Azatropolones. Part II.[1] The Schmidt Reaction of 2-Methoxy-5-methylbenzoquinone

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2-Methoxy-5-methylbenzoquinone undergoes reaction with sodium azide in sulfuric acid to give (*a*) 3-hydroxy-6-methyl-1*H*-azepin-2,5-dione, which undergoes ring contraction with base to give 5-methyl-4-pyridone-2-carboxylic acid; (*b*) 4-methoxy-7-methyl-1*H*-azepin-2,5-dione, which reacts with phosphorus oxychloride to give methyl 2-chloro-6-methylpyridine-4-carboxylate, not 2-chloro-4-methoxy-7-methyl-5*H*-azepin-5-one; (*c*) 7-methoxy-4-methyl-1*H*-azepin-2,5-dione. The reactions of these compounds are discussed and the evidence for their structures is presented.

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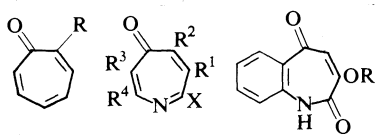
La méthoxy-2 méthyl-5 benzoquinone réagit avec l'azoture de sodium dans l'acide sulfurique pour donner (*a*) l'hydroxy-3 méthyl-6 1*H*-azépinedione-2,5 qui subit une contraction de cycle en présence de bases pour conduire à l'acide méthyl-5 pyridone-4 carboxylique-2; (*b*) la méthoxy-4 méthyl-7 1*H*-azépinedione-2,5 qui réagit avec l'oxychlorure de phosphore pour conduire à l'ester méthylique de l'acide chloro-2 méthyl-6 pyridinecarboxylique-4 et non pas à la chloro-2 méthoxy-4 méthyl-7 1*H*-azépinone-5; (*c*) la méthoxy-7 méthyl-4 1*H*-azépinedione-2,5. On discute des réactions de ces composés et l'on présente des preuves pour leur structure.
[Traduit par le journal]

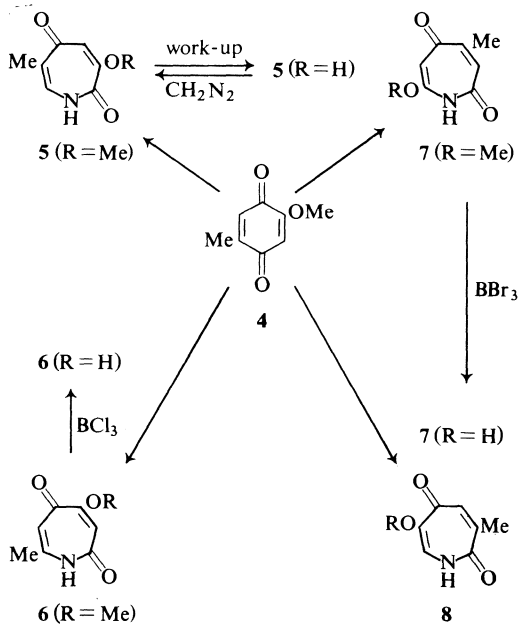
The aromaticity of tropone (**1**, R = H) and tropolone (**1**, R = OH) (1) has recently been questioned (2). Having long been interested in aza analogs of tropolone (3), we now describe the synthesis of hydroxy derivatives of 5-azatropone (**2**) and discuss their nature.



1 **2** **3**

The reaction of quinones with hydrogen azide has given azatropones (4*a*) and benzazatropones (4*b*). We have reported the ring expansion of alkoxynaphthoquinones to give benzazatropolones **3** (5). Hydroxyquinones undergo an alternative reaction leading to ring contraction (6).

When 2-methoxy-5-methylbenzoquinone (**4**) was treated with sodium azide in sulfuric acid, three of the four possible ring expansion products were isolated. These were compounds **5** (R = H), **6** (R = Me), and **7** (R = Me). Lactam **8** was not found. One of the products gave a red ferric chloride color, demethylation having occurred. By analogy with compound **3** which tends to demethylate (R = Me → H) on work-up, we suspected structure **5** (R = H) for our enolic product. When it was treated with diazomethane, it gave a methyl ether which differed from the two other ethers isolated.



[1]For Part I see ref. 3.
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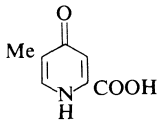
Alkaline ring contraction of **5** (R = H) gave a methylpyridone carboxylic acid. Zinc dust pyrolysis of this acid gave a pyridine base identified by v.p.c.–m.s. as β-picoline.[3]

We synthesized 5-methyl-4-pyridone-2-carboxylic acid (7) and though the melting point differed from the literature value, the compound was identical in all respects with our ring contracted product, thus confirming the structure **9** and hence **5** (R = H) for the precursor.[4]

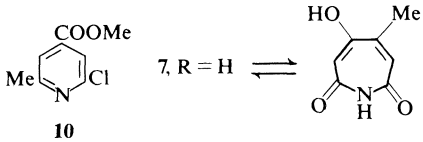


9

A less polar product isolated from the Schmidt reaction has been assigned structure **6** (R = Me). It was readily demethylated by boron trichloride to **6** (R = H), which gave a red color with ferric chloride.

The nonaromatic nature of **6** (R = H) became apparent on reaction with alkali when the molecule was completely hydrolyzed. Zinc dust pyrolysis of the alkaline reaction product did not yield any trace of picoline.

Reaction of **6** (R = H) with phosphorus oxychloride gave a polymer. When the ether **6** (R = Me) was treated with this reagent however, the product was methyl 2-chloro-6-methylisonicotinate (**10**), identical in all respects with a sample prepared from genuine 2-chloro-6-methylisonicotinic acid (8).[5] The least polar product from the Schmidt reaction was assigned structure **7** (R = Me). It could not be demethylated by boron trichloride (9). Boron tribromide gave **7** (R = H) which on structural grounds is not expected to give a ferric chloride color. None was in fact given. The n.m.r. (Table 1) and u.v. (Table 2) spectra are in accord with the proposed structure. Reaction of **7** (R = H) with alkali gave no characterizable product.



10

[3]We thank the Reilly Tar & Chemical Co. for generous samples of pure picolines.

[4]A significant point about this compound is that its n.m.r. spectrum (Table 1) shows strong coupling (8 Hz) between H-1 and H-7. This is within the range for *ortho* aromatic protons and suggests some bond delocalization as would be expected when mesomeric structures contribute. There are also tautomeric factors in the energy profile but their absence in the ether **5** (R = Me) does not alter $J_{1,7}$ which is still 8 Hz. This is at the lower end of the *ortho* coupling range of 7–10 Hz but still leaves the hetero atom with appreciable sp^2 character. A reasonable postulate is that the compound has some measure of aromaticity and may be termed an azatropolone.

[5]We thank Dr. H. Gutmann of Hoffmann-La Roche & Co. for a sample of this acid.

Experimental

Unless otherwise stated, i.r. spectra (Unicam S.P. 200) are in potassium bromide, quoting ν_{max} in cm^{-1}; u.v. spectra (S.P. 800) are in methanol, quoting λ_{max} in nm (log ε); n.m.r. spectra (Jeol Co. C60 HL) are in DMSO-d_6 quoting τ values relative to TMS (internal); mass spectra (A.E.I. M.S. 12) are at 70 eV on the probe quoting *m/e* (relative intensity); m.p.'s are taken in capillary tubes. Recrystallization solvents are given in parentheses after the melting point.

Vapor phase chromatography was done on a Pye 104 instrument using a 5 ft. × ¼ in. glass column of 10% SE-30 on Chromosorb W, carrier gas helium at 65°. Connection to the M.S. 12 was made via a Watson-Biemann separator.

The Schmidt Reaction of 2-Methoxy-5-methylbenzoquinone (4)

To 50 ml concentrated sulfuric acid, stirred at 0°, 5.84 g of **4** (10) was added over 20 min. Sodium azide, 2.6 g, was then added over 15 min and the red solution was stirred for 1 h (frothing). The flask was stoppered and stirred at 0° for 1 h and at 20° for 70 h. The solution was then poured into 500 ml water and extracted for 72 h in a chloroform extractor. The solvent flask then held 80 ml solution plus a solid which was collected.

The aqueous layer was re-extracted giving 80 ml clear solution. The filtrate from the first extraction was combined with this and concentrated to a small volume which was again filtered. The combined solid from both extracts was washed with chloroform and dried to give **5** (R = H) as a brown powder, m.p. 253–255°, 1.26 g, 22%; i.r. 3400, 3210, 1667, 1639, 1553, 1250, 1220; m.s. M^+ 153 (100).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.15. Found: C, 54.9; H, 4.6; N, 9.0.

The filtrate from the collection of **5** (R = H) was diluted with 2 vol. of ether and the precipitated material was filtered off. From the concentrated filtrate, a second crop of solid was obtained, total yield of **6** (R = Me), 1.05 g, 16%. After sublimation (170°/0.1 mm), the compound had m.p. 226–226.5° (ethanol), almost colorless microcrystals; i.r. 3210, 1671, 1613br, 1225, 1155; m.s. M^+ 167 (35), 69 (100).

Anal. Calcd. for $C_8H_9NO_3$ (mol. wt. 167.0582): C, 57.5; H, 5.4; N, 8.4. Found (mol. wt. 167.0585): C,[6]; H, 5.5; N, 8.5.

The filtrate from the collection of **6** (R = Me) was

[6]The carbon analysis was variable. We thank Prof. A. G. Harrison of the University of Toronto for high resolution mass spectra.

TABLE 1. Nuclear magnetic resonance spectra of 2-methoxy-5-methylbenzoquinone and derived azepines

Compound	R	τ NH	CH = CMe	CH	OMe, s	OH
4		—	3.4d 8.05d	3.95d	6.25	—
5	H	−1.2d*	3.25d* 8.15d	3.65s	—	6.15
			J = 8 Hz			
			3.25s(br) after D_2O exchange			
6	Me	−1.0d*	3.25d* 8.15s(br)	3.75s	6.25	
	Me	−0.8	3.98br 7.85s	4.31br	6.25	
	H	−0.9	3.91d 7.8s	4.2br	—	−0.1
			J = 2 Hz			
7	Me	−0.4br	3.85br 7.9d	4.55s	6.3	—
			3.85q after D_2O exchange			
	H	−2.5	3.9q 7.9d	4.6s	—	0.6

*Each component of doublet broad.

TABLE 2. Ultraviolet spectra of 2-hydroxy-5-methylbenzoquinone, derived azepines and their methyl ethers

Compound	R	ν_{max} (log ε) Neutral	Alkaline*	Acidic*
4 (De-Me)		262	268	262
4		261 (4.28)	261	261
5	H	245 (4.41)	255 = 262 > 335	—
		~295br (3.41)		
	Me	245 (4.44)	245 > 339	245 > 300
		300br (3.54)		
6	Me	241 (4.43)	244 > 340	241 > 320
		320br (3.57)		
	H	240 (4.37)	259 > 315	240 > 322
		~322br (3.36)		
7	Me	277 (4.19)	277	277
		~315sh (3.95)	315sh	315sh
	H	277 (4.11)	277	277
		~315sh (3.84)		315sh

*One drop 2 N NaOH solution added to 1 cm cell for alkaline spectrum, then one drop concentrated HCl for acid spectrum.

chromatographed on Grade I neutral alumina, eluting with chloroform. Compound **7** (R = Me), 0.85 g, 13%, was obtained, m.p. 111–112° (dichloromethane–hexane), colorless prisms or feathery needles; i.r. 3400, 1710, 1674, 1613, 1200, 1180; m.s. M^+ 167 (75), 136 (100).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.5; H, 5.45; N, 8.4. Found: C, 57.7; H, 5.5; N, 8.2.

*Conversion of 3-Hydroxy-5-methyl-1H-azepin-2,5-dione (**5**, R = H), to its Methyl Ether (**5**, R = Me)*

To a stirred suspension of the enol in excess methanol, diazomethane (*ca.* 10-fold excess) in ether was added. After 15 min the solvent was evaporated leaving **5** (R = Me), m.p. 285–287° (ethanol) in 100% yield; i.r. 3150, 1681, 1644, 1606, 1542, 1240, 1200; m.s. M^+ 167 (100), 139 (63), 65 (68).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.5; H, 5.45; N, 8.4. Found: C, 57.6; H, 5.4; N, 8.15.

*Ring Contraction of **5** (R = H)*

Compound **5** (R = H), 200 mg in 2 ml 30% aqueous sodium hydroxide solution was refluxed 1 h, then cooled to 0°. Addition of concentrated hydrochloric acid precipitated a crystalline solid which was collected (centrifuge). After successive washing with water, ethanol, and ether, the compound was dried, 135 mg, 67%, m.p. 270–272° (ethanol); i.r. 3460, 3110, 1665, 1615, 1595br, 1220, 810.

We prepared with difficulty, see below, 5-methyl-4-pyridone-2-carboxylic acid **9** (7). In our hands, this had m.p. 270–271°, (lit. (7) m.p. 255–256°). Mixture m.p. with the ring contraction product above was 270–272°. The i.r. spectra of the two samples were identical.

*Synthesis of 5-Methyl-4-pyridone-2-carboxylic Acid **9***

2,5-Lutidine, 6 g, was converted (7) to 2-acetoxymethyl-5-methyl-4-nitropyridine, mobile orange liquid,

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14% yield; i.r. (film) 1742 br, 1610, 1574, 1540, 1376, 1228, 1198, 1055. The alcohol had (hot-stage) m.p. 67–68° (dichloromethane–hexane), (lit. m.p. 66–67°); i.r. 3700, 1615, 1570, 1547; u.v. 226, 297; (H^+) 221, 291. This was oxidized to the aldehyde, m.p. 38° (ether–hexane) (lit. (7) m.p. 39–40°); i.r. (CH_2Cl_2) 1718, 1609, 1550; m.s. 166 (68), 149 (75), 138 (75), 120 (9), 92 (80), 65 (100).

The final stage succeeded only after adding nitric acid which is normally produced and consumed in the reaction.

The aldehyde, 157 mg, 8 ml 5% hydrogen peroxide, and 20 drops concentrated nitric acid were refluxed 1 h. After evaporation of the solution, water was added and evaporated off at 25°. This process was repeated then the residue was triturated with 3 ml water and filtered leaving 62 mg off-white solid which was dried over potassium hydroxide in vacuum. Compound **9**, colorless microprisms, had m.p. 270–271° (ethanol), (lit. m.p. 255–256° (acetic acid)); the m.p. of our sample remained 270–271° (acetic acid); u.v. 222, 255; (OH^-) 225, 269; (H^+) 218, 256; m.s. M^+ 153 (6), 109 (100). These spectra were identical with those of the ring contraction derived acid **9**, above.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.15. Found: C, 55.0; H, 4.7; N, 9.2.

Zinc Dust Pyrolysis of the Ring Contracted Product ***9***

An intimate mixture of 27 mg **9** and an equal bulk of zinc dust was covered with 10 vol. of zinc dust and sealed in an evacuated glass tube. A break-seal divided this tube from the rest of an evacuated and sealed U-tube. The mixture was heated below red heat for 3 min. The break-seal was broken and the other arm of the U-tube was cooled in liquid nitrogen. The rest of the apparatus was warmed and the cooled tube was then cut off.

Methanol, 50 μl, was added to the frozen volatiles and the u.v. spectrum of a 2-μl portion was taken showing the presence of picoline, about 2.1 mg, 13% total. The remaining solution was injected into a g.c.–m.s. machine which showed that the pyrolysate consisted essentially of one component with the retention time and mass spectrum of β-picoline.

α-Picoline: m.s. M^+ 93 (100), 92 (20), 79 (14), 78 (15), 66 (30), 65 (13), 52 (15), 51 (15), 40 (14), 39 (20).

β-Picoline: m.s. M^+ 93 (100), 92 (20), 79 (9), 78 (17), 66 (30), 65 (15), 52 (9), 51 (12), 40 (18), 39 (20).

γ-Picoline: m.s. M^+ 93 (40), 92 (7), 79 (1), 78 (5), 66 (23), 65 (14), 52 (8), 51 (15), 40 (15), 39 (100).

The α- and β-isomers differ only slightly in mass spectrum but have quite different retention times. The γ-isomer which is not a theoretical product, has a retention time of the same order as the β-isomer but its mass spectrum is quite distinct.

*Reaction of 4-Methoxy-6-methyl-1H-azepin-2,5-dione (***6***, R = Me) with Phosphorus Oxychloride*

Compound **6**, (R = Me) 100 mg, was heated under nitrogen with 20 ml phosphorus oxychloride at 95° for 1 h. The dark solution was evaporated (80°/1 mm) and the residue was sublimed (150°/1 mm) twice, giving 41 mg, 37% white crystalline solid, m.p. 54–55° (hexane).

This product, unlike the starting material, was not demethylated by boron trichloride. Boron tribromide did effect demethylation but the product was an acid.

Authentic 2-chloro-6-methylpyridine-4-carboxylic acid was esterified (diazomethane). The ester had m.p. 56–57° (hexane), (8) mixture m.p. with the above sublimate, 56–57°. The spectra of the two samples were identical; i.r. 1730, 1600, 1560, 1310, 1220, 770; u.v. 219 (3.54), 290 (3.54); n.m.r. ($CDCl_3$) 7.4 (CMe), 6.1 (OMe), 2.45br (H5), 2.4br (H3); m.s. M^+ 185 (100), 154 (89).

Demethylation of ***6*** *(R = Me)*

A suspension of 104 mg **6** (R = Me), in 3 ml dichloromethane containing 500 mg boron trichloride was stirred at 25° for 20 h. The mixture was poured into water, extracted with 9 × 20 ml chloroform and the combined extracts were filtered. Evaporation of the filtrate gave 80 mg **6** (R = H) as an off-white solid, colorless microcrescents, m.p. 250–251° (dec.) (ethanol–cyclohexane); i.r. 3450, 1664, 1644, 1598, 1430, 1390, 1200, 770; m.s. 153 (43), 84 (100), 69 (27), 42 (60), 39 (13).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.15. Found: C, 54.95; H, 4.6; N, 8.9.

Demethylation of ***7*** *(R = Me)*

Compound **7** (R = Me), 103 mg, was demethylated as above but by 536 mg boron tribromide (no reaction with the trichloride). The crude product, 94 mg of **7** (R = H), was an off-white solid. Pure, it has m.p. 197.5–199° (ethanol–hexane); i.r. 3410, 3300, 1706, 1691, 1649, 1430, 1390, 1180, 850; m.s. 153 (100), 136 (23), 109 (80), 68 (42), 39 (55).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.15. Found: C, 54.9; H, 4.6; N, 9.0.

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