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SYNTHESIS OF 2,5-H-2,5-AZEPINDIONES FROM QUINONES AND HYDRAZOIC ACID[1]

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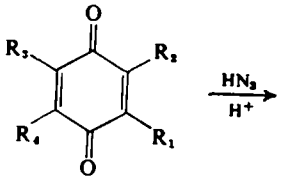
Abstract—2,5-H-2,5-Azepindiones have been prepared by the reaction of substituted quinones with hydrazoic acid in a significantly clarified manner. Such 7-membered ring compounds are now readily available in high yields. The reaction conditions are important to obtain these and not other products.

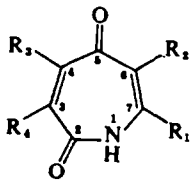
2,5-H-2,3,6-Trimethyl-2,5-azepindione, 2,5-H-3-methyl-6-isopropyl-2,5-azepindione, 2,5-H-6-methyl-3,4-benzoazepin-2,5-dione, 2,5-H-3,6-dimethyl-2,5-azepindione and 2,5-H-3,4,6,7-tetramethyl-2,5-azepindione have been synthesized.

The NMR spectra of the azepindiones and their bromo derivatives are essential data to substantiate structural assignments. The reaction takes place on the least hindered carbonyl group and the inserted NH group is attached to the least substituted carbon atom.

THE reaction of some alkyl-substituted quinones with hydrazoic acid in concentrated sulfuric acid has given high yields of 2,5-H-2,5-azepindiones (II); such substituted azepindiones with the seven-membered ring system are very difficult to obtain by other methods. An account of the initial findings on these azepindiones has been communicated.[3]



I



II

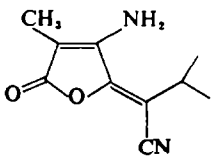
	R_1	R_3	R_5	R_4
(a)	H	CH_3	CH_3	CH_3
(b)	H	$CH(CH_3)_2$	H	CH_3
(c)	H	CH_3		
(d)	H	CH_3	H	CH_3
(e)	CH_3	CH_3	CH_3	CH_3

The reaction conditions to obtain azepindiones (conc. H_2SO_4 at 0°) are very important, since many of the quinones that were used have been previously subjected to the Schmidt reaction using other solvents and acids, but with quite different reaction products. For example, 2-methyl-1,4-naphthoquinone (Ic) was reported[4] to be unreactive at 40° in acetic acid with sodium azide. Rees[5,6] has recently described the reaction of thymoquinone (Ib) with hydrogen azide using trichloroacetic acid as solvent; the reaction gave a ring-contracted lactone (III) arising from the reaction of one

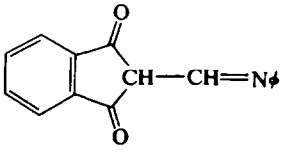
[1] This paper is Contribution LXX in the Coenzyme Q Series.
[2] Istituto Superiore di Sanità, Rome (Italy); holder of an Italian National Research Council fellowship during 1964.
[3] D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Letters* No **16**, 1071 (1965).
[4] L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.* **57**, 1482 (1935).
[5] A. H. Rees, *J. Chem. Soc.* 3097 (1962).
[6] A. H. Rees, *Chem. & Ind.* 931 (1964).

mole of the quinone with two molecules of hydrogen azide. Caronna and Palazzo[7,8] reported that *p*-xyloquinone (Id) and thymoquinone (Ib) gave products of unknown structure when subjected to the Schmidt reaction in conc. sulfuric acid; however, the reported m.p. and analytical data of their products suggest they are the same as the products reported in our study from *p*-xyloquinone and thymoquinone, i.e., 2,5-H-3-methyl-6-isopropyl-2,5-azepindione (IIb) and 2,5-H-3,6-dimethyl-2,5-azepindione (IId), respectively. Coronna and Palazzo[9] also found that various substituted anthroquinones did react with hydrazoic acid in conc. sulfuric acid with ring expansion to give the corresponding 2,5-H-2,5-azepindiones.

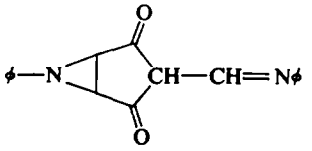
Chloranil and 2,3-dichloro-*p*-naphthoquinone react with sodium azide in ethanol or acetic acid with displacement of the chloro group to give azidoquinones.[10,11] A reaction of quinones with azides, which has been described by Wolff,[12] has been interpreted as addition of the azide to a double bond to form a dihydrotriazole which may lose nitrogen with or without consequent rearrangement. Thus, *p*-naphthoquinone gave the anil (IV) when reacted with phenylazide while *p*-benzoquinone gave V.



III



IV



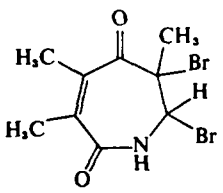
V

The following reaction conditions were used to prepare the azepindiones. A solution of the quinone in conc. sulfuric acid was cooled to 0° and an equimolar amount of sodium azide was slowly added. When nitrogen evolution ceased, the reaction mixture was poured into a mixture of ice and water, and the resulting precipitate was recrystallized from aqueous ethanol. This is not a general reaction for all quinones; when chloranil was subjected to these reaction conditions no reaction occurred, and 2,3-dimethyl- and 2,6-dimethyl-1,4-benzoquinone decomposed.

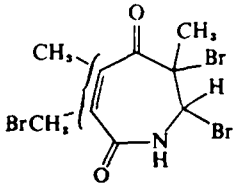
It is evident from the chemical and physical data of the azepindione products that the reaction takes place on the least hindered carbonyl group and that the NH group has inserted in such a manner that it is attached to the least substituted carbon atom. The NMR spectra are the best criterion for their structural assignment. The azepindione (IIa) shows vinyl proton absorption corresponding to one proton as a multiplet at τ, 3·22. Decoupling experiments have shown that this proton is adjacent to the amide nitrogen and is coupled to both the amide nitrogen proton and the methyl protons at C_6. Irradiation at the —NH proton frequency resulted in collapse of this multiplet to a quartet. Confirmation of this assignment was obtained from the NMR

[7] G. Caronna, *Gazz. Chim. Ital.* **75**, 91 (1945).
[8] G. Caronna and S. Palazzo, *Gazz. Chim. Ital.* **83**, 315 (1953).
[9] G. Caronna and S. Palazzo, *Gazz. Chim. Ital.* **84**, 1135 (1954).
[10] A. Korczynsky and St. Namylslowski, *Bull. Soc. Chim. Fr.* **35**, 1186 (1924)
[11] K. Fries and P. Ochwat, *Ber. Dtsch. Chem. Ges* **56**, 1291 (1923).
[12] L. Wolff, *Liebigs Ann.* **394**, 68 and 86 (1912); *Ibid.* **399**, 274 (1913).

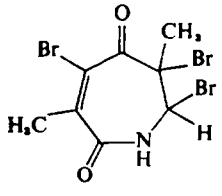
spectra of two bromo derivatives (VI and VII) of IIa, obtained by the reaction of bromine with the azepindione.



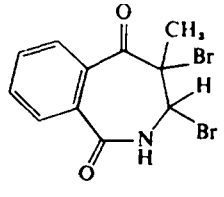
VI



VII



VIII



IX

The NMR spectra of VI and VII showed absorption of one proton as a doublet ($J = 2$ c/s) at τ, 5·26 and 5·23, respectively, which is assigned to the methine proton at C_7. Decoupling by irradiation at the —NH frequency caused the collapse of the doublet to a sharp singlet. The presence of a bromomethyl group in VII is evidenced by the presence of a broad singlet corresponding to two protons at τ, 5·77.

The NMR spectrum of IIb shows vinyl proton absorption, one as a doublet ($J =$ 1·2 c/s) at τ, 3·35, and another as a multiplet at τ, 4·12. The peak at τ, 3·35 is assigned to the vinyl proton adjacent to the amido nitrogen; decoupling caused the collapse of this absorption to a sharp singlet, while the multiplet at τ, 4·12 was unaffected. The lack of coupling between the C_7-proton and the protons on the substituent at C_6 lends support for structure IIb in which the C_6-substituent is an isopropyl group. For compounds with a C_6-methyl group (IIa, IIc, IId), the methyl protons were coupled to the C_7 vinyl proton. For example, the NMR spectrum of the azepindione IId shows two absorption peaks in the vinyl region, a multiplet at τ, 3·16, and a broad singlet at τ, 4·12. Decoupling between the C_7 proton and the amido proton caused the collapse of the multiplet (τ, 3·16) to a well-defined quartet ($J \cong 1{\cdot}0$ c/s). Addition of bromine to IIb gave the tribromo derivative (VIII) which gave an NMR spectrum showing the C_7 proton absorption as a doublet ($J \cong 0{\cdot}5$ c/s) at τ, 5·19. This peak collapsed to a singlet upon irradiation at the —NH frequency.

For the azepindione (IIc) obtained from 2-methyl-1,4-naphthoquinone, the NMR spectrum and decoupling experiments between the vinyl and amido protons are not sufficient for a definite structural assignment. The broad singlet vinyl absorption at τ, 3·19 collapsed to an unresolved quartet when —NH decoupling was carried out, and to an unresolved doublet upon irradiation at the C_6 methyl proton frequency. The structure of this compound IIc was confirmed from the NMR data obtained on the dibromo derivative (IX). The C_7 proton in IX appears as a doublet ($J \cong 1{\cdot}0$ c/s) at τ, 5·03, which collapsed to a sharp singlet upon irradiation at the —NH frequency.

For the product IIe, obtained from the symmetrical quinone, duroquinone, only one azepindione structure is possible, and structure IIe is consistent with the observed spectral data. (Experimental.)

EXPERIMENTAL[14]

Synthesis of 2,5-H-2,5-azepindiones

General procedure.[13] To a solution of 0·1 mole quinone in 5 ml conc. H_2SO_4 at 0°, 0·1 mole sodium azide was added with stirring in small portions over ½ hr. The mixture was then poured into a mixture

[13] P. A. S. Smith, *J. Amer Chem. Soc.* **70**, 320 (1948).

[14] The IR carbonyl absorptions were reported incorrectly in Ref. 3.

of ice water, and the precipitated compound was filtered off and washed with water and benzene. The compound was purified by crystallization from aqueous alcohol and then by sublimation.

2,5-H-2,3,6-*Trimethyl*-2,5-*azepindione* (IIa). This compound was synthesized using the general procedure and was purified by crystallization from EtOH and by sublimation at 100–110°/0·01 mm to give an 80% yield of a white crystalline solid, m.p. 194–196°. (Found: C, 65·21; H, 6·78; N, 8·69. Calc. for $C_9H_{11}NO_2$: C, 65·44; H, 6·71; N, 8·48%.)

The UV spectrum of IIa in EtOH showed absorption at 228 mμ (ε, 1134) and 287·5 mμ (ε, 332). A $CHCl_3$ solution of the compound showed characteristic IR absorption at 3320 cm^{-1} (—NH), 3150 cm^{-1} (C—H), 1650 cm^{-1} (C=O). The NMR spectrum showed absorption at τ, −0·05 (1) b, N—H; 3·22 (1) m, =C—H; 7·71 (3) s, $—CH_3$; 7·82 (3) d, $—CH_3$ at C_6; 7·98 (3) s, $—CH_3$.

2,5-H-3-*Methyl*-6-*isopropyl*-2,5-*azepindione* (IIb). This product, m.p. 168°, was prepared in 75% yield by the general procedure and was purified by crystallization from EtOH and by sublimation at 120–130°/0·05 mm. (Found: C, 66·98; H, 7·51; N, 7.89. Calc. for $C_{10}H_{13}NO_2$: C, 67·02; H, 7·31; N, 7·82%.)

The UV spectrum of an ethanolic solution of IIb showed absorption at 228 mμ (ε, 1450) and 288 mμ (ε, 292). The IR spectrum of a $CHCl_3$ solution of IIb showed characteristic peaks for N—H stretching at 3320 and 3200 cm^{-1} and carbonyl absorption at 1665, 1640 cm^{-1}. The NMR spectrum was in agreement with structure IIb, showing peaks at τ, −0·04 (1) b, —N—H; 3·35 (1) d and 4·12 (1) m, =C—H; 6·69 (1) h, —CH<; 7·82 (3) s, $—CH_3$; 8·90 (6) d, —C(CH₃)₂. The azepindione IIb was reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone, m.p 291° dec. (Found: C, 53·21; H, 4·86; N, 19·31. Calc. for $C_{16}H_{17}N_5O_5$: C, 53·48 H, 4·77; N, 19·49%.)

2,5-H-6-*Methyl*-3,4-*benzoazepin*-2,5-*dione* (IIc). This compound was prepared by the general method to give an 85% yield of IIc, m.p. 203–204°. Purification was accomplished by crystallization from EtOH followed by sublimation at 120–130°/0·05 mm. (Found: C, 70·60; H, 4·82; N, 7·68. Calc. for $C_9H_9NO_2$: C, 70·58; H, 4·84; N, 7·48%.)

The UV spectrum showed absorption at 207 mμ (ε, 1548), 233 mμ (ε, 1205), and 274 mμ (ε, 541). The IR spectrum of a $CHCl_3$ solution of IIc showed N—H stretching absorption at 3320 and 3200 cm^{-1} and carbonyl absorption at 1650, 1620 cm^{-1}. The NMR spectrum showed peaks at τ, −0·4 (1) b, N—H; 3·19 (1) b, =CH; 1·62 (4) m, aromatic —H; 7·75 (3) d, $—CH_3$.

2,5-H-3,6-*Dimethyl*-2,5-*azepindione* (IId). This product was obtained by the general procedure to give an 80% yield of a white crystalline solid, m.p. 216–217°. (Found: C, 63·32; H, 5·93; N, 9·48. Calc. for $C_8H_9NO_2$: C, 63·56; H, 6·00; N, 9·27%.)

The UV spectrum showed absorption at 228 mμ (ε, 1808) and 288 mμ (ε, 337). A nujol IR spectrum of IId showed N—H stretching absorption at 3220 and carbonyl absorption at 1670, 1640, and 1610 cm^{-1}. The NMR spectrum showed peaks at τ, 0·09 (1) b, N—H; 3·16 (1) m, =CH; 4·16 (1) s, =CH; 7·77 (3) s, $—CH_3$ at C_3; and 7·83 (3) d, $—CH_3$ at C_6.

2,5-H-3,4,6,7-*Tetramethyl*-2,5-*azepindione* (IIe). This product, synthesized in an 80% yield, was a white crystalline solid, m.p. 214–215°. The UV spectrum of an ethanolic solution of IIe showed absorption at 233 mμ (ε, 1188) and 298 mμ (ε, 266). A $CHCl_3$ solution of IIe showed IR absorption characteristic of N—H stretching at 3350 and 3220 cm^{-1}, and carbonyl absorption at 1650 cm^{-1}. The NMR spectrum showed peaks at τ, 0·39 (1) b, —NH; 7·85 (9) s, $—CH_3$; and 8·05 (3) s, $—CH_3$.

2,5,6,7-H-3,4,6-*Trimethyl*-6,7-*dibromo*-2,5-*azepindione* (VI) *and* 2,5,6,7-H-(3 *or* 4)-*bromomethyl*-(4 *or* 3),6-*dimethyl*-6,7-*dibromo*-,5-*azepindione* (VII). A solution of 300 mg IIa in 20 ml $CHCl_3$ was treated with Br_2 until the solution remained colored. After 1 hr at room temp, the reaction solution was concentrated *in vacuo* and the solid residue was subjected to preparative TLC using silica gel G plates as a developing solvent of ether. Compound VI, (R_f = 0·80) was collected and recrystallized from aqueous EtOH, m.p. 118–120° dec. (Found: C, 33·02; H, 3·25; N, 4·00; Br, 48·88. Calc. for $C_9H_{11}Br_2NO_2$: C, 33·26; H, 3·33; N, 4·31; Br, 49·17%.)

The NMR spectrum of VI showed absorption at τ, 1·71 (1) b, N—H; 5·26 (1) d, —C(Br)—H; 7·77 (3) s, $—CH_3$; 7·95 (3) s, $—CH_3$; and 8·01 (3) s, $—CH_3$. Compound VII was also isolated by TLC

(R_f = 0·9) and recrystallized from aqueous EtOH, m.p. 127–129°. (Found: C, 26·51; H, 2·23; N, 3·15; Br, 59·02. Calc. for $C_9H_{10}Br_2NO_2$: C, 26·76; H, 2·49; N, 3·47; Br, 59·35%.)

The NMR spectrum of VII shows absorption at τ, 1·36 (1) b, N—H; 5·23 (1) d, —C(—H)—; 5·77 (2) b, —CH_2Br; 2·08 (3) s, —CH_3; and 2·12 (3) s, —CH_3.

Addition of bromine to 2,5-H-6-*methyl*-3,4-*benzoazepin*-2,5-*dione*

Preparation of 2,5,6,7-H-6-*methyl*-6,7-*dibromo*-3,4-*benzoazepin*-2,5-*dione* (IX). Br_2 (0·05 ml) was added to a $CHCl_3$ solution of 100 mg 2,5-H-6-methyl-3,4-benzoazepin-2,5-dione. After 2 hr at room temp, the reaction solution was concentrated *in vacuo* and the solid residue was crystallized several times from aqueous EtOH, m.p. 174–176° dec. (Found: C, 38·23; H, 2·68; N, 4·17; Br, 45·78. Calc. for $C_{11}H_9Br_2NO_2$: C, 38·08; H, 2·61; N, 4·04; Br, 46·05%.)

The NMR spectrum of IX showed absorption at τ, 0·42 (1) b, N—H; 1·35 (1) m, aromatic —H; 2·55 (3) m, aromatic —H; 5·03 (1) d, —C(—H)—; and 7·77 (3) s, —CH_3.

Addition of bromine to 2,5-H-3,6-*dimethyl*-2,5-*azepindione*

Preparation of 2,5,6,7-H-3,6-*dimethyl*-4,6,7-*tribromo*-2,5-*azepindione* (VIII). A $CHCl_3$ solution of 151 mg of IIe was treated with 0·1 ml Br_2. After 2 hr at room temp, the solvent was removed *in vacuo* to give 300 mg of a crystalline solid residue. Recrystallization of this compound from aqueous EtOH gave the analytical sample, m.p. 119–120° dec. (Found: C, 24·91; H, 1·94; N, 3·58; Br, 61·80. Calc. for $C_8H_5Br_3NO_2$: C, 24·64; H, 2·07; N, 3·59; Br, 61·48%.)

The NMR spectrum showed absorption at τ, 0·77 (1) b, N—H; 5·19 (1) d, —C(—H)—; 7·39 (3) s, —CH_3; and 7·88 (3) s, —CH_3.