Some Derivatives of 1-Benzazepine. Part II[1]

G. R. BIRCHALL[2] AND A. H. REES

Department of Chemistry, Trent University, Peterborough, Ontario K9J 7B8

Received July 16, 1973

We have investigated the ring expansion of some substituted 1,4-naphthoquinones by hydrazoic acid to yield new 1-benzazepine derivatives of the "azatropolone" type. Ring contraction of those products, which are 2,5-dihydro-3-hydroxy-2,5-dioxo-1-benzazepines, gives 4-quinolone-2-carboxylic acids. Some of the reactions of the new benzazepine system were investigated. Attempts to prepare substituted derivatives suitable for making 1-benzazatrop-5-one were not successful.

The effect of substituents on the ring expansion reaction is discussed and an anomalous ring expansion to a 2,5-dihydro-4-hydroxy-2,5-dioxo-1-benzazepine is described and explained mechanistically.

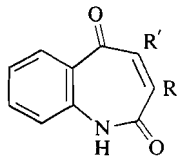
Nous avons étudié l'extension de cycle de quelques naphtoquinones-1,4 substituées en présence d'acide hydrazoique qui a conduit aux nouveaux dérivés benzazépine-1 du type "azatropolone". La contraction de cycle de ces composés, identifiés comme étant des dihydro-2,5 hydroxy-3 dioxo-2,5 benzazépines-1 a conduit aux acides quinolone-4 carboxyliques-2. On a aussi étudié quelques réactions du nouveau système benzazépine. Les essais de synthèse de dérivés substitués susceptibles de conduire au benzazatrop-1 one-5 furent infructueux.

On discute de l'effet des substituants sur la réaction d'extension de cycle. On décrit et on explique selon un mécanisme l'extension de cycle anormale conduisant au dihydro-2,5 hydroxy-4 dioxo-2,5 benzazépine-1. [Traduit par le journal]

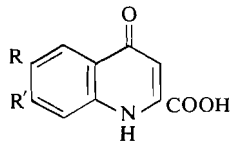
Can. J. Chem., **52**, 610 (1974)

The reaction of naphthoquinones with hydrazoic acid has been reported (1) to give 2,5-dihydro-2,5-dioxo-1*H*-1-benzazepines (**1**), in accord with previous work (2, 3). This showed that attack took place predominantly at the less hindered carbonyl group of *p*-quinones, accompanied by migration of the larger substituent.

We have continued our studies in this field (4, 5) and now report the anomalous ring expansion reaction of 2-alkoxy-1,4-naphthoquinones.



1 R and R′ = Alkyl
2 R = OH; R′ = H
3 R = H; R′ = OH
6 R = OMe; R′ = H
7 R = AcO; R′ = H
8 R = OH; R′ = Br



4 R = R′ = H
10 R = R′ = Me
21 R = HO; R′ = H

These expand following attack at the more hindered carbonyl group to give 3-alkoxy(or hydroxy)-2,5-dihydro-2,5-dioxo-1*H*-1-benzazepines. Thus, 2-methoxy-1,4-naphthoquinone gives 2,5-dihydro-3-hydroxy-2,5-dioxo-1*H*-1-benzazepine (**2**), in which the vinylic proton is a singlet, in sharp contrast to the isomer (**3**) where long range coupling of the NH with the vinyl proton at position 3 of the structure —NH—CO—CH=C— has been observed (6).

Proof of the structure **2** came from the alkaline ring contraction of a known type (5), which gave a quantititative yield of kynurenic acid (**4**), identical with a commercial sample. This also confirmed that the nitrogen atom was introduced adjacent to the benzene ring.

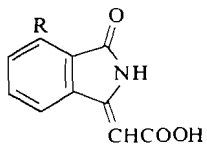
This ring expansion provides a short and easy synthesis of the biologically important kynurenic acid and certain analogs. That the reaction took place at the more hindered carbonyl group must be due to protonation of the ether, increasing the polarization of the adjacent carbonyl group, thus making it more susceptible to attack.

The same reaction was observed with 2-ethoxy- and 2-*n*-propoxy-1,4-naphthoquinone. With 2-isopropoxy-, 2-benzyloxy-, or 2-acetoxy-1,4-naphthoquinone, however, initial hydrolysis took place giving the known (6) reaction product (**5**) of 2-hydroxy-1,4-naphthoquinone and hydrogen azide.

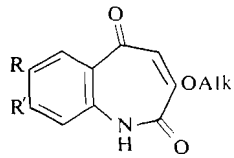
Compound **2** gave the 3-methyl ether (**6**) with diazomethane and the 3-acetate (**7**) on acetyla-

[1]For Part I see ref. 4.

[2]Present address: Imperial Chemical Industries, Pharmaceutical Division, Alderley Park, Macclesfield, Cheshire, England.



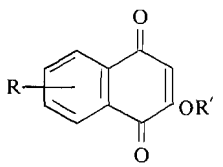
5 R = H
15 R = MeO

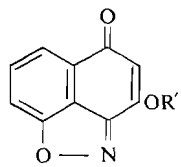


9

tion. Bromination of **2** gave the 4-bromo derivative (**8**). We also prepared some substituted derivatives, *e.g.* **9** where R = R′ = Me. This compound was dealkylated and ring contraction of the resulting enol gave 6,7-dimethylkynurenic acid (**10**).

We also attempted to expand the quinone **11** to the benzazepine which should lead to xanthurenic acid (8-hydroxykynurenic acid). An unexpected reaction took place giving a product with a different type of u.v. spectrum. Demethylation had occurred and the product was assigned structure **12**.[3] The loss of the other methyl group would result in cyanolactone **13** (7, 8), for which there was no spectroscopic evidence.

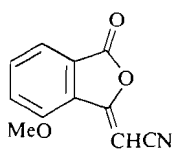




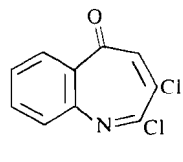
11 R = 8-MeO; R′ = Me
14 R = 8-MeO; R′ = H
16 R = 8-MeO; R′ = Et
22 R = 6-MeO; R′ = Alkyl

12 R′ = Me
17 R′ = Et

The reaction of quinone **14** with hydrogen azide gave only acid **15** but quinone **16** gave compound **17** with retention of the ethyl group. A similar result was found when R′ = isoBu.

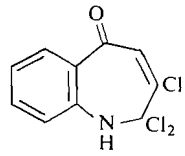


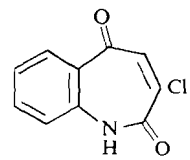
13



18

We attempted to produce the dichlorobenzazatropone **18** by treating compound **2** with phosphorus oxychloride. A trichloro compound, considered to be **19**, resulted but it readily lost hydrogen chloride to give an intermediate formulated as **18**. This was very reactive and rapidly hydrolyzed giving monochloro compound **20** as the only stable product isolated.





19 20

Satisfactory microanalysis results were obtained for **19** but on running the n.m.r. spectrum in DMSO-d_6 a reaction took place in the tube and the peaks shifted. The final product isolated was the chlorolactam **20**.

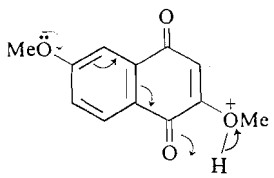
Attempts at dehydrohalogenation of **19** with pyridine, lithium chloride (9), or 1,5-diazabicyclo[5.4.0]undec-5-ene led, after work-up, to compound **20**. This suggests that the chloroimine **18** is very reactive. On steric grounds this is acceptable as there is considerable compression between the eclipsed chlorine atoms in **18** as compared with the staggered configuration of structure **19**. This is in part due to the increased strain in seven- over six-membered rings (5).

The confirmation for the structure of **20** came from its synthesis by the action of thionyl chloride on the corresponding hydroxy compound, **2**, as well as by comparison of its spectra with those of the corresponding bromo compound, prepared by a different route (10).

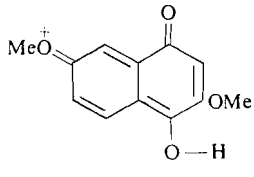
Since 6-hydroxykynurenic acid (**21**) is a natural product (11, 12), we decided to try to synthesize it via the benzazepine **9** where R = MeO and R′ = H. Accordingly, we prepared some 6-substituted 2-alkoxy-1,4-naphthoquinones, including in particular **22**, for ring expansion experiments. From this compound we obtained a product at first presumed to be **9**, R = MeO, R′ = Alkyl = H. However, the quinolone acid obtained by ring contraction was not 6-methoxykynurenic acid as it was not identical with a sample prepared by the literature method (13). Hence the benzazepine precursor was not of type **9**.

On considering the mechanism of the ring expansion of the protonated quinone, it is seen that one of the forms, **23**, is in equilibrium with another, **24**, which has the 4-carbonyl group as the logical site of azide attack. This would give the alternative 2,5-dihydro-4-hydroxy-8-methoxy-2,5-dioxobenzazepine (**25**). This type of

[3]We thank the referees for suggesting this structure for our product.

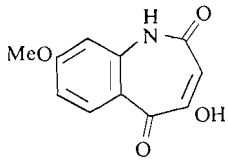


23

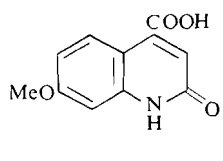


24

compound has been synthesized previously by two other routes (14, 6) and its ring contraction shown to give 2-quinolone-4-carboxylic acids. We therefore made the acid **26** from the appropriate *N*-acetylizatin (15) and found it was identical with the product obtained from quinone **23** via ring expansion. This confirms that the benzazepine intermediate had structure **25**.



25

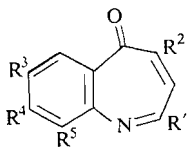


26

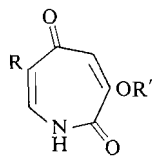
Hence the ring expansion of substituted *p*-quinones is influenced by subtle electronic effects.

We have not yet succeeded in synthesizing a simple benzazatropone and our work parallels that of Proctor and co-workers (9) in producing compounds of type **27**.

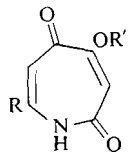
There is no evidence from our or from other work (16–18) for heteroaromaticity in benzazatropones or benzazatropolones. Therefore, we are investigating the monocyclic azepines **28** and **29**, obtained by ring expansion of alkoxybenzoquinones. An encouraging feature of compound **28** (R′ = H or Me) is that $J_{1,7}$ = 8 Hz, suggesting there is a ring current.



27



28



29

Results of this work, also the exploration of new routes to **2** will be reported later.

Experimental

Infrared spectra (Unicam S.P. 200) are in Nujol, quoting ν_{max} in cm^{-1}. Ultraviolet spectra (S.P. 800) are in ethanol quoting λ_{max} in nm (log ε). Nuclear magnetic resonance spectra (JeolCo. C60 HL) are in $CDCl_3$ unless stated and quote 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). Recrystallization solvents are given in parentheses, immediately following the melting points.

2-Alkoxy-1,4-naphthoquinones

These were prepared according to the literature: methyl (19), ethyl (20), *n*-propyl (21), isopropyl (22), and benzyl (23). The i.r. showed carbonyls at *ca.* 1630 and 1680; u.v. 242, 247, 277, 328; n.m.r. showed the appropriate alkyl pattern, a vinyl proton (1H, s) at about 3.9 and two multiplets at around 1.9 (H5 and H8) and about 2.2 (H6 and H7).

2,5-Dihydro-3-hydroxy-2,5-dioxo-1H-1-benzazepine (2)

2-Methoxy-1,4-naphthoquinone, 11.4 g, in concentrated sulfuric acid, 75 ml, at 0° was treated portionwise with sodium azide, 4.2 g. The system was left to warm to 25°. After 2 days, the dark red solution was poured into ice water and the precipitate collected. 2,5-Dihydro-3-hydroxy-2,5-dioxo-1*H*-1-benzazepine formed colorless plates, 6.5 g (60%), m.p. 245–248° (aqueous alcohol); i.r. 3230, 3395, 3470, 1679, 1647, 1594, 1574, 1527; u.v. 239 (4.36), 272 (4.36); n.m.r. Table 1; mass spectrum 189 (100), 161 (70), 143 (18), 133 (28), 115 (18), 104 (19), 92 (18).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.4; H, 3.7; N, 7.4. Found: C, 63.4; H, 3.85; N, 7.2.

When the reaction mixture was slowly poured onto stirred ice and the product triturated with sodium bicarbonate solution, the residue was the unhydrolyzed 3-methyl ether **6** (see below). Acidification of the alkaline solution gave compound **2**.

Reaction of 0.8 g of 2-ethoxy-1,4-naphthoquinone as above, gave, after separation of the neutral and acidic products, 0.2 g of **2** and 0.11 g of the ethyl ether, m.p. 219° (ethanol); i.r. 3300, 3150, 1679, 1645, 1612, 1515; u.v. 241 (4.38), 270 (4.38); mass spectrum 217 (90), 202 (32), 174 (36), 173 (36), 172 (42), 161 (100), 133 (52), 132 (60), 117 (40), 104 (30), 92 (40), 90 (45).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.1; N, 6.45. Found: C, 66.2; H, 5.1; N, 6.6

Reaction of 0.86 g of 2-*n*-propoxy-1,4-naphthoquinone as above gave 0.3 g of compound **2**.

Reaction of 2-acetoxy-1,4-naphthoquinone with Hydrogen Azide

The acetate (24), reacted in sulfuric acid at 0° as above, on work-up gave the acid **5**, identical with a sample made from the hydroxyquinone (6). This same product was similarly obtained from 2-isopropoxy- or 2-benzyloxy-1,4-naphthoquinone, indicating hydrolysis before the azide reaction.

Reactions of 2,5-Dihydro-3-hydroxy-2,5-dioxo-1-benzazepine

(*a*) Bromination. To 190 mg of **2** in 25 ml acetic acid, 180 mg bromine was added with stirring. After 20 h at 25°, the precipitate was collected and washed with ether giving 235 mg 4-bromo-2,5-dihydro-3-hydroxy-2,5-dioxo-1-benzazepine (**8**), buff prisms m.p. 260–265° dec. (ethanol); i.r. 3438, 1666, 1650, 1615, 1495; n.m.r. Table 1; mass spectrum 269 (100), 267 (100), 241 (80),

TABLE 1. Nuclear magnetic resonance spectra, in DMSO-d_6, except as indicated

	τ						
Compound	1	3	4	6	7	8	9
2	−1.6	Under aromatic	3.5s	1.7m		2.3 −2.8m	
6	−1.2	OMe, 3H 6.08s	3.6s	2.05m		2.4 −2.9m	
7	−1.63	OAc, 3H 7.58s	3.0s	2.05m		2.3 −2.8m	
8	−1.7	−0.1	Br	2.2m		2.4 −3.0m	
9	−1.4	OEt 2H 5.95q 3H 8.5t	3.62	1.45s	Me 7.65s	Me 7.65s	2.9s
19*	1.3	Cl	3.4s	1.25m		1.4 −3.3m	
20	−1.65	Cl	2.95s	2.0m		2.15–3.0m	
20*	0.25	Cl	2.6s	2.05m		2.25–3.0m	
20†	−0.5	Cl	2.6s	2.05m		2.15–3.0m	

*In $CDCl_3$.
†In $SOCl_2$.

239 (80), 213 (10), 211 (10), 160 (44), 132 (36), 120 (44), 104 (42), 103 (38), 92 (54), 90 (40), 77 (80), 76 (60).

Anal. Calcd. for $C_{10}H_6BrNO_3$: C, 44.8; H, 2.25; Br, 29.8; N, 5.2. Found: C, 45.0; H, 2.3; Br, 29.7; N, 5.1.

(*b*) Acetylation (pyridine – acetic anhydride) gave 3-acetoxy-2,5-dihydro-2,5-dioxo-1-benzazepine (**7**) as buff needles, m.p. 201–203° (aqueous ethanol); i.r. 1770, 1679, 1647, 1628, 1603, 1588, 1451; n.m.r. Table 1; mass spectrum 231 (30), 189 (65), 161 (100), 134 (25), 133 (11).

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.3; H, 3.9; N, 6.1. Found: C, 62.45; H, 3.9; N, 5.9.

(*c*) Methylation of the azepine **2**, 250 mg in 20 ml pure methanol, was effected by adding an ethereal solution of diazomethane in excess at 0°. 2,5-Dihydro-3-methoxy-2,5-dioxo-1-benzazepine (**6**), 250 mg, was precipitated, colorless plates, m.p. 255° (methanol); i.r. 3400, 3310, 1687, 1630, 1597, 1576, 1529; u.v. 241 (4.37), 269 (4.37); n.m.r. Table 1; mass spectrum 203 (100), 175 (52), 147 (12), 146 (56), 145 (30), 132 (56), 129 (20), 117 (32), 92 (30), 90 (32), 77 (32).

This compound was identical with the neutral ring expansion product from 2-methoxy-1,4-naphthoquinone, above.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9. Found: C, 64.9; H, 4.5; N, 6.8.

(*d*) Ring contraction of **2**, 100 mg, was effected by treatment with 10 ml of 2 *N* alkali solution at 90° for 45 min. Acidification precipitated 100 mg kynurenic acid (**4**), m.p. 250° (acetic acid – water, 20:1), identical (spectra, mixture m.p.) with a commercial sample (Fluka, A.G.); u.v. 247, 342, 360; n.m.r. H3 (NaOD), 3.33 (s); mass spectrum 189 (100), 145 (48), 143 (100), 115 (36), 105 (28), 89 (36).

Preparation and Ring Expansion of 2-Methoxy-6,7-dimethyl-1,4-naphthoquinone

6,7-Dimethyltetral-1-one (25) was oxidized (26) to 2-hydroxy-6,7-dimethyl-1,4-naphthoquinone, m.p. 168–170°, which was converted to the methyl ether, m.p. 167–168° (methanol) (lit. (27) m.p. 166°); n.m.r. 7.6 (2Me, s), 6.1 (OMe, s), 4.0 (H3, s), 2.33 (1H, s), 2.3 (1H, s).

The methoxyquinone, 0.86 g, when reacted as above gave 0.8 g of 2,5-dihydro-3-methoxy-7,8-dimethyl-2,5-dioxo-1-benzazepine, colorless needles, m.p. 295–298° (methanol); i.r. 3400, 1682, 1617, 1579, 1515; u.v. 247 (4.44), 273 (4.34); mass spectrum 231 (100), 203 (19), 202 (62), 174 (60), 173 (25), 160 (45).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.5; H, 5.7; N, 6.15.

When the crude product was recrystallized from ethanol, exchange took place giving 3-ethoxy-2,5-dihydro-7,8-dimethyl-2,5-dioxo-1-benzazepine (**9**, R = R′ = Me; Alkyl = Et), m.p. 256°; i.r. 3400, 1676, 1650, 1617, 1589, 1567; n.m.r. Table 1; mass spectrum 245 (100), 202 (42), 201 (36), 189 (62), 174 (28), 160 (34).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.2; N, 5.7. Found: C, 68.5; H, 6.1; N, 5.5.

*Preparation of 6,7-Dimethylkynurenic Acid (**10**)*

The methyl ether **9**, above, 250 mg, was demethylated (hydrogen bromide – acetic acid) at 60° over 2 h. The precipitated enol was collected and washed with water giving colorless needles, m.p. 288° dec. (ethanol), 80 mg; i.r. 3480, 3250, 1671, 1647, 1584, 1517; u.v. 244 (4.48), 275 (4.44); mass spectrum 217 (100), 189 (100), 174 (24), 171 (14), 161 (12), 160 (16), 143 (12), 91 (20).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1; N, 6.45. Found: C, 66.3; H, 5.1; N, 6.4.

Ring contraction of this azepine, as above, gave a high yield of 6,7-dimethylkynurenic acid, m.p. 278–280° (aqueous acetic acid 1:20); i.r. 3150, 1640, 1590, 810, 780; u.v. 220, 248, 344, 360; n.m.r. (NaOD) 7.8 (2Me, s), 3.3 (H3, s), 2.66 (H8, s), 2.3 (H6, s); mass spectrum 217 (13), 173 (21), 171 (15), 60 (100), 45 (100), 43 (100).

Anal. Calcd. for $C_{12}H_{11}NO_3.\frac{3}{4}CH_3COOH$: C, 62.25; H, 5.35; N, 5.44. Found: C, 62.3; H, 5.25; N, 5.4.

Preparation of 2-Alkoxy-8-methoxy-1,4-naphthoquinones and Reaction with Hydrogen Azide

8-Methoxy-2-tetralone (28) was oxidized to the known quinone **14** (26), which was methylated to give the dimethoxyquinone **11**, m.p. 195°.

2-Ethoxy-8-methoxy-1,4-naphthoquinone (**16**) was prepared in like manner, m.p. 178–179°; i.r. 1684, 1649, 1618, 1589; n.m.r. 8.53 (3H, t, J = 6 Hz), 6.27 (OMe, s), 6.02 (2H, q, J = 6 Hz), 4.07 (H3, s), 2.87 (H5, m), 2.43 (2H, m).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 67.2; H, 5.2. Found: C, 67.6; H, 5.1.

2-Isobutoxy-8-methoxy-1,4-naphthoquinone was prepared as above, m.p. 118° (aqueous ethanol); i.r. 1677, 1646, 1617, 1590; n.m.r. 8.98 (Me_2, d, J = 6 Hz), 7.83 (1H, m), 6.35 (CH_2, d, J = 6 Hz), 6.07 (OMe, s), 4.02 (H3, s), 2.4–2.9 (3H, m).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.2; H, 6.1.

Quinone **11**, 160 mg, reacted with hydrogen azide as above, gave 60 mg product, m.p. 200–230° (ethanol); mass spectrum 201 M^+ (50), 117 (100).

Quinone **16** similarly gave a product, m.p. 160–165° (aqueous ethanol, charcoaled); i.r. 1646, 1606, 1568, 1517; u.v. 299 (4.3); n.m.r. (DMSO-d_6 at 60°) 8.17 (3H, t, J = 6 Hz, OCH_2CH_3), 5.5 (2H, q, J = 6 Hz, OCH_2CH_3), 3.77 (1H, s), 2.1 (3H, m); mass spectrum 215 M^+ (94), 200 (36), 187 (18), 159 (60), 146 (100), 145 (44).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 67.0; H, 4.2; N, 6.5. Found: C, 66.8; H, 4.2; N, 6.5.

This compound is considered to be 3-ethoxy-5-oxo-5*H*-naphth[1,8-*cd*]isoxazole (**17**).

The corresponding 3-isobutoxy compound, 50 mg, was likewise prepared from 180 mg 2-isobutoxy-8-methoxy-1,4-naphthoquinone. The isoxazole had m.p. 131–133° (aqueous ethanol); i.r. 1655, 1610, 1572, 1522; u.v. 299 (4.3); mass spectrum 243 M^+ (24), 188 (43), 187 (100), 146 (63).

Quinone **14**, 150 mg, reacted with hydrogen azide to give 60 mg 4-methoxy-3-oxo-$\Delta^{1\alpha}$-isoindolineacetic acid (**15**), m.p. 218–220° dec. (aqueous ethanol); i.r. 3550, 1736, 1678, 1610, 1500; u.v. 286 (4.17), 348 (4.1); n.m.r. (DMSO-d_6) 6.12 (O*Me*, s), 4.19 (1H, s), 2.92 (1H, m), 2.35 (2H, m), 0.2 (OH, s), −2.5 (NH, br); mass spectrum 219 (100), 201 (76), 173 (95), 44 (79).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.3; H, 4.1; N, 6.4. Found: C, 60.1; H, 4.0; N, 6.4.

*2,2,3-Trichloro-2,5-dihydro-5-oxo-1-benzazepine (**19**)*

2,5-Dihydro-3-hydroxy-2,5-dioxo-1-benzazepine (**2**), 1 g, was heated 1.5 h in 15 ml phosphorus oxychloride at 90°. The cooled mixture was poured onto ice and the solid collected and dried giving the trichloro compound **19**, colorless needles, m.p. 190° dec. (benzene – light petroleum); i.r. 1694, 1621, 1582; u.v. 209, 231, 261 (sh); n.m.r. Table 1; mass spectrum 265 (4), 263 (12), 261 (12), 228 (66), 226 (100), 200 (26), 198 (38), 164 (24), 163 (24), 162 (42).

Anal. Calcd. for $C_{10}H_6Cl_3NO$: C, 45.75; H, 2.3; Cl, 40.5; N, 5.3. Found: C, 45.9; H, 2.3; Cl, 40.3; N, 5.2.

*3-Chloro-2,5-dihydro-2,5-dioxo-1-benzazepine (**20**)*

The trichloro compound (**19**) gave an unstable spectrum in DMSO-d_6. Following t.l.c., the monochloro compound **20** was isolated, yellow needles, m.p. 204° (benzene – light petroleum); i.r. 1670, 1625, 1605; u.v. 215, 239, 264, 350; n.m.r. Table 1; mass spectrum 207 (60), 179 (100), 151 (86), 89 (63). Contrast the 2-chloro isomer (1).

Anal. Calcd. for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.9. Found: C, 58.05; H, 3.0.

The trichloro compound, 50 mg in dry benzene, when treated overnight with 2.2 equiv piperidine at 25°, gave a precipitate of piperidine hydrochloride. This was filtered off and the filtrate was evaporated. On t.l.c. the monochloro compound **20**, 15 mg, was obtained from the residue.

The n.m.r. spectrum ($SOCl_2$) of hydroxy compound **2**, after gentle warming, was that of compound **20**, Table 1. After evaporation of the solvent, the residue was sublimed in vacuum and recrystallized, giving a product identical with **20**, above.

*Ring Expansion of 2,6-Dimethoxy-1,4-naphthoquinone (**22**)*

The quinone **29**, 0.65 g, reacted with hydrogen azide as above, gave only a few milligrams of neutral product, colorless needles, m.p. 278° (aqueous ethanol); i.r. 1675, 1640, 1610; u.v. 233, 253, 275, 345; mass spectrum 233 M^+ (20), 215 (100), 162 (70), 69 (40).

This compound is probably the methyl ether of compound **25**, below.

Preparation of 6-Benzyloxy-2-methoxy-1,4-naphthoquinone

6-Hydroxy-1-tetralone (30, 31), 0.35 g, as its crude oily tetrahydropyranyl ether, was oxidized (24). After acidification, the solution was left 72 h to hydrolyze the ether. Work-up gave 2,6-dihydroxy-1,4-naphthoquinone, 0.1 g orange needles, m.p. >300° dec. (aqueous ethanol).

Methylation (methanol – hydrochloric acid gas) gave 80 mg of 6-hydroxy-2-methoxy-1,4-naphthoquinone, m.p. 285–295° (methanol); n.m.r. (DMSO-d_6) 6.15 (OMe, s), 3.9 (H3, s), 2.85 (H5, d, J = 2 Hz), 3.0 (H7, q, $J_{5,7}$ = 2 Hz, $J_{7,8}$ = 8 Hz), 2.25 (H8, J = 8 Hz), −0.8 (OH, br).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.95. Found: C, 64.5; H, 3.95.

The 6-acetyl derivative (acetic anhydride – pyridine), formed yellow needles, m.p. 187° (ethanol).

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.4; H, 4.1. Found: C, 63.6; H, 4.05.

6-Hydroxy-2-methoxy-1,4-naphthoquinone, 0.5 g in acetone, was benzylated (benzyl bromide – anhydrous potassium carbonate). The benzyl ether, 0.5 g, had m.p. 160–162° (benzene – light petroleum).

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.5; H, 4.1. Found: C, 73.5; H, 4.1.

A preliminary attempt at ring expansion of 6-hydroxy-2-methoxy-1,4-naphthoquinone failed. Because of other results, below, the benzyl ether was not utilized.

*Preparation and Ring Expansion of 2-Ethoxy-6-methoxy-1,4-naphthoquinone (**22**)*

6-Methoxy-2-hydroxy-1,4-naphthoquinone (29) was ethylated (ethanol – hydrogen chloride) giving the ether, m.p. 154–155° (aqueous ethanol).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.2; H, 5.2.

The 2-ethoxy compound, 80 mg, was ring expanded as above, giving 5 mg of acidic product, slightly greenish needles, m.p. 260–262°; i.r. 1670, 1620, 1590; u.v. 222, 252, 276; mass spectrum 219 (60), 204 (6), 191 (31), 150 (100).

Ring contraction of the available material gave an acid, m.p. 290–310°; i.r. (KBr) 1740, 1660, 1620; u.v. 219, 344;

mass spectrum 219 (100), 204 (2), 176 (24), 147 (12), 104 (12).

This acid was compared with 6-methoxykynurenic acid and 7-methoxy-2-quinolone-4-carboxylic acid (**26**), below, and found to be identical with the latter.

The ring expansion product above was therefore 2,5-dihydro-4-hydroxy-8-methoxy-2,5-dioxo-1-benzazepine(25).

6-Methoxykynurenic Acid

The literature preparation (13) gave material with m.p. 282° dec.; i.r. 1740 (br), 1680, 1605; u.v. 215, 227, 258, 351; mass spectrum 219 (58), 175 (100), 173 (40), 132 (20).

Preparation of 7-Methoxy-2-quinolone-4-carboxylic Acid (26)

6-Methoxyisatin (32), 3.3 g, was acetylated (15) to give 2.4 g of *N*-acetyl derivative, m.p. 143–144° (toluene); mass spectrum 219 (17), 176 (100).

Alkaline rearrangement (15) of the acetyl derivative gave a 50% yield of acid **26**, whose i.r. spectrum (KBr, Perkin–Elmer 621) was superimposable with that of the material obtained by the azepine route. The pure acid had m.p. 313–314° (acetic acid).

Anal. Calcd. for $C_{11}H_9NO_4 \cdot \frac{1}{2}CH_3COOH$: C, 54.4; H, 4.9; N, 4.55. Found: C, 54.7; H, 4.9; N, 4.55.

We thank the National Research Council of Canada for financial support.

1. G. JONES. J. Chem. Soc. C, 1808 (1967).
2. R. W. RICKARDS and R. M. SMITH. Tetrahedron Lett. **22**, 2361 (1966).
3. G. R. BEDFORD, G. JONES, and B. R. WEBSTER. Tetrahedron Lett. **22**, 2367 (1966).
4. A. H. REES and K. SIMON. Can. J. Chem. **47**, 1227 (1969).
5. C. G. HUGHES and A. H. REES. Chem. Ind. 1439 (1971).
6. H. W. MOORE, H. R. SHELDON, and W. WEYLER. Tetrahedron Lett. 1243 (1969).
7. A. H. REES. Chem. Ind. 931 (1964).
8. A. H. REES. Chem. Ind. 1298 (1965).
9. A. CROMARTY, G. R. PROCTOR, and M. SHABBIR. J. Chem. Soc. (Perkin I), 2012 (1972).
10. R. A. JAMES. Thesis in progress.
11. P. K. MACNICOL. Biochem. J. **107**, 473 (1968).
12. M. SLAYTOR, L. COPELAND, and P. K. MACNICOL. Phytochemistry, **7**, 1779 (1968).
13. B. P. 942 524, 1963. Chem. Abstr. **60**, 5469b (1964).
14. A. H. REES. J. Chem. Soc. 3111 (1959).
15. Org. Synth. Coll. Vol. III, 456 (1955).
16. E. J. MORICONI and I. M. MANISCALCO. J. Org. Chem. **37**, 208 (1972).
17. R. G. COOKE and I. M. RUSSELL. Aust. J. Chem. **37**, 2421 (1972).
18. W. A. DENNE and M. F. MACKOY. Tetrahedron, **28**, 1795 (1972).
19. L. F. FIESER. J. Am. Chem. Soc. **48**, 2922 (1926).
20. L. HORNER and S. GOWECKE. Chem. Ber. **94**, 1291 (1961).
21. L. F. FIESER. J. Am. Chem. Soc. **50**, 459 (1928).
22. L. F. FIESER. J. Am. Chem. Soc. **70**, 3165 (1948).
23. L. F. FIESER. J. Am. Chem. Soc. **48**, 3201 (1926).
24. J. THIELE and A. WINTER. Ann. **311**, 347 (1900).
25. E. DE BARRY BARNETT and F. G. SANDERS. J. Chem. Soc. 434 (1933).
26. A. C. BAILLIE and R. H. THOMSON. J. Chem. Soc. C, 2184 (1966).
27. R. TRAVE, L. GARNATI, and M. PAVAN. Chim. Ind. (Milan) **41**, 19 (1959).
28. SANDOZ Ltd. Neth. Appl. 6 504 614. Chem. Abstr. **64**, 15771f (1966).
29. T. R. KASTURI and T. ARUNACHALAM. Can. J. Chem. **44**, 1086 (1966).
30. G. HABERLAND. Chem. Ber. **69**, 1380 (1936).
31. E. MOSETTIG and E. L. MAY. J. Org. Chem. **5**, 528 (1940).
32. P. W. SADLER. J. Org. Chem. **21**, 169 (1956).