NUCLEOPHILIC REPLACEMENT OF METHOXYL IN THE REACTION OF A STERICALLY HINDERED *o*-BENZOQUINONE WITH *o*-PHENYLENEDIAMINE

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Summary

With *o*-phenylenediamine, 3-t-butyl-5-methoxy-1,2-benzoquinone gives the quinone imine (VII), but only a trace of the expected phenazine (II). Dilute acid converts (VII) to the anilinophenazine (III). Chemical and spectroscopic evidence for the structures of these compounds is presented.

The reaction of *o*-benzoquinones with *o*-phenylenediamines has often been used to characterize either as a phenazine. In this paper we report the anomalous behaviour of 3-t-butyl-5-methoxy-1,2-benzoquinone (I). When set aside with *o*-phenylenediamine in chloroform, the quinone (I) gave a purple solution. Chromatography on acid-washed alumina gave two products, one orange, the other purple. When neutral alumina was used, the product was almost entirely the purple material. A longer reaction time resulted mainly in black material which we could not purify, together with a trace (0·1%) of the expected phenazine (II).

The molecular formula, $C_{22}H_{22}N_4$, showing the absence of oxygen, the compound's solubility in acid, and the formation of an acetamide, in conjunction with spectral evidence discussed below, suggested structure (III) for the orange product. Further evidence for the replacement of the methoxyl group by an *o*-aminoanilino group is the formation of the benzotriazole (IV) by reaction of (III) with nitrous acid, a reaction characteristic of *o*-aminoanilines.[1] Also, when treated with formic acid, the anilinophenazine (III) gave a formamide which, though it could not be cyclized by heating with dilute acid (Phillips[2] method), gave the benziminazole (V) on fusion. We were unable to debutylate the anilinophenazine (III) with hydrobromic acid. This usually effective reagent also fails to debutylate some dibenzofuran derivatives.[3] An attempt to cleave (III) by heating in a sealed tube with hydrochloric acid did not result in identifiable 2-hydroxyphenazine or 1-t-butyl-3-hydroxyphenazine. In a similar reaction Barry *et al.*[4] reported very low yields of degradation products from an anilinophenazine.

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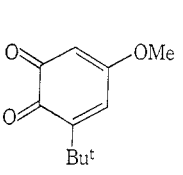
[1] Zincke, von T., Stoffel, F., and Petermann, E., *Liebigs Ann.*, 1900, **311**, 276.

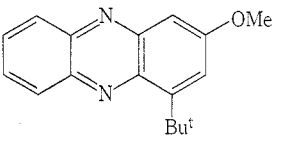
[2] Phillips, M. A., *J. Chem. Soc.*, 1928, 2393.

[3] Hewgill, F. R., and Kennedy, B. R., unpublished data.

[4] Barry, V. C., Belton, J. G., O'Sullivan, J. F., and Twomey, D., *J. Chem. Soc.*, 1956, 888.



(I)



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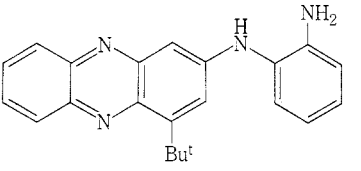

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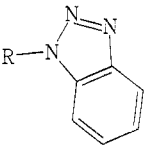

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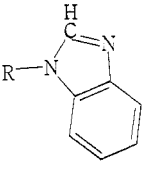

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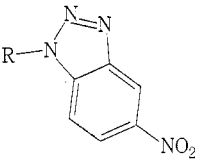


(VI)

R = 1-t-butyl-3-phenazinyl

With nitric acid the anilinophenazine (III) gave material considered to be 1-(1-t-butyl-3-phenazinyl)-5-nitrobenzotriazole (VI). The analogous reaction of nitric acid with *o*-phenylenediamine has been reported[5] to yield 5-nitrobenzotriazole. From the failure of the benzotriazole (IV) to give (VI) under various conditions of nitration, coupled with the suggestion of Katritzky and Lagowski[6] that nitration of benzotriazoles results in substitution at the 4- and 7-positions, we conclude that nitration has preceded triazole formation. Thus preferential protonation of the primary amino group of the anilinophenazine (III) should lead to the 5- rather than to the 6-nitrobenzotriazole. In support of this argument, it was found that nitration of 2-aminodiphenylamine gave exclusively 1-(4-nitrophenyl)benzotriazole.

Considerable spectroscopic evidence for the structures of compounds (II–VI) exists. Thus the infrared spectra of these compounds and of 2-methoxy-, 3-t-butyl-2-methoxy-, and 3-t-butyl-1-methoxyphenazine show C–H in-plane deformation bands between 1230 and 950 cm^{-1} characteristic of phenazines.[7] The two triazoles (IV) and (VI) show strong absorption at 1040 and 1045 cm^{-1} respectively which O'Sullivan[8] finds characteristic of benzotriazoles. Other characteristic bands in this region cannot be differentiated from bands due to the phenazine system. From the out-of-plane deformation bands (Table 1) it will be seen that absorption at 753–758 cm^{-1} can be assigned to an unsubstituted phenazine carbocyclic ring in each compound, whereas bands at 745–738 cm^{-1} must arise from the *o*-aminoanilino residue, as *o*-phenylenediamine itself absorbs at 745 cm^{-1}. The band of moderate intensity at 694 cm^{-1} in the spectrum of the nitrobenzotriazole (VI) is significant, as O'Sullivan[8] reports a band in this position only for 5-substituted benzotriazoles.

[5] Macciotta, E., *Chem. Abstr.*, 1933, **27**, 4528.

[6] Katritzky, A. R., and Lagowski, J. M., "Heterocyclic Chemistry." p. 230. (Methuen: London 1960.)

[7] Stammer, C., and Taurino, A., *Spectrochim. Acta*, 1963, **19**, 1625.

[8] O'Sullivan, D. G., *J. Chem. Soc.*, 1960, 3653.

It can be seen from the ultraviolet spectra recorded in Table 1 that, with the exception of the dianilinophenazines, absorption of comparable intensity at 357–372 mμ is shown by all the phenazines and, with the additional exception of the anilinophenazine (III) and its formamide, absorption between 255 and 267 mμ takes place in each case. Absorption in these two regions is typical of the phenazine system.[9] The red shift observed for (III) and for its formamide is closely paralleled by the dianilinophenazines

TABLE 1

Compound	Electronic Absorption Spectra* λ_{max} (mμ) (log ε)	Infrared Absorption†	Ref.
(II)	218 (4·28) 258 (4·81) 357 (3·90)	756	
2-Methoxyphenazine	255 (4·9) 360 (4·0) *395 (3·9)*	757	9
3-t-Butyl-2-methoxyphenazine	219 (4·41) 259 (4·88) 370 (4·03)	758	
3-t-Butyl-1-methoxyphenazine	215 (4·45) 267 (5·05) 368 (4·15) *402 (3·66)*	758 754	10
1-Methoxyphenazine	260 (4·74) 360 (3·87) 402 (3·45)		11
(III) (Orange product)	235 (4·55) 285 (4·63) 362 (3·76) 475 (4·00)	756 745	
2-Aminodiphenylamine	233 (4·00) 286 (3·85)		12
2,3-Dianilinophenazine	285 480		13
2,7-Dianilinophenazine	285 490		13
Formamide from (III)	235 (4·62) 286 (4·60) 357 (3·71) 456 (3·97)		
(IV) (Triazole)	*232 (4·37)* 258 (4·70) 302 (4·15) 372 (4·20)	785 *765* 756 742	
(V) (Benziminazole)	215 (4·84) 260 (4·99) 370 (4·29)	*730 775* 753 738	
(VI) (Nitrotriazole)	255 (4·70) 372 (4·25)	756 730 694	
(VII) (Purple product)	228 (4·34) 298 (4·10) 540 (3·70)	742 674	
5-Amino-2-methyl-*N*-*p*-tolylbenzo-1,4-quinone imine	230 (4·2) 300 (4·2) 480 (3·8)		14

* In ethanol. Shoulders are in *italics*.

† Between 790 and 670 cm^{-1} in CS_2. Weak bands in *italics*.

and has been noticed previously for aminophenazines.[11] As has been suggested by Ramage and Landquist,[15] it seems likely that a tautomeric change to a 10*H*-2-iminophenazine is responsible for this shift, as it no longer occurs in the triazoles (IV) and (VI) or in the benziminazole (V) in which amino hydrogens are lacking. Moreover, acetylation of (III) gave only a monoacetamide: also, tautomerism of this kind would favour preferential protonation of the primary amino group in the nitration of (III). The spectra of compounds (IV), (V), and (VI) show absorptions characteristic only of the phenazine system.

Little information could be obtained from the n.m.r. spectra of the anilinophenazine (III) and its acetate because of the complex nature of the aromatic proton

[9] Badger, G. M., Pearce, R. S., and Pettit, R., *J. Chem. Soc.*, 1951, 3199, 3204.

[10] Hewgill, F. R., and Middleton, B. S., *J. Chem. Soc.*, 1965, 2914.

[11] Gray, A., and Holliman, F. G., *Tetrahedron*, 1962, **18**, 1095.

[12] Grammaticakis, P., *Bull. Soc. Chim. Fr.*, 1954, 99.

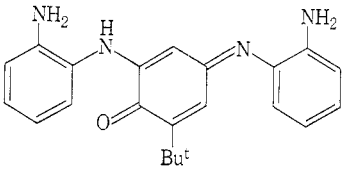
[13] Kehrmann, F., and Sandoz, M., *Helv. Chim. Acta*, 1920, **3**, 104.

[14] Teuber, H.-J., and Jellinek, G., *Chem. Ber.*, 1954, **87**, 1841.

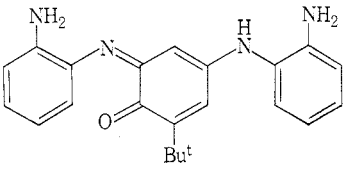
[15] Ramage, G. R., and Landquist, J. K., in "Chemistry of Carbon Compounds." p. 1379. (Ed. E. H. Rodd.) (Elselvier: Amsterdam 1959.)

resonances. The presence of a t-butyl resonance in each was noted, and only one acetyl group was present in the amide.

Structure (VII) proposed for the purple reaction product is based on the following evidence. The action of dilute acid converts the purple material to the anilinophenazine



(VIIa)



(VIIb)

(III): a change which, from the elementary analyses, involves loss of one molecule of water. On hydrogenation the purple solution becomes colourless, absorbing one mole of hydrogen, but on exposure to air instantly reverts to purple. This behaviour is common in quinone imines.[16] The infrared spectrum of the purple compound shows absorption at 3465 (NH_2) and 3355 cm^{-1} (NH), and a band at 1640 cm^{-1} consistent with the carbonyl absorption of a quinone imine.[17] A strong band at 742 cm^{-1} was attributed to the *o*-aminoanilino residues. The ultraviolet spectrum showed no phenazine absorption, but was very similar to that of 5-amino-2-methyl-*N*-*p*-tolylbenzo-1,4-quinone imine.[14]

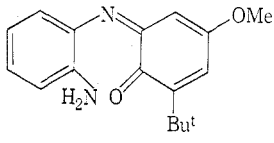
The n.m.r. spectrum of the purple compound in deuterochloroform at 60 Mc/s showed complex resonances (τ 2·7–3·5) integrating for nine protons, a doublet of doublets (τ 2·90 and 3·92) with J 2·5 c/s which is assigned to two *meta*-coupled vinylic protons, a broad resonance at τ 6·3 integrating for 3·6 protons (amino), and two resonances (τ 8·61, 8·72) in the intensity ratio 6:1, the total integral of which is taken as equivalent to nine t-butyl protons. The integral of the doublet of doublets indicates that these arise from the vinylic protons of the more abundant isomer. The doublet splittings for the less abundant isomer could not be distinguished from background noise. The signal at τ 6·3 and one-ninth of the signal at τ 2·7–3·5 were removed on exchanging with deuterium oxide, leaving the vinylic protons unaffected. The chemical shift of the t-butyl resonances is 0·3–0·4 τ upfield from that of the anilinophenazine (III), and of the same order as that found for 2-t-butyl groups in cyclohexadienones.[18]

We are of the opinion that tautomerism between structures (VIIa) and (VIIb) need not be invoked to account for the presence of two t-butyl resonances. These could arise from the change in magnetic environment of this group brought about by geometrical isomerism of either *o*-aminophenylimino group. We are unable to distinguish between structures (VIIa) and (VIIb) on present evidence, but assume the *p*-quinone imine to be thermodynamically more stable.

Campbell,[19] using acetic acid as solvent, has obtained a phenazine in 21% yield from 4,6-di-t-butyl-3-hydroxy-1,2-benzoquinone, which has the same degree of

[16] Horner, L., and Sturm, K., *Chem. Ber.*, 1955, **88**, 329.
[17] Musso, H., and Matthies, H.-G., *Chem. Ber.*, 1957, **90**, 1814.
[18] Hewgill, F. R., Kennedy, B. R., and Kilpin, D., *J. Chem. Soc.*, 1965, 2904.
[19] Campbell. T. W., *J. Org. Chem.*, 1957, **22**, 1731.

steric hindrance as the quinone (I). In this solvent, (I) gave the phenazine (II) in only 2·5% yield. It is thus apparent that the low yield of phenazine in the present case is caused by steric hindrance from the t-butyl group slowing phenazine formation to such an extent that nucleophilic substitution of the methoxyl group by *o*-phenylenediamine takes almost complete precedence. Whether this substitution takes place in the quinone (I) or in a possible intermediate (VIII) or in both is not clear, but it does not occur after phenazine formation, as 2-methoxyphenazine fails to react with *o*-phenylenediamine under these conditions.



(VIII)

In conclusion, we suggest that the black material isolated after longer reaction between the quinone (I) and *o*-phenylenediamine is largely a polymer of the quinone imine (VII). Its infrared spectrum is very similar to that of the quinone imine, a significant feature being the low absorption between 753 and 758 cm^{-1}, indicating the almost complete absence of an anilinophenazine moiety. This constitutes additional evidence that the anilinophenazine (III) is not a major constituent of the reaction mixture, but an artefact produced from the quinone imine (VII) by the action of acid.

Experimental

Melting points were determined on a Kofler block. Infrared and ultraviolet spectra were recorded on Perkin–Elmer instruments 137, 137G, and 137UV; n.m.r. spectra on a Varian A60 spectrometer at 60 Mc/s with tetramethylsilane as internal reference. Light petroleum refers to the fraction of b.p. 56–60°. Microanalyses are by the Australian Microanalytical Service, Melbourne.

3-t-Butyl-5-methoxy-1,2-benzoquinone

The quinone, m.p. 74–75° (Found: C, 67·9; H, 7·2. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%), was prepared in 90% yield from 2-t-butyl-4-methoxyphenol by the method described for its isomer.[20] Flaig, Ploetz, and Biergans[21] give m.p. 72–73°.

Reaction of 3-t-Butyl-5-methoxy-1,2-benzoquinone with o-Phenylenediamine

(i) The quinone (9·2 g) and the diamine (10·3 g, 2 equiv.) in chloroform (500 ml) were left over anhydrous sodium sulphate (40 g) for 4 days. After filtration and evaporation of the purple filtrate under reduced pressure, the residue was chromatographed on acid-washed alumina (400 g). Elution with benzene/light petroleum gave the *quinone imine* (VII) (1·8 g) as dark purple plates (from light petroleum), m.p. 167–169° (Found: C, 72·9; H, 6·7; N, 15·8. $C_{22}H_{24}N_4O$ requires: C, 73·3; H, 6·7; N, 15·6%). Elution with benzene/chloroform gave *3-(2-aminoanilino)-1-t-butylphenazine* (7·6 g), orange plates (from benzene), m.p. 226–227° (Found: C, 76·7; H, 6·5; N, 16·4. $C_{22}H_{22}N_4$ requires C, 77·1; H, 6·5; N, 16·1%); ν_{max} (in CS_2) 3465 (NH_2), 3390 (NH); τ (in $CDCl_3$) 1·7–3·3 (10 × ArH), 4·12 (1 × NH), 6·51 (1 × NH_2), 8·31 (1 × Bu^t). The same products were also obtained with equimolar quantities of reactants. Chromatography on neutral alumina gave the quinone imine (VII), with only a trace of 3-(2-aminoanilino)-1-t-butylphenazine.

[20] Hewgill, F. R., *J. Chem. Soc.*, 1962, 4987.

[21] Flaig, W., Ploetz, T., and Biergans H., *Liebigs Ann.*, 1955, **597**, 196.

(ii) When the reaction conditions were varied by either heating the solution or allowing it to stand at room temperature for longer, e.g. for 6 days, the main product was a black material, m.p. 120–145°, ν_{max} (in CS_2) 3465, 3355 (NH), 1645 (C=O), and 741 cm^{-1}, which could not be purified and was not investigated further. On attempted chromatography of this material on acid-washed alumina, elution with light petroleum and recrystallation from the same solvent gave a 0·1% yield of *1-t-butyl-3-methoxyphenazine*, yellow needles, m.p. 158–159° (Found: C, 76·4; H, 6·7; N, 10·5. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%); ν_{max} (in CS_2) 2830 cm^{-1} (OMe).

(iii) The quinone (0·89 g) and *o*-phenylenediamine (0·59 g) were dissolved in glacial acetic acid (50 ml). After 48 hr the red solution was evaporated under reduced pressure, leaving a brown glass which was extracted with methanol (10 ml) containing concentrated hydrochloric acid (1 ml). The extract was made alkaline with sodium methoxide in methanol, the methanol removed, and the residue chromatographed on alumina. Elution with benzene/light petroleum (1 : 1) followed by recrystallization from light petroleum gave 1-t-butyl-3-methoxyphenazine (20 mg), m.p. and mixed m.p. 158–159°.

3-(2-N-Acetylaminoanilino)-1-t-butylphenazine

3-(2-Aminoanilino)-1-t-butylphenazine (500 mg) in pyridine (10 ml) was heated at 100° with acetic anhydride (2 ml) for 1 hr. The crude product obtained on pouring the reaction mixture into water was recrystallized from aqueous ethanol giving the N-*acetate* (400 mg) as red plates, m.p. 193–194° (Found: C, 74·1; H, 6·3; N, 14·0. $C_{24}H_{24}N_4O$ requires C, 74·0; H, 6·3; N, 14·6%); ν_{max} (in $CHCl_3$) 3400 (NH), 3300, broad (bonded NH), 1685 cm^{-1} (C=O); τ (in $CHCl_3$) 7·86 (1 × $NCOCH_3$), 8·26 (1 × Bu^t).

3-(1-Benziminazolyl)-1-t-butylphenazine

3-(2-Aminoanilino)-1-t-butylphenazine (300 mg) was heated in formic acid for 2 hr at 100°. On cooling, the solution was neutralized to Congo Red by aqueous potassium hydroxide and extracted with chloroform. The dried extract was chromatographed on alumina. Elution with benzene/chloroform gave *1-t-butyl-3-(2-N-formylaminoanilino)phenazine* (220 mg) as red prisms (from benzene), m.p. 197–198° (Found: C, 74·4; H, 5·8; N, 14·9. $C_{23}H_{22}N_4O$ requires C, 74·6; H, 6·0; N, 15·1%); ν_{max} (in CS_2) 3390 (NH), 3300, broad (bonded NH), 1695 cm^{-1} (C=O).

The formamide (120 mg) was fused till it became yellow. The cooled material was chromatographed on alumina, elution with benzene/light petroleum giving *3-(1-benziminazolyl)-1-t-butylphenazine* (70 mg) as yellow plates (from light petroleum), m.p. 157–158° (Found: C, 78·9; H, 5·9; N, 16·2. $C_{23}H_{20}N_4$ requires C, 78·4; H, 5·7; N, 15·9%).

Reaction of 3-(2-Aminoanilino)-1-t-butylphenazine with Nitrous Acid

The anilinophenazine (250 mg) in ethanol was added to dilute aqueous hydrochloric acid giving a red solution. Aqueous sodium nitrite was added until the red colour was replaced by a yellow-brown precipitate. Extraction with chloroform and chromatography of the dried extract on alumina gave, on elution with benzene/light petroleum, *3-(1-benzotriazolyl)-1-t-butylphenazine* as yellow needles, m.p. 160–161° (from light petroleum) (Found: C, 75·3; H, 5·4; N, 19·7. $C_{22}H_{19}N_5$ requires C, 74·8; H, 5·4; N, 19·8%).

Reaction of 3-(2-Aminoanilino)-1-t-butylphenazine with Nitric Acid

The anilinophenazine (300 mg) was heated in nitric acid (50 ml of 20%) for 4 hr at 100°. On cooling, a yellow-brown precipitate was filtered off and chromatographed on alumina. Elution with benzene/light petroleum (3 : 1) gave *1-(1-t-butyl-3-phenazinyl)-5-nitrobenzotriazole* (230 mg), yellow needles (from benzene), m.p. 238–239° (Found: C, 66·3; H, 4·6; N, 20·7. $C_{22}H_{18}N_6O_2$ requires C, 66·3; H, 4·6; N, 21·1%).

Nitration of 3-(1-Benzotriazolyl)-1-t-butylphenazine

The benzotriazole (27 mg) was heated at 100° with nitric acid (7 ml of 40%) for 5 hr. Filtration of the cooled solution gave the unchanged benzotriazole (25 mg), m.p. and mixed m.p. 160–161°. The unchanged benzotriazole was also recovered, unchanged after treatment with 60% nitric acid (1 part) in acetic acid (1 part) at room temperature, or at 100°.

The benzotriazole (100 mg) in concentrated sulphuric acid was treated with concentrated nitric acid at 0°, then heated to 40° for 20 min. After cooling, dilution with water, basification, and extraction with chloroform gave material which crystallized from benzene as yellow needles, m.p. 279–281° (80 mg). Analysis (Found: C, 58·9; H, 4·4; N, 21·3%) indicated an impure dinitrobenzotriazolyl-t-butylphenazine; ν_{max} (in CS_2) 735 cm^{-1}, but no absorption near 694 cm^{-1}.

Nitration of 2-Aminodiphenylamine

Concentrated nitric acid (0·5 ml) was added dropwise to a solution of 2-aminodiphenylamine (100 mg) in concentrated sulphuric acid (10 ml) at 0°. The solution was then poured onto ice, filtered, and the residue chromatographed on alumina. Ether eluted 1-(4-nitrophenyl)-benzotriazole (50 mg), m.p. 238–239° (lit.[22] m.p. 239°).

Attempted Degradations of 3-(2-Aminoanilino)-1-t-butylphenazine

A solution of the anilinophenazine (100 mg) in acetic acid (6 ml) and hydrobromic acid (5 ml of 48%) was boiled under reflux for 6 hr. Only the unchanged anilinophenazine (86 mg) could be recovered.

A solution of the anilinophenazine (250 mg) in concentrated hydrochloric acid (5 ml) was heated for 8 hr in a sealed tube at 190°. The contents of the cooled tube were basified and extracted with chloroform. Chromatography of the extract on alumina gave no crystalline fraction. Acidification of the alkaline solution gave a dark precipitate, which gave a blue solution in ethanol, but no pure material could be obtained.

The anilinophenazine also proved completely stable to boiling aqueous ethanolic potassium hydroxide (30%).

Conversion of the Quinone Imine (VII) to 3-(2-Aminoanilino)-1-t-butylphenazine

The quinone imine (100 mg) in chloroform (10 ml) was shaken with aqueous hydrochloric acid (3 ml of 2%). Addition of alkali changed the colour of the chloroform layer to orange. Separation and evaporation of the chloroform gave 3-(2-aminoanilino)-1-t-butylphenazine (86 mg), m.p. and mixed m.p. 226–227°. The infrared spectrum was identical with that of an authentic specimen.

Hydrogenation of the Quinone Imine (VII)

The quinone imine (24 mg) was hydrogenated in ethanol over palladium–charcoal. Uptake of hydrogen (1·60 ml; 0·99 mole) ceased when the solution became colourless. On exposure to air the colour instantly returned and the quinone imine itself was recovered.

Attempted Reaction of 2-Methoxyphenazine with o-Phenylenediamine

A solution of 2-methoxyphenazine (52 mg) and *o*-phenylenediamine (27 mg) in chloroform containing anhydrous sodium sulphate was set aside for 4 days at room temperature. Filtration, evaporation of the solvent, and chromatography on alumina gave 2-methoxyphenazine (49 mg), m.p. and mixed m.p. 123–123·5°. No reaction occurred when the solution was boiled under reflux for 3 hr.

[22] Nietzki, R., and Almenräder, K., *Ber. dt. chem. Ges.*, 1895, **28**, 2969.