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THE SYNTHESIS OF 1H, 2H, 5H-AZEPINE-2, 5-DIONES BY SCHMIDT REARRANGEMENT OF QUINONES

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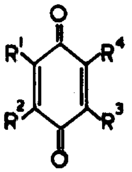
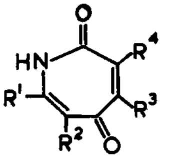
From the reaction of the 2, 5-dialkylbenzoquinones (Ia or b) with sodium azide in sulphuric acid at 40-50°, Caronna (1) obtained products which he suggested were imines (II: R, R, R = alkyl, alkyl, hydrogen). Recently, Folkers, Misiti and Moore (2) reacted the benzoquinones (Ia - d) and 2-methylnaphthoquinone (Ig) with the same reagents at 0°, and on the basis of proton magnetic resonance spectra formulated the products as the azepinediones (IIIa - d, g), (IIIa) and (IIIb) being clearly identical in m.p. with Caronna's products (1). Spin decoupling experiments with the products (IIIb, c, g) showed that the NH proton was directly coupled to a =CH proton. This was said (2) to necessitate that these groupings were adjacent, thus providing the main argument for the orientation of substituents on the ring system.

From the reaction of various benzo- (Ia - d) and naphthoquinones (If, g) with the same reagents at room temperature, we have isolated the azepinediones (IVa - e and IVf - i, respectively), whose structures follow from the chemical and spectroscopic evidence. Of our compounds, the major products (IVa - d, g) from their respective reactions agree in m.p., p.m.r. spectra, and ultraviolet wavelength maximum with the corresponding sole reaction products obtained by Folkers et al. (2). Accordingly, with the single exception of the tetramethyl-azepinedione (IIId), the structures (IIIa - c, g) proposed by these workers (2) are incorrect, as is their explanation of the reaction pathway. The true structures (IVa - i) of these azepinediones, and their relative yields in cases where more than one isomer is formed

(IVb:e = 3:1; IVg:h:i = 4:2:1), are fully consistent with the view (3) that the Schmidt reaction proceeds primarily under steric control with electronic effects exerting only minor influence. Preferential attack at the less hindered, more basic carbonyl function of the quinone (I) is followed by preferential migration of the larger adjacent group.



I.



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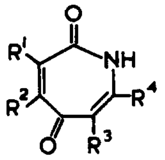

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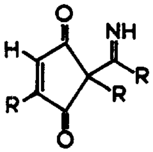
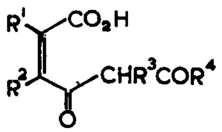


II.

Compound	R^1	R^2	R^3	R^4
(a)	H	Me	H	Me
(b)	H	Pr^i	H	Me
(c)	H	Me	Me	Me
(d)	Me	Me	Me	Me
(e)	H	Me	H	Pr^i
(f)	H	H	Benzo	
(g)	H	Me	Benzo	
(h)	Me	H	Benzo	
(i)	Benzo		H	Me



V.

The monocyclic azepinediones (IVa - e) all show ultraviolet maxima (in ethanol) in the regions 227-236 (log ε 4.0-4.5), 287-300 (log ε 3.4-3.7), and 311-328 mμ (log ε 3.4-3.6), and infrared maxima (in Nujol) at 1676-1670 (amide carbonyl), 1648-1625 (unsaturated ketone), and 1610-1595 cm.$^{-1}$ (olefin). We do not observe the inexplicably high infrared maxima above 1700 and even 1800 cm.$^{-1}$ recorded by Folkers <u>et al</u>. (2). These compounds dissolve in aqueous alkali and upon refluxing are hydrolysed, presumably via the diketo-acids (V), to a mixture of acids and steam-volatile ketones, the structures of which (cf. Table) unequivocally define the structures (IVa - c) of the parent azepinediones. Aldehydes, which would result from hydrolysis of the previously suggested (2) structures (IIIa - c), were not formed in these hydrolyses. The structures of compounds (IVd, e) follow from comparison of spectra (cf. Table) with those of the chemically-proven azepinediones.

TABLE

Compound	M.p.°	Alkaline Hydrolysis	P.M.R. Absorption in τ*	
(IV)		Products	$-COCR^2=CHCO-$	$-COCH=CR^4NH-$
(a)	216-217	Acetone Et Me ketone Mesaconic acid	3.28 m (q)	4.26 m (sb)
(b)	169-170	Acetone Bu^i Me ketone	3.41 q (d)	4.20 m (sb)
(c)	199-200	Et Me ketone Et$_2$ ketone Mesaconic acid	3.26 m (q)	-
(d)	201-202	-	-	-
(e)	156-158	-	3.16 m	4.14 q
(f)	222-223	-	3.07 sb (2H)	-
(g)	200-201	-	3.10 m (q)	-
(h)	217-218	-	2.88 q (q)	-
(i)	245-250	Acetone o-Acetyl benzoic acid	-	4.08 m

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* Spectra were recorded at 60 Mc./sec. for ca. 6% solutions in deuterochloroform (IVa - e) or dimethylsulphoxide (IVf - i), with TMS internal reference. Multiplicities are indicated by sb, broad singlet; d, doublet; q, quartet; m, multiplet. Multiplicity on D$_2$O addition is shown in brackets.

All the benzazepinediones (IVf - i) showed similar infrared absorption at 1680 (amide carbonyl) and 1657-1645 cm.$^{-1}$ (unsaturated ketone), whilst the single benz[*c*]azepinedione (IVi) differed markedly in ultraviolet absorption ($\lambda_{max.}$ 235, 310 mμ, log ε 4.34, 3.92) from the three benz[*f*]azepinediones (IVf - h) ($\lambda_{max.}$ 228-235, 273-283, 348-353 mμ, log ε 4.3-4.4, 3.9, 3.4). Of the four possible Schmidt products from 2-methyl-1,4-naphthoquinone (Ig), three (IVg - i) were isolated in a 4:2:1 yield ratio. The minor of these was proved to be 7-methyl-1*H*, 2*H*, 5*H*-benz[*c*]azepine-2,5-dione (IVi) by alkaline hydrolysis (*cf.* Table). The major product was shown to be the benz[f]azepinedione (IVg) by catalytic reduction over palladium-charcoal to the dihydro-derivative. This latter had ultraviolet absorption ($\lambda_{max.}$ in ethanol 229, 265, 317 mμ, log ε 4.47, 3.88, 3.43) closely resembling that of *N*-acetyl-*o*-amino-acetophenone (4) ($\lambda_{max.}$ 260, 323 mμ, log ε 4.1, 3.6), indicating insertion of the NH group next to the benzenoid ring, and contained only one hydrogen adjacent to carbonyl which was susceptible to deuterium exchange, thus positioning the methyl substituent. The third isomer formed from 2-methyl-1,4-naphthoquinone, and the only product from naphthoquinone itself, are clearly the benz[f]azepinediones (IVf, h), as shown by comparison of spectra with the established structure (IVg).

The most important features of the p.m.r. spectra of these azepinediones (IVa - i) concern the olefinic proton resonances, which fall into two groups (*cf.* Table). Those at lower field, between τ 2.9-3.4, are very similar in chemical shift to the olefinic protons in the parent quinones, and are due to protons in the system $-COCR^2=CHCO-$. Those resonating at higher field, between τ 4.0-4.3, correspond to protons on the more electron-rich $-COCH=CR^4NH-$ system. The spectra are considerably complicated by long-range interactions, including allylic coupling ($-CH=CCH-$ and $-CH=CNH-$) and even homo-allylic coupling ($-H_3CC=CCH_3-$) in (IVc, d). More unusual, however, is the occurrence of appreciable cross-carbonyl coupling (5) in the system $=CHCONH-$, the feature which misled

Folkers et al. (2). Thus addition of deuterium oxide to solutions of compounds (IVa - c, g) caused simplification of the olefinic multiplets to the patterns expected from allylically coupled protons.

Bedford, Jones and Webster (6) have independently reached similar conclusions as to the correct structures of the azepinediones (IVb, g).

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