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ON THE REACTION OF A γ-NITROKETONE WITH ACIDS

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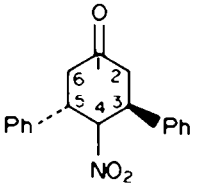
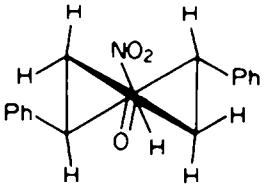
Abstract—The aromatisation of *trans*-3,5-diphenyl-4-nitrocyclohexanone by acids is described, the structures of the products reported, and a mechanism for the reaction proposed.

During some investigations into the bromination of *trans*-3,5-diphenyl-4-nitrocyclohexanone (**1**) an interesting aromatisation reaction was discovered. The bromination of ketones is frequently carried out with bromine in acetic acid containing hydrogen bromide as a catalyst. It was found that the nitroketone (**1**) suffered aromatisation with hydrogen bromide, hydrogen chloride or sulphuric acid in acetic acid at 20° to give the crystalline products (**3**, **4** and **8**) described in this paper.

The synthesis of the nitroketone (**1**) by the reaction of 1,5-diphenylpenta-1,4-dien-3-one with nitromethane in the presence of sodium methoxide was reported by Kohler and Dewey in 1924.[2] The spectral properties of the compound are in accord with the structure **1**, in particular $\nu_{C=O}$ 1709 cm^{-1}, the quartet of lines at δ 5.9 ($CHNO_2$ $(CHPh\text{-})_2$) and the ^{13}C resonances at δ 90.5 (C-NO_2) and 207.7 (>C=O). The quartet of lines in the ^1H spectrum at δ 5.9 attributable to the C-4 proton in **1** shows J = 7 Hz, 10 Hz. These values are consistent with the conformation **2** if an analogy is drawn with vicinal coupling in the steroids and its dependence upon dihedral angle.[3] Moreover the flexible conformation **2** allows both phenyl groups a stable orientation, and is compatible with the usual reversible mechanism of the Michael reaction which gives thermodynamically stable products. In addition the conformation **2** is similar to that assigned to the product of the Michael reaction of 1,5-diphenylpenta-1,4-dien-3-one with dimethylmalonate.[1]

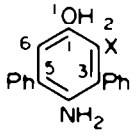


1

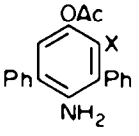


2

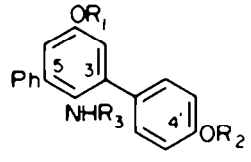
The nitroketone (**1**) on treatment with a saturated solution of hydrogen bromide or hydrogen chloride in acetic acid at 20° gave the crystalline compounds **3** and **4** respectively. The aromatic nature of the compounds **3** and **4** was clear from their IR, ^1H and ^{13}C spectra which are compatible with the structures proposed. Their molecular formulae were established by exact mass measurements. During their purification the compounds frequently developed a pale green or pink colouration, behaviour often associated with *p*-aminophenols and related substances. The functional groups present were confirmed by the results of acetylation with acetic anhydride in pyridine. The IR spectra of the products (**6** and **7**) showed O-acetylation only, and a doublet typical of an $-NH_2$ group.



3 X = Br
4 X = Cl
5 X = H



6 X = Br
7 X = Cl



8 $R_1=R_2=R_3=H$
9 $R=R_2=R_3=Ac$

The position of the halogen in **3** and **4** (and incidentally the overall structures of **3** and **4**) was revealed by X-ray crystallographic studies† on the bromo compound **3**. These studies besides fixing the halogen atom at position-2 disclosed extensive H-bonding in the crystal between the $-NH_2$ group of one molecule and the –OH group of another, and showed that in the solid phase the two phenyl rings at C-3 and C-5 are not coplanar with the central benzene ring. The torsion angle for the C-5 phenyl group is given as 61° and that for the C-3 phenyl group as 74°. More interestingly it was apparent that there was always contamination of **3**, occasionally by as much as about 25% of the unhalogenated compound **5** however carefully **3** was purified, a finding which was confirmed by the fact that the microanalytical figures for **3** were in varying degrees always high in C and low in Br. Moreover in the mass spectrum of **3** there was a significant peak at mass 261 whose exact mass corresponded to that of **5**.

In the case of the chloro compound **4** comparable evidence from microanalysis and mass spectrometry shows that there is far less contamination of **4** by the unhalogenated compound **5**. This difference between the bromo- and chloro compounds **3** and **4** was reflected in the mass spectra of the corresponding acetates **6** and **7**.

†These were carried out by Dr. R. Pritchard at UMIST. The details of these studies will be published elsewhere.

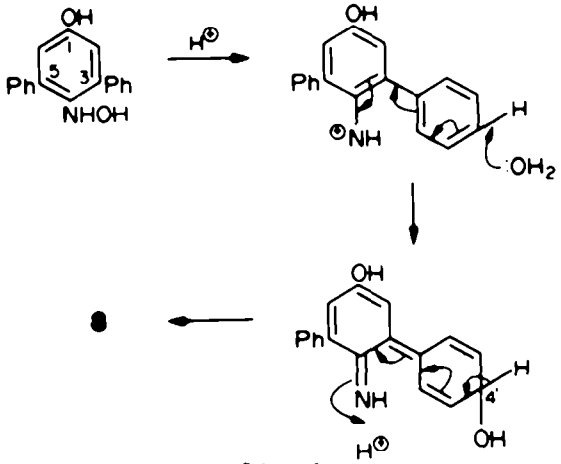
No mass peak at 303 corresponding to the acetate of **5** (required exact mass 303.1259) was recorded in the spectrum of **7** whereas it was present in the spectrum of **6** (measured exact mass 303.1254). The mechanistic significance of this difference between the bromo- and chloro compounds (**3** and **4**) will be mentioned below.

The mechanism suggested for the rearrangement of **1** to **3** or **4** is shown in Scheme 1.

In support of this suggestion, the acid-catalysed rearrangement of steroidal nitro compounds to oximes *via* nitroso compounds has been reported,[4] but in the case of the system discussed in this paper, the nitroso compound is very easily aromatised by a series of tautomerisations (Scheme 1, a→b). However the intermediacy of a nitrosocompound in the conversion of **1** to **3** or **4** is directly supported by the observation of a fleeting turquoise colour (λ_{max} 658 mμ)[5] during the reaction. The final stages (b) to (c) to (d) proposed in the conversion of **1** to **3** or **4** are supported by the known reaction of phenylhydroxylamine and nitrosobenzene with hydrogen chloride and hydrogen bromide to give 4-chloro- and 4-bromoaniline respectively together with 2,4-dichloro- and 2,4-dibromoaniline,[6] though the intermediates involved in the stage (b) to (c) are not known.[7]

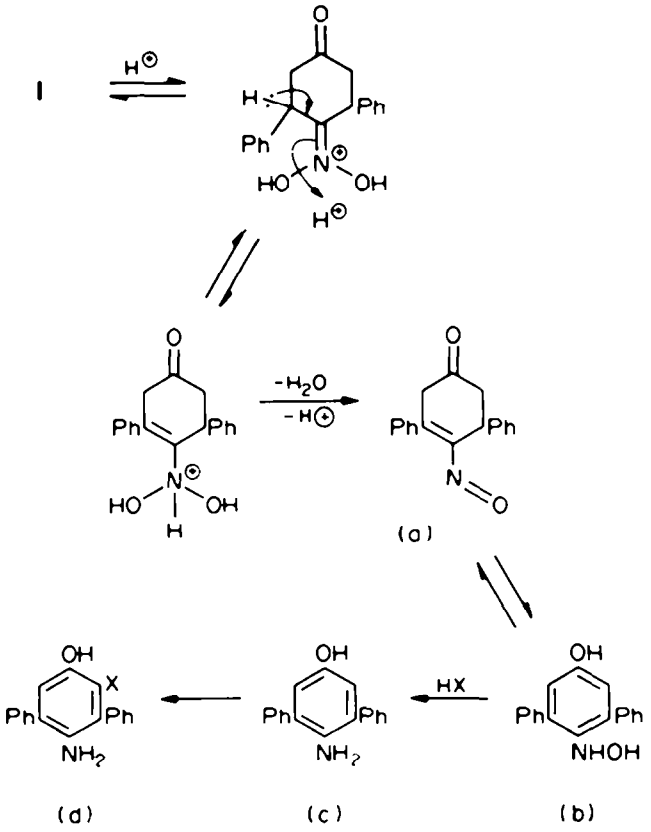
In the last stage (c) to (d), the halogenation could take place at any activated aromatic site. But the X-ray analysis shows that in the solid state the 3- and 5- phenyl groups are twisted out of the plane of the central ring, and so cannot be conjugated with the C-4 NH_2 group. If this is also the case in solution, then this leaves position 2 as the most feasible site for halogenation. The halogenation (c) to (d) proposed as the final stage in the rearrangement of **1** to **3** or **4** is independent of the aromatisation, so that it is not necessary that it goes to completion. And the evidence of contamination of **3** by **5** shows indeed that it does not. The fact that the contamination of **4** by **5** is far less could mean that bromination of this crowded system is subject to steric hindrance compared to chlorination. However it may be that the chloro compound can be purified more effectively for crystallographic reasons to do with molecular packing.†

The nitroketone **1** was aromatised also by sulphuric acid in acetic acid to give a compound **8** whose exact



Scheme 2.

†These were carried out by Dr. R. Pritchard at UMIST. The details of these studies will be published elsewhere.



Scheme 1.

mass was compatible with it being the hydroxylamine (Scheme 1, b). This would actually be a feasible end product of the rearrangement in this case. That **8** was not the hydroxylamine (Scheme 1b) was shown by the fact that it did not react with either hydrogen bromide or hydrogen chloride in acetic acid to give **3** or **4**. Moreover it was recovered unchanged from reaction with tin and hydrochloric acid. The IR spectrum of its triacetate **9** (formed with acetic anhydride in pyridine) showed di-O-acetylation and mono-N-acetylation together with -NH-absorption. Thus the compound **8** must be a dihydroxyamine. The resonance at δ 154.5 in the ^{13}C spectrum shows that one of the -OH groups occupies a *para*-rather than an *ortho*- position in one of the phenyl rings at C-3 or C-5, and does not occupy the site at C-2 in the central ring. And if it is assumed that the compound **8** is formed by a Bamberger rearrangement[7] of the hydroxylamine (Scheme 1b), the most likely position for the OH group will be 4' (Scheme 2).

EXPERIMENTAL

M.ps were determined in capillary tubes. IR spectra were recorded in Nujol and $CHCl_3$ solns on P-E 257 and Infracord 137 spectrophotometers. ^1H NMR spectra were obtained on P-E R32, P-E R34 and Bruker WP80 instruments, and ^{13}C spectra on a Bruker WP80 instrument using the solvents specified and TMS as internal standard. Mass spectra were obtained from a Kratos M45 instrument. All solvents and reagents used were AnalaR grade. Alumina was Peter Spence Grade H deactivated with 5% of 10% AcOH.

trans-3,5-Diphenyl-4-nitrocyclohexanone (**1**). The preparation used the method of Kohler and Dewey[2]. The *nitroketone* (**1**) was crystallised from glacial AcOH at 100° as prisms, m.p. 168° (Lit. value[2] m.p. 93–4° (from MeOH); ν_{max} 1709, 1625, 1587, 1361 cm^{-1}; δ_H (C_5D_5N) 3.10 (4H, m), 4.15 (2H, m), 5.98 (1H, q, J10, 7 Hz), 7.27 (10H, m); δ_C (DMSO-D_6) 41.1, 42.3, 42.9, 45.1, 90.5, 127.4, 127.9, 128.1, 128.6, 128.9, 138.0, 138.1, 140.3, 207.7 (Found: C, 73.4; H, 6.1; N, 4.6. $C_{18}H_{17}NO_3$ requires: C, 73.2; H, 5.8; N, 4.8%).

The reaction of the nitroketone (**1**) *with (a) hydrogen bromide and (b) hydrogen chloride in acetic acid*

(a) The nitroketone **1** (200 mg) was dissolved in a saturated solution of HBr in AcOH (4 ml), and the soln kept in the dark at 20° for 16 hr. The ppt was recrystallised from EtOH to give *2-bromo-3,5-diphenyl-4-aminophenol* (**3**) as small prisms (80 mg), m.p. 244–6°; ν_{max} 3340, 3250, 1560, 754, 696 cm^{-1}; δ_H (C_5D_5N) 4.01 (2H, s), 4.14 (1H, s), 7.45 (11H, m); δ_C (DMSO-D_6) 111.0, 116.4, 117.0, 127.1, 127.3, 127.7, 128.8, 128.9, 129.0, 129.8, 135.2, 138.8, 139.1, 139.9, 145.9, 149.3 (Found: M$^+$ 339 (exact mass 339.0255), 341 (exact mass 341.0206); C, 64.2; H, 3.9; N, 4.2; Br, 23.4. $C_{18}H_{14}NOBr$ requires: M 339 (exact mass 339.0259), 341 (exact mass 341.0239), C, 63.5; H, 4.1; N, 4.1; Br, 23.5%). There was also observed in the mass spectrum a mass peak at 261 (exact mass 261.1150) due to **5** as contaminant ($C_{18}H_{15}NO$ requires exact mass 261.1153). The principal peaks in the mass spectrum of **3** were 341 (10.7%), 339 (11.3%), 261 (8.1%), 18 (100%).

(b) Similar treatment of **1** (200 mg) with HCl in AcOH gave *2-chloro-3,5-diphenyl-4-aminophenol* (**4**) as prisms (55 mg, from EtOH), m.p. 254°; ν_{max} 3390, 3270, 1580, 758, 700 cm^{-1}; δ_H (C_5D_5N) 4.60 (3H, broad), 7.45 (11H, m); δ_C (DMSO-D_6) 117.3, 119.3, 126.3, 127.1, 127.4, 127.8, 128.9, 129.1, 130.0, 135.3, 136.9, 139.1, 144.9 (Found: M$^+$ 297 (exact mass 297.0748), 295 (exact mass 295.0761); C, 73.0; H, 4.7; N, 4.5; Cl, 11.8. $C_{18}H_{14}NOCl$ requires M 297 (exact mass 297.0762), 295 (exact mass 295.0758); C, 73.0; H, 4.7; N, 4.7; Cl, 12.0%). The mass peak at 261 was of low intensity. The principal peaks in the mass spectrum of **4** were 297 (44.2%), 295 (100%), 261 (9.8%).

Acetylation of the aminophenols (**3** *and* **4**). The aminophenols (150 mg) were dissolved in pyridine (6 ml) and Ac_2O (3 ml) and the soln kept at 20° for 16 hr. The product was recovered in ether and excess reagents removed with $NaHCO_3$ and HCl.

2-Bromo-3,5-diphenyl-4-aminophenyl acetate (**6**) crystallised from ether-pentane as prisms (110 mg), m.p. 133°; ν_{max} 3500, 3400, 1770, 1600, 1200 cm^{-1}; δ_H ($CDCl_3$) 2.30 (3H, s), 3.6 (2H, s, broad), 7.40 (11H, m) (Found: M$^+$ 381 (exact mass 381.0377), 383; C, 63.6; H, 4.0; N, 3.8; Br, 20.3. $C_{20}H_{16}NO_2Br$ requires: M 381 (exact mass 381.0364), 383; C, 62.8; H, 4.2; N, 3.7; Br, 20.9%). The principal peaks in the mass spectrum were 383 (8.3%), 381 (8.3%), 341 (97%), 339 (100%), 303 (4.6%), 261 (25.3%).

2-Chloro-3,5-diphenyl-4-aminophenyl acetate (**7**) separated from ether-pentane as an amorphous solid, (85 mg), m.p. 150–5°; ν_{max} 3520, 3410, 1780, 1205 cm^{-1}; δ_H ($CDCl_3$) 2.25 (3H, s), 3.60 (2H, s, broad), 7.40 (11H, m) (Found: M$^+$ 337 (exact mass 337.0889), 339. $C_{20}H_{16}NO_2Cl$ requires: M 337 (exact mass 337.0869), 339). This compound was not obtained analytically pure. The principal peaks in the mass spectrum were 339 (2.9%), 337 (7.9%), 297 (32.9%) 295 (100%) and 261 (0.6%). There was no peak at 303.

The reaction of the nitroketone (**1**) *with sulphuric acid in acetic acid.* Nitroketone **1** (400 mg) was dissolved in a mixture of H_2SO_4 (4 ml) and AcOH (12 ml), and the soln kept at 20° for 20 hr. A solid was precipitated on the addition of $NaHCO_3$, and was recrystallised from EtOH-water to give *3-phenyl-4-amino-5-(4'-hydroxy-phenyl)-phenol* (**8**) as pale brown prisms (95 mg), m.p. 198–200°; ν_{max} 3575, 3400, 3310, 1590 cm^{-1}; δ_H(C_5D_5O) 5.65 (v. broad), 7.13 (m) (the OH and NH resonances were not clear enough to be identified and so allow the integration of the spectrum); δ_C (DMSO-D_6) 116.1, 116.5, 117.5, 119.6, 127.1, 127.9, 128.7, 128.9, 129.0, 129.1, 131.5, 133.6, 140.1, 149.4, 154.5 (Found: M$^+$ 277 (exact mass 277.1076); C, 77.3; H, 5.4; N, 4.9. $C_{18}H_{15}NO_2$ requires: M277 (exact mass 277.1103); C, 77.9; H, 5.4; N, 5.1%). The principal peaks in the mass spectrum were 277 (100%), 260 (26.3%).

The *triacetate* (**9**) obtained from the reaction of **8** with Ac_2O in pyridine, was isolated as a glass by elution from alumina in pentane-ether (10:1). It showed ν_{max} 3320, 3240, 3170, 1786, 1764, 1686 cm^{-1}; δ_H ($CDCl_3$) 1.48 (s, 3H), 1.90 (s, 3H), 2.14 (s, 3H), 7.10 (m, 12H (aromatic + NH) (Found: M$^+$ 403 (exact mass 403.1420). $C_{24}H_{21}NO_5$ requires: M 403 (exact mass 403.1419)). This compound was not obtained analytically pure. The principal peaks in the mass spectrum were 403 (4.2%), 361 (43%), 319 (100%) and 277 (89%).

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