4), 79 (2.3), 78 (3.2), 77 (14.2), 76 (2.9), 75 (4.9), 51 (6.8)
6c	360, 440,	1665 s (COCH ₃), 1640 (C=O), 1600 s, 1590 w, 1515 m, 1560 w, 1530 sh, 1495 sh	2.23 (s, 3H, COCH ₃), 7.0-8.6 (m, 12H, aromatic protons)	381 (M ⁺ , 1.4), 380 (5.1), 340 (3.9), 338 (100), 337 (9.2), 322 (2.5), 321 (8.9), 309 (5.6), 235 (4.0), 234 (14.3), 212 (2.4), 190 (2.2), 179 (2.1), 178 (2.8), 177 (5.1), 152 (2.4), 151 (5.6), 118 (2.4), 109 (7.2), 80 (4.0), 77 (4.6), 63 (2.3), 51 (5.9), 50 (2.9)

of structure **9** was provided by the pmr spectrum in which the methyl protons of acetoxy group exhibit a singlet at δ 2.4, methyl protons of acetyl group appeared at δ 2.3 and aromatic protons occurred between δ 6.73-8.2, but could not be individually distinguished. Under more vigorous conditions (Experimental) the acetylation occurred on both nitrogen and oxygen affording **10** and the structure was assigned on the basis of elemental analysis and spectroscopic data. Several attempts were made to convert **9** and **10** into the corresponding sulfoxides **11** and **12** with 30% hydrogen peroxide in glacial acetic acid under various conditions [25]. Instead of yielding the desired products **11** and **12**, oxidative deacetylation occurred, in each case, with the formation of **7** and other unidentifiable products. The formation of phenothiazones under these conditions from acetyl- and acetoxyphenothiazine derivatives is explained in the literature [25]. Contrary to this, the oxidation of **10** with 30% hydrogen peroxide in ethanol-acetone under various conditions led surprisingly to the starting material instead of **12**.

The reaction of **2** with substituted *o*-aminophenol (**4**) in the presence of anhydrous sodium acetate in ethanol afforded 6-*N*-(acetylanilino)-5*H*-benzo[*a*]phenoxazin-5-one (**6**) and **1**. The structures of compounds **6** were fully supported by microanalytical results and spectral data (Table 1 and 2). It appears that the reaction of **2** with **4** proceeds under these conditions mainly in two directions. i) We have already established [20] that **2** in the presence of anhydrous sodium acetate exists as a phenoxide anion, thus in the main reaction phenoxide anion attacks the carbon atom to which the chlorine atom of **2** is attached affording the presumed intermediate **5** and subsequent ring closure to yield **6**. There is no chance to isolate **5** because under drastic conditions **5** will rapidly cyclize to **6**. ii) Simultaneously, in a side reaction sodium acetate present in the reaction mixture will cause the deacetylation of **2** to give **1**. This argument has been further strengthened as in a separate experiment **2** can be deacetylated in good yield to **1** with anhydrous sodium acetate in ethanol. Several attempts met with failure to deacetylate **7** and **6** with sodium

acetate or aqueous sodium hydroxide, in all cases it yielded starting material and other undesired products.

EXPERIMENTAL

Melting points were taken in open capillary tubes using a Toshniwal melting point apparatus and are uncorrected. The infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer 377 grating spectrophotometer, and nmr spectra were determined on a T-60A Varian spectrophotometer using tetramethylsilane as the internal reference. The letters, s, d and m are used to indicate broad singlet, doublet and multiplet respectively. Ultraviolet spectra were determined on a SP8-100 UV spectrophotometer using matched 1 cm quartz cells. Low resolution mass spectra were recorded on JEOL JMS-D300 equipped with a Model MJS-2000 data system at an ionizing energy of 70 eV, and an ion source temperature of 250°. Purity of all the synthesized compounds was ascertained on thin layer chromatography [26] of silica gel in various non-aqueous solvent system. 2-Anilino-3-chloro-1,4-naphthoquinone (**1**) was prepared by the method of Van Allan *et al.* [24].

2-*N*-(Acetylanilino)-3-chloro-1,4-naphthoquinone (**2**).

To a stirred solution of 2-anilino-3-chloro-1,4-naphthoquinone (40 g, 0.14 mole) in 200 ml of acetic anhydride at 80° was added a few drops of concentrated sulfuric acid. The stirring was continued at the same temperature (1.5 hours). It was then allowed to cool to room temperature and poured into ice-cooled water. The precipitate was isolated, dried over anhydrous calcium chloride, and crystallized from dichloroethane to yield **2** as yellow crystals (45 g, 97%), mp 140° [24]; uv (methanol): λ max 330 nm; ir (potassium bromide): 1670 s (COCH₃), 1660 m (C=O), 1640 w, 1595 s, 1540 w, 1525 w, 1490 vs, 1470 w, 1450 w, 1425 w, 1405 w, 1350 vs, 1310 s, 1310 s, 1290 s, 1265 m, 1250 vs, 1165 m, 1135 w, 1095 s, 1060 w, 1020 w, 1010 w, 995 w, 980 w, 960 w, 950 m, 910 sh, 895 w, 815 w, 830 vs, 770 m, 750 m, 725 m cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.13 (s, 3H, COCH₃), 7.07-8.47 (m, 9H, aromatic protons); ms: m/e (relative intensity) 325 (M⁺, 2.2), 291 (4.0), 290 (10.11), 286 (5.7), 285 (3.1), 284 (17.0), 283 (83.4), 282 (3.5), 250 (2.5), 249 (20.7), 248 (100), 247 (5.4), 220 (5.4), 219 (5.4), 192 (2.0), 191 (5.1), 190 (9.2), 180 (2.0), 164 (2.9), 163 (2.7), 135 (2.6), 123 (5.6), 114 (3.5), 105 (10.1), 104 (7.1), 99 (3.3), 89 (4.0), 88 (3.4), 87 (2.1), 78 (4.8), 77 (4.8), 76 (1.6), 75 (4.3), 74 (2.8), 64 (7.9), 63 (3.0), 51 (21.3), 50 (7.1).

Anal. Calcd. for C₁₈H₁₂ClNO₂: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.50; H, 3.50; N, 4.60.

6-*N*-(Acetylanilino)-5*H*-benzo[*a*]phenothiazin-5-one (**7**).

A mixture of 2-*N*-(acetylanilino)-3-chloro-1,4-naphthoquinone (3.2 g, 0.01 mole) and zinc mercaptide of 2-aminothiophenol (1.56 g, 0.005 mole) in absolute ethanol (100 ml) was heated to reflux for 2 hours. The reaction mixture was allowed to cool overnight. The resulting solid was filtered, dried, crystallized from dichloroethane-hexane to give **7** as red crystals (3.2 g, 80%) mp 232°; uv (methanol): λ max 416, 348, 276 nm; ir (potassium bromide): λ max 1670 m (COCH₃), 1620 s, (C=O), 1595 m, 1580 m, 1340 m, 1320 m, 1280 sh, 1235 m, 840 s, 720 m cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.24 (s, 3H, COCH₃), 7.1-8.58 (m, 13H, aromatic protons); ms: m/e (relative intensity) 396 (M⁺, 9.6), 354 (100), 337 (4.4), 325 (5.9), 321 (7.3), 293 (2.2), 262 (3.0), 250 (28.0), 248 (2.5), 233 (2.1), 223 (7.6), 222 (14.4), 220 (3.3), 196 (2.1), 195 (2.8), 190 (7.1), 178 (2.4), 177 (3.7), 152 (2.0), 151 (3.8), 146 (7.4), 121 (3.8), 120 (4.7), 119 (4.2), 118 (3.5), 102 (2.0), 77 (11.0), 76 (3.0), 69 (3.1), 51 (8.1), 50 (2.3).

Anal. Calcd. for C₂₂H₁₆N₂O₃S: C, 72.73; H, 4.06; N, 7.07. Found: C, 72.90; H, 4.20; N, 6.78.

6-*N*-(Acetylanilino)-12*H*-benzo[*a*]phenothiazin-5-ol (**8**).

A mixture of 6-*N*-(acetylanilino)-5*H*-benzo[*a*]phenothiazin-5-one (1.0 g, 0.004 mole), acetic anhydride (5 ml), absolute ethanol (25 ml) and 0.5 g of zinc dust was refluxed for 30 minutes. Acetone was removed under reduced

pressure from reaction mixture. The crude mass was suspended in acetone-ethyl acetate (3:1), and filtered. The filtrate was poured into 250 ml of petroleum ether (40-60°), and resulting solid was collected to give **8** as yellow powder (0.9, 72%), mp 192°; ir (potassium bromide): ν max 3300 w, 1650 s, (OCOCH₃), 1630 sh, 1615 sh, 1595 s, 1550 sh, 1535 sh, 1460 m, 1430 s, 1280 s, 1305 sh, 1280 s, 1240 w, 1220 w, 1202 w, 1180 m, 1130 m, 1102 sh, 1095 sh, 1035 w, 1010 m, 990 m, 960 m, 920 w, 880 m, 870 m, 825 m, 795 sh, 750 s, 710 s cm⁻¹; ms: m/e (relative intensity) 357 (2.7), 356 (10.7), 355 (10), 354 (11.5), 337 (2.1), 330 (3.3), 325 (8.0), 324 (2.4), 323 (2.1), 322 (4.0), 321 (7.4), 320 (2.2), 308 (2.3), 307 (5.5), 266 (3.5), 265 (17.2), 264 (12), 263 (35.3), 262 (2.7), 252 (9.3), 251 (18.0), 250 (25.6), 237 (2.1), 236 (8.6), 235 (27.2), 234 (6.6), 233 (6.1), 232 (6.8), 223 (15.5), 222 (21.8), 221 (3.5), 220 (6.6), 219 (8.8), 218 (3.0), 217 (2.4), 216 (2.1), 204 (7.2), 203 (7.5), 202 (2.7), 191 (3.9), 190 (7.2), 172 (2.1), 170 (2.6), 169 (2.1), 165 (6.7), 164 (8.9), 163 (9.1), 162 (2.8), 153 (4.2), 152 (7.9), 151 (8.9), 150 (6.8), 149 (18.4), 148 (6.2), 147 (2.5), 146 (12.0), 145 (2.3), 137 (2.5), 136 (11.1), 135 (65.5), 133 (5.0), 132 (3.6), 130 (3.2), 128 (2.4), 118 (2.9), 108 (2.9), 102 (3.6), 96 (2.1), 94 (9.9), 93 (2.2), 66 (31.8), 65 (54.2), 63 (22.4), 62 (11.5), 61 (5.3), 58 (2.8), 55 (3.2), 54 (7.5), 53 (6.0), 52 (19), 51 (46), 50 (25.4), 49 (2.6), 47 (2.6), 45 (25.8), 44 (14.7), 43 (M⁺, 100), 42 (42), 37 (9.8), 28 (13.5), 27 (2.3), 15 (2.5).

Anal. Calcd. for C₂₂H₁₈N₂O₂S: C, 72.36; H, 4.55; N, 7.03. Found: C, 72.10; H, 4.80; N, 6.87.

5-Acetoxy-6-*N*-(acetylanilino)-12*H*-benzo[*a*]phenothiazine (**9**).

A mixture of 6-*N*-(acetylanilino)-5*H*-benzo[*a*]phenothiazin-5-one (1.30 g, 3.3 mmoles), acetic anhydride (25 ml), dry pyridine (0.5 ml) and 0.5 g of zinc dust was stirred at ambient temperature for 30 minutes. Then reaction mixture was refluxed on water bath for next 10 minutes. The light green reaction mixture was filtered and poured into ice-cooled water. The precipitate was collected, dried and crystallized from dichloroethane-hexane to provide **9** as light yellow powder (1.1 g, 72%), mp 224°; uv (methanol): λ max 366 nm; ir (potassium bromide): ν max 3250 m (NH), 1765 s (O-C(O)-CH₃), 1660 vs (COCH₃), 1600 m, 1590 m, 1550 m, 1510 s, 1470 vs, 1430 w, 1420 m, 1370 sh, 1340 m, 1280 s, 1225 s, 1160 s, 1135 s, 1102 w, 1050 m, 1020 s, 1000 s, 980 w, 920 w, 895 s, 860 s, 810 s, 800 m, 715 vs, 722 s cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.3 (s, 3H, 6-NCOCH₃), 2.4 (s, 3H, 5-OCOCH₃), 6.73-8.2 (m, 13H, aromatic protons); ms: m/e (relative intensity) 442 (M⁺, 12.4), 441 (M⁺, 3.4), 440 (M⁺, 100), 400 (2.8), 399 (8.8), 398 (29.4), 381 (4.2), 358 (2.8), 357 (18.2), 356 (36.4), 355 (29.4), 354 (7.1), 331 (2.8), 336 (24.0), 329 (2.6), 302 (8.2), 279 (3.7), 264 (5.1), 252 (5.6), 251 (6.0), 250 (3.7), 235 (2.9), 224 (4.3), 223 (8.5), 222 (3.4), 190 (2.6), 121 (3.0), 118 (4.0), 104 (2.2), 78 (2.9), 77 (10.6), 76 (2.9), 69 (2.3), 65 (3.0), 63 (3.0), 62 (5.7), 51 (9.9), 50 (2.5).

Anal. Calcd. for C₂₂H₂₀N₂O₃S: C, 70.89; H, 4.58; N, 6.36. Found: C, 70.50; H, 4.80; N, 6.45.

5-Acetoxy-12-acetyl-6-*N*-(acetylanilino)-12*H*-benzo[*a*]phenothiazine (**10**).

A mixture of 6-*N*-(acetylanilino)-5*H*-benzo[*a*]phenothiazin-5-one (2.1 g, 0.009 mole), acetic anhydride (45 ml) and pyridine (2 ml) was heated to reflux for 2.5 hours in presence of 0.5 g of zinc dust. The colorless reaction solution was filtered and poured into ice cooled water. The resulting yellow solid was filtered, crystallized from cyclohexane to afford **10** as light yellow crystals (1.76 g, 70%), mp 234°; uv (methanol): λ max 279 nm; ir (potassium bromide): ν max 1780 s, 1660 s, 1600 s, 1570 m, 1480 m, 1425 m, 1340 s, 1300 w, 1265 w, 1185 w, 1160 s, 1145 s, 1065 w, 1040 w, 1010 sh, 990 w, 970 w, 860 m, 820 w, 810 w, 756 w, 710 s cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.07 (s, 3H, 12-COCH₃), 2.27 (s, 3H, 6N-COCH₃), 2.40 (s, 3H, 5-OCOCH₃), 7.1-8.4 (m, 13H, aromatic protons); ms: m/e (relative intensity), 482 (M⁺, 8.3), 439 (37.2), 422 (3.8), 397 (18.0), 396 (22.2), 390 (2.2), 379 (2.2), 356 (10.7), 355 (36.0), 354 (100), 337 (2.3), 336 (2.7), 324 (3.0), 320 (3.4), 305 (2.1), 278 (2.2), 277 (4.3), 264 (3.5), 263 (13.1), 262 (18.8), 252 (2.2), 251 (9.8), 250 (7.1), 249 (13.9), 248 (2.6), 247 (2.3), 237 (3.2), 234 (3.2), 233 (3.9), 222 (6.6), 221 (5.4), 218 (2.5), 190 (4.7), 177 (3.2), 166 (2.4), 150 (7.5), 145 (2.9), 135 (3.8), 124 (2.7), 122 (4.2), 121 (3.0), 120 (2.2), 118 (5.4), 108 (12.4), 107 (3.0), 106 (3.0), 104 (2.4), 93 (3.6), 84 (3.7), 80 (4.7), 77 (6.6), 56 (5.4), 55 (2.3), 51 (2.9).

Anal. Calcd. for C₂₈H₂₂N₂O₄S: C, 69.71; H, 4.59; N, 5.81. Found: C,

69.69; H, 4.70; N, 5.87.

General Procedure for the Preparation of 6-(*N*-Acetylanilino)-5*H*-benzo-[*a*]phenoxazin-5-ones (**6a-c**).

A mixture of 2-*N*-(acetylanilino)-3-chloro-1,4-naphthoquinone (3.25 g, 0.01 mole), corresponding substituted *o*-aminophenol (0.01 mole) in presence of the anhydrous sodium acetate (1.62 g, 0.02 mole) in 100 ml of dry ethanol, was heated to reflux under stirring for 2 hours. It was kept for 12 hours in the refrigerator, filtered, washed with hot water and dried. The precipitate was column chromatographed, eluted first with benzene to afford the 2-anilino-3-chloro-1,4-naphthoquinone (**1**). Further elution with acetone-chloroform (1:1) provided **6**. Analytical samples of the compound **6** were obtained by crystallizing them with chloroform-hexane. The yields and other physical data are summarized in Table 1.

Reaction of 2-*N*-(Acetylanilino)-3-chloro-1,4-naphthoquinone (**2**) with Anhydrous Sodium Acetate in Ethanol.

A mixture of **2** (3.2 g, 0.01 mole) and anhydrous sodium acetate (1.64 g, 0.02 mole) in 25 ml of absolute ethanol was refluxed for 2 hours. The reaction mixture was cooled and filtered. The precipitate was poured into water, extracted dichloromethane-ethyl acetate (6:4) and organic phase was dried over anhydrous sodium sulphate and concentrated under reduced pressure. This was poured into 250 ml of ether giving 2 g (65%) of **1**, mp 218°. It was identical in every respect (ir, mass and mixed melting point) with the authentic sample [22].

Acknowledgement.

We are thankful to Prof. Dr. W. Schäfer for encouragement and interest in this work. Our thanks are also due to the Instrumentation Division for recording the spectra.

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