On the Reaction of *p*-Cresol with 4-Aminoantipyrine[1]

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The structure of the yellow product from the ferricyanide oxidation of *p*-cresol and 4-aminoantipyrine is shown to be **1** and not **3**. Borohydride reduction of the imine **1** gave **2** which underwent elimination to **5***a*. Ferricyanide oxidation of **5***a* regenerated **1**.

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On démontre que le produit jaune, obtenu lors de l'oxydation au ferricyanure du *p*-crésol et de l'amino-4 antipyrine, possède la structure **1** et non la structure **3**. La réduction de l'imine **1** par le borohydrure conduit à **2** qui subit une élimination pour fournir **5***a*. L'oxydation au ferricyanure du produit **5** regénère le produit **1**. [Traduit par le journal]

In a recent publication in this journal structure **3** was proposed for the yellow compound, m.p. 150°, formed on ferricyanide oxidation of a mixture of *p*-cresol and 4-aminoantipyrine (1). One experimental fact, the position of the methyl signal at δ 1.52 in the ^{1}Hm.r. spectrum of the compound, was not in keeping with formula **3**, and the authors attributed this discrepancy to strong shielding of the 5-methyl group of the antipyrine moiety by the adjacent *o*-quinoneimide. However, the "unusually high field position" of this methyl group could more plausibly be explained by its being on an sp^3 carbon instead of an sp^2 carbon. Moreover, **3** would be expected to undergo fast electrocyclic ring closure to **1** which does place this methyl group on an sp^3 carbon. In the following is presented evidence that the structure of the yellow compound is indeed **1** and not **3**.

The ^{13}Cm.r. spectrum of the yellow compound (Table 1) had signals from four sp^3 carbon atoms, three from methyl carbon (19.7, 20.3, and 39.7 p.p.m.) and one from carbon not bearing hydrogen (87.4 p.p.m.), in agreement with **1** but not with **3**. When the yellow compound in methanol–tetrahydrofuran was treated with sodium borohydride at −10°, the yellow color was discharged within 2½ min. There was isolated a colorless crystalline solid **2**, m.p. 155–175° (dec.), whose i.r. spectrum contained an NH peak at 3350 cm^{-1}. Its ^{1}Hm.r. spectrum contained, in addition to three methyl singlets, a one-proton (non-exchangeable) singlet at δ 4.27 which is required by structure **2**. The ^{13}Cm.r. spectrum of the reduction product now contained five sp^3 carbons: three methyl (19.4, 20.8, and 38.1 p.p.m.), one quaternary (90.4 p.p.m.), and a new methine carbon (57.6 p.p.m.) in agreement with **2**. On standing, the borohydride reduction product underwent elimination of the phenol oxygen part of the carbinolamine ether and tautomerization to **5***a*, m.p. 205°. Its ^{13}C, ^{1}H, and u.v. (Fig. 1) spectra agree with this formulation. In addition, acetylation produced an *O*,*N*-diacetate **5***b*,

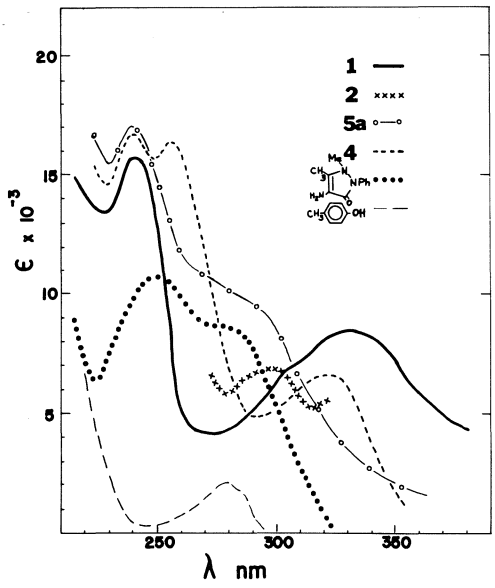
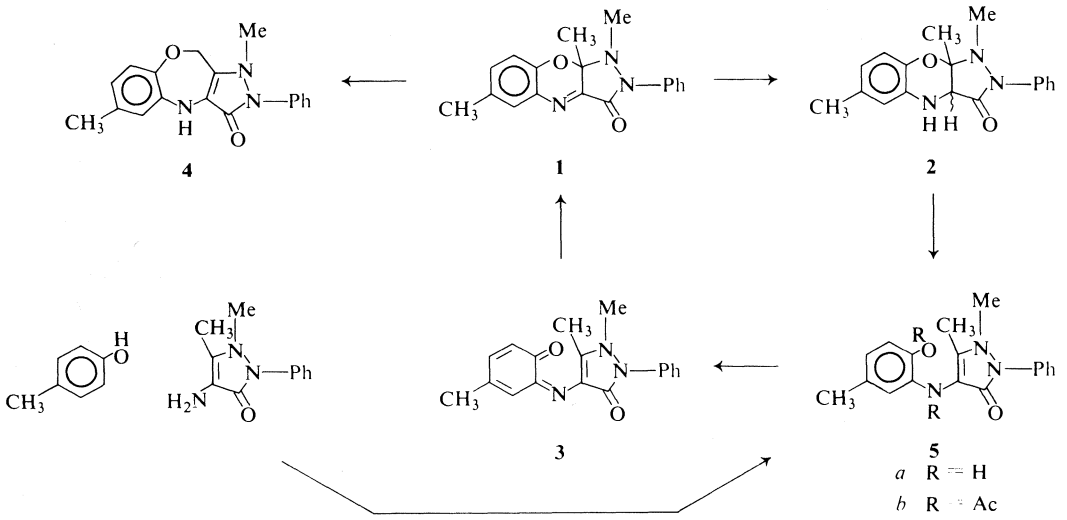


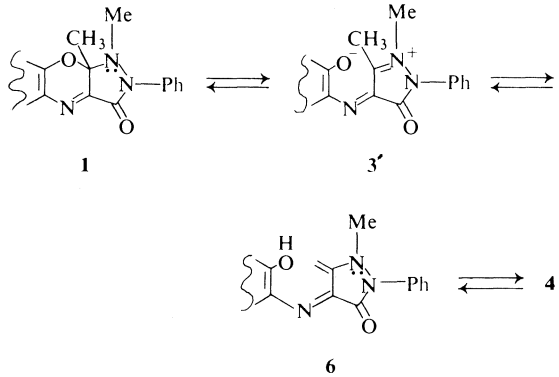
FIG. 1. Ultraviolet spectra of *p*-cresol – 4-aminoantipyrine transformation products.

[1]Part 41 of ^{13}Cm.r. Studies; for Part 40, ref. 5.



m.p. 151°, which was hydrolyzed in aqueous hydrochloric acid back to **5***a*. Since aminophenol **5***a* would be expected to be the first-stage intermediate in the two-stage oxidation of *p*-cresol and 4-aminoantipyrine to **1**, it is not surprising that treatment of **5***a* with ferricyanide gave **1** in very high yield.

With the revised structure **1**, the formation of compound **4**, whose structure was correctly assigned (1), can be regarded in a more familiar alternative way than the [1,7] sigmatropic shift suggested in ref. 1. Thus, the carbinolamine ether of **1** opens to the imonium ion **3′** (merely a canonical form of **3**) which, after proton loss from the methyl group, can undergo readdition of the phenol to the conjugated imine **6** to produce **4**. This interpretation accommodates both the thermal reaction and the catalysis by hydroxylic solvents. The suggested base catalysis (1) could well be just the effect of the greater polarity of pyridine (*vs.* $CDCl_3$) on formation of the polar resonance hybrid **3** ↔ **3′**. A further point of interest is that the ring closure of **6** to **4** is reversible. When **4** was heated at 105° in ethanol-*O*-*d*, the recovered **4** had partially exchanged the protons of the —OCH_2— group for deuterium, a result which is only possible if the reaction sequence **4** → **6** → **3′** occurs. Although compound **6** can cyclize either to a 6-membered ring (**1**) or to a 7-membered ring (**4**), the unusual result is that the 7-membered ring is strongly favored at equilibrium.



The very low-field position (δ 8.00–8.22) for two of the aromatic protons of the cresyl ring of **1** is not exceptional; quinoxaline and quinoline derivatives also have such low-field protons (2). Nor is the yellow color of **1** surprising when it is noted that **1** has more extended conjugation than 4-aminoantipyrine which is yellow.

Therefore, although **3** is probably an intermediate in the formation of **1**, it remains undetected as yet.

Experimental

General

Procedures and apparatus were the same as in ref. 3 except for the following. Infrared spectra were recorded on Beckman IR-5A and IR-20A instruments. Aromatic protons in the ^{1}Hm.r. spectra are not reported. ^{13}Cm.r. spectra were obtained with a Varian XL-100-15 system operating in the Fourier transform mode with proton decoupling. The nature of specific carbons (*i.e.* quaternary, methyl, etc.) was determined by off-resonance decoupling with and without noise modulation. Samples of ~20 mg/0.3 ml were examined in the solvents noted (Table 1). Merck aluminum oxide PF-254 (type E) was used for some thick-layer chromatography. Thin layer

TABLE 1. ^{13}Cm.r. absorption data relative to TMS standard

Compound (solvent)	Antipyrine ring					*N*-Phenyl				Cresol ring[a]		
	C-5	C-4	C-3	N-Me	C-Me	C-1	C-2	C-3	C-4	CH	C	Me
4-NH_2 antipyrine ($CDCl_3$)	137.9	119.1	162.1	37.9	10.1	135.5	122.8	129.0	125.8	—	—	—
1 (C_6D_6)	87.4	159.3	161.1	39.7	19.7	133.4	118.9	129.3	125.7	116.7 (C-6) 130.2 131.7	133.2 (C-4) 138.3 (C-2) 141.6 (C-1)	20.3
2 (Ac-d_6)	90.4	57.6		38.1	19.4	131.7	120.1	129.5	125.3	115.5 117.5 119.6	120.4 (C-4) 129.8 (C-2) 138.9 (C-1)	20.8
5*a* ($CDCl_3$)	144.2	113.8	163.9	36.4	11.1	134.7	124.5	129.3	127.1	114.0 114.9 119.7	128.5 (C-4) 134.4 (C-2) 150.8 (C-1)	21.1
4 ($CDCl_3$)	137.5	119.2	159.6	39.2	68.5[b]	135.1	123.1	129.2	126.4	119.4 (C-6) 122.3 123.4	134.8 135.1 146.1 (C-1)	20.7

[a]The assignments indicated for the aryl carbons were made by comparison with those observed for benzoxazole (4), *p*-cresol, and *o*-aminophenol.
[b]—CH_2O— signal.

chromatography plates were sprayed with a 4:1 mixture of concentrated H_2SO_4 – concentrated HNO_3.

Reaction of p-Cresol with 4-Aminoantipyrine

The reaction was performed as described by Jones and Johnson (1) with *p*-cresol (175 mg, B.D.H.), 4-aminoantipyrine (550 mg, Matheson), $K_3Fe(CN)_6$ (10.5 g), and p*H* 10 phosphate buffer (Coleman) solution (125 ml). The filtered material was dried under reduced pressure to give a yellowish-brown solid (420 mg, 85%), m.p. 130–134°. The ^{1}Hm.r. spectrum of the crude material showed methyl peaks corresponding only to the yellow oxidation product **1**, and it could be used without further purification (*vide infra*). For spectroscopy, the compound was purified by recrystallization from *n*-pentane or by preparative t.l.c. on alumina with benzene–ether (75:25) eluent. The yellow band at R_f 0.65 yielded bright yellow granules of **1**, m.p. 146–148°, after recrystallization from ether; ν_{max} ($CHCl_3$) 1689 (amide C=O) and 1658 (weak)[2] cm^{-1}, λ_{max} (MeOH) 242 (15 800) and 330 nm (8600); δ ($CDCl_3$) 1.54 (3H, s, CH_3), 2.40 (3H, s, $ArCH_3$), and 2.76 p.p.m. (3H, s, NCH_3).

[2]The absorption peak at 1658 cm^{-1} has only about one sixth of the intensity of the 1689 cm^{-1} peak (amide C=O) and therefore cannot be due to a carbonyl group.

Borohydride Reduction of 1

To a stirred (magnetic bar) solution of **1** (25 mg) in a mixture of methanol (1.0 ml) and tetrahydrofuran (1.0 ml) at −10° was added $NaBH_4$ (25 mg). Within 2.5 min the yellow color was discharged. After stirring at −10° for another 0.5 min, the reaction mixture was diluted with cold ether, washed with ice-cold water, dried, and concentrated at room temperature to give an almost colorless crystalline solid. Three recrystallizations from acetone – petroleum ether (b.p. 30–60°) gave colorless granules (7 mg) of essentially one stereoisomer of **2**, m.p. 155–175° (dec.);[3] ν_{max} ($CHCl_3$) 3350 (NH) and 1725 cm^{-1} (amide C=O); λ_{max} (MeOH) 245 (16 000) and 295 nm (~7000); δ ($CDCl_3$) 1.63 (3H, s, CH_3), 2.13 (3H, s, $ArCH_3$), 2.73 (3H, s, NCH_3), and 4.27 p.p.m. (1H, s, N—CH—C=O); *m/e* 309 (molecular ion).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$ (309.4): C, 69.88; H, 6.19. Found: C, 69.57; H, 6.03.

[3]The clean ^{1}Hm.r. spectrum is the best indication that a single stereoisomer of **2** is present. The wide m.p. is probably caused by some elimination to **5***a* which is apparent from t.l.c. of the melt. It is also possible that the *cis* and *trans* stereoisomers of **2** are being interconverted via **3** ↔ **3**′ during t.l.c. or melting.

Thin-layer chromatography on silica gel in ether–benzene (75:25) showed two overlapping spots more polar than **1** but less polar than **5***a*.[3]

Elimination Product 5a

(*a*) The ^{1}Hm.r. solution of **2** in $CDCl_3$ was allowed to stand overnight, whereupon the three methyl signals due to **2** had disappeared and three new methyl signals had appeared. Recrystallization from chloroform – petroleum ether (b.p. 60–80°) gave colorless microcrystals of **5***a*, m.p. 199–205° (dec.); ν_{max} ($CHCl_3$) 3100–3500 (broad, OH, NH) and 1675 cm^{-1} (amide C=O); λ_{max} (MeOH) 240 (17 000) and λ_{inf} (MeOH) ~280 nm (10 000); δ ($CDCl_3$) 2.14 (3H, s, CH_3), 2.18 (3H, s, CH_3), and 3.09 p.p.m. (3H, s, NCH_3); *m/e* 309 (molecular ion). This sample was identical with that prepared in *b*.

(*b*) To a stirred (magnetic bar) solution of crude **1** (100 mg) in a mixture of methanol (1.0 ml) and tetrahydrofuran (1.5 ml) at room temperature was added $NaBH_4$ (100 mg). After being stirred for 0.5 h, the mixture was diluted with ether, washed with water, dried, and evaporated to leave an oily solid (102 mg). The crude solid dissolved in acetone (5 ml) was treated with 0.1 *N* aqueous HCl (1 ml) for 1 h. Work-up and two recrystallizations from chloroform – petroleum ether (b.p. 60–80°) gave colorless crystals of **5***a* (40 mg), m.p. 199–205° (dec.).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$ (309.4): C, 69.88; H, 6.19. Found: C, 69.42; H, 6.40.

Diacetate 5b

A solution of aminophenol **5***a* (100 mg), pyridine (1.0 ml), and acetic anhydride (1.5 ml) was stirred (magnetic bar) under nitrogen at 100° for 2.5 days. After distillation of the pyridine and excess anhydride at reduced pressure, the residual mass was taken into chloroform, washed with 5% aqueous $NaHCO_3$ and water, dried, and concentrated to an amber oil. Thin-layer chromatography on 20 g of silica gel with ether–methanol (85:15) gave under u.v. a band at R_f 0.43 which was extracted several times with ether to yield 60 mg of solid. Recrystallization of 40 mg from acetone – petroleum ether (b.p. 30–60°) gave colorless granules of **5***b* (30 mg), m.p. 150–151°; ν_{max} ($CHCl_3$) 1760 (acetate C=O) and 1675 cm^{-1} (2 amide C=O); λ_{max} (MeOH) 275 nm (12 670); δ ($CDCl_3$) 2.08 (3H, broad hump, CH_3 of acetate, sharpened at 80° to a singlet), 2.18 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.33 (3H, s, CH_3), and 3.10 p.p.m. (3H, s, NCH_3); *m/e* 393 (molecular ion).

Anal. Calcd. for $C_{22}H_{23}N_3O_4$ (393.4): C, 67.16; H, 5.89; N, 10.68. Found: C, 67.85; H, 6.05; N, 10.21.[4]

Acid hydrolysis of **5***b* (10 mg) with 10% aqueous HCl (0.8 ml) in a sealed glass tube at 100° for 2.5 h gave 4 mg of oily solid. Four recrystallizations from chloroform – petroleum ether (b.p. 60–80°) gave colorless **5***a* (1.3 mg) identical (m.p., mixture m.p., t.l.c.) with an authentic sample.

Ferricyanide Oxidation of 5a

To a stirred (magnetic bar) solution of **5***a* (2.0 mg) in tetrahydrofuran (0.1 ml) and p*H* 10 buffer solution (0.5 ml) was added 20 mg of $K_3Fe(CN)_6$. A yellow solid precipitated immediately. After 0.5 h the solid was filtered, washed thoroughly with water, and dried to yield 0.5 mg of bright yellow granules of **1** identical with an authentic sample (m.p., mixture m.p., and t.l.c.). Extraction of the filtrate with ether gave 1.5 mg more of yellow oily solid which t.l.c. showed to be essentially pure **1**.

Deuterium Exchange with 4

A solution of **4** (10 mg) in ethanol-*O*-*d* (1 ml) was heated in a sealed tube at 105° for 2 days. Two recrystallizations of the product from ethanol to remove ND gave 7.3 mg of colorless **4**, m.p. 215–218°. Deuterium analysis by mass spectroscopy gave 52% d_0, 32% d_1, and 16% d_2. The ^{1}Hm.r. spectrum of the recovered **4** revealed a considerable decrease (~40%) in the intensity of the —OCH_2— peak at δ 5.07.

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1. P. F. Jones and K. E. Johnson. Can. J. Chem. **51**, 3733 (1973).
2. Varian NMR Spectra Catalog, Vol. 2, spectra 494 and 578. Varian Associates. 1963.
3. V. Dave and E. W. Warnhoff. Can. J. Chem. **49**, 1911 (1971).
4. L. F. Johnson and W. C. Jankowski. Carbon-13 NMR spectra. Wiley-Interscience, New York. 1972.
5. G. I. Birnbaum, A. Stoessl, S. H. Grover, and J. B. Stothers. Can. J. Chem. **52**, 993 (1974).

[4]Three analyses of the same sample of **5***b* gave carbon values varying by 1.8%. However, the sharp melting point, single t.l.c. spot, molecular ion at *m/e* 393, and the absence of extraneous absorption in the ^{1}Hm.r. spectrum are convincing evidence of its formula and purity.