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Studies on the Reaction of Benzoyl Peroxide with NN-Dialkyl Aromatic Amines and Other Related Compounds. Part II.¹ Reactions of Some **Primary and Secondary Amines**

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The reaction of benzoyl peroxide with N-methylaniline and N-ethylaniline yields NN'-dimethylhydrazobenzene and NN'-diethylhydrazobenzene, respectively, in addition to previously reported products. The yields of 2-(Nalkylbenzamido) phenols can be increased by carrying out the reaction in benzene in the presence of aqueous sodium hydroxide; this reaction provides a preparative method for the o-hydroxylation of N-alkylanilines. This modification also enables o-benzamidophenols to be obtained from primary aromatic amines.

GAMBARJAN² found that diphenylamine could be oxidised by benzoyl peroxide to 2-(N-phenylbenzamido)phenol in 38% yield. Later, Edward studied the reaction of benzoyl peroxide at room temperature with a variety of primary³ and secondary⁴ aromatic amines. *N*-Methylaniline afforded 2-(N-methylbenzamido)phenol in 30% yield, but the yields of phenols obtained from primary amines were very low, and in the cases of aniline, p-toluidine, and p-anisidine, no phenol was isolated. Horner and Kirmse,⁵ by working at -10° , succeeded in obtaining phenols from aniline and ptoluidine and in increasing the yield of the phenol obtained from o-toluidine.

As this o-hydroxylation is of synthetic interest, we studied the reaction further, particularly with a view to obtaining higher yields of phenolic products. Our vields are all based on benzoyl peroxide; the amine was present in equimolar quantity or in excess. The reaction mixture was not usually worked up until at least eleven hours after the addition of benzoyl peroxide was over, although in most cases reaction was probably complete much earlier.

Reaction of benzoyl peroxide (1 mol.) with N-methylaniline (3.6 mol.) in benzene at 40-45° gave 2-(N-methylbenzamido)phenol (18%), together with NN'-dimethylhydrazobenzene and a trace of p-benzoyloxy-N-methylaniline. Likewise, N-ethylaniline afforded 2-(N-ethylbenzamido)phenol (33%) and NN'-diethylhydrazobenzene. With chloroform or acetonitrile as solvent, yields were lower.

Yields of phenols could be increased by carrying out the reaction in benzene solution in the presence of aqueous sodium hydroxide at 5°. In this way N-methylaniline gave 2-(N-methylbenzamido)phenol (73%) and primary amines gave much higher yields of phenols than those reported by Edward (see Table). We also obtained phenols from aniline, p-toluidine, and p-anisidine, but not from methyl anthranilate. Except in the case of aniline our yields of phenols from primary amines were also higher than those reported by Horner and Kirmse. We also isolated azo-compounds and benzanilides from primary amines, and the dianil of 2,5-dianilino-p-benzoquinone from aniline. The increased yields of phenols in the presence of sodium hydroxide may be the result of the phenol passing into the aqueous layer as soon as formed and therefore being protected from further attack by benzoyl peroxide. On the other hand, the presence of acid has an inhibiting effect on the reaction,⁶ and so the removal of benzoic acid from the organic layer, as fast as it is formed, may be beneficial. The alkaline medium should facilitate the migration of the benzoyl group from oxygen to nitrogen.

Edward⁴ and Horner and Kirmse⁵ favoured a radical mechanism for the formation of benzamidophenols from benzoyl peroxide and secondary aromatic amines. However, in the absence of sound evidence for the radical nature of the reaction (see ref. 7), Huisgen and Bayerlein⁸ suggested nucleophilic attack by the amine to give an arylhydroxylamine benzoate, followed by two migrations. This mechanism is not in agreement with the work of Denney and Denney 9 on diphenylamine and cannot hold for N-ethylaniline, because the rearrangement of N-ethyl-N-phenylhydroxylamine benzoate to 2-(N-ethylbenzamido)phenol is very slow at room temperature (cf. ref. 10). Huisgen and Bayerlein⁸ therefore suggested an alternative mechanism involving nucleophilic attack by the amine through its o-position, followed by one migration.

Although there seems to be no reason to doubt this to be the main reaction, our isolation of NN'-dialkylhydrazobenzenes appears to point to the production of PhNEt radicals in benzene at 40-45°. Huisgen and Bayerlein's mechanism is not in agreement with Denney's work, but it may be that the reactions of benzoyl peroxide with N-ethylaniline and with diphenylamine proceed by different mechanisms.

In the case of primary amines, azo-compounds might arise through hydrazo-compounds, although Horner and Schwenk¹¹ considered an alternative path. Horner

¹ Part I, J. M. Fayadh, (the late) D. W. Jessop, and G. A. Swan, J. Chem. Soc. (C), 1966, 1605.

² S. Gambarjan, Ber., 1909, 42, 4003

³ J. T. Edward, J. Chem. Soc., 1956, 222. ⁴ J. T. Edward, J. Chem. Soc., 1954, 1464.

⁵ L. Horner and W. Kirmse, Annalen, 1955, 597, 66.

⁶ O. A. Chaltykyan, Vopr. Khim. Kinetiki, Kataliza i Reaktsionnoi Sposobnosti, Akad. Nauk S.S.S.R., Otdel. khim. Nauk, 1955, 354.

⁷ R. Huisgen, F. Bayerlein, and W. Heydkamp, Chem. Ber., 1959, **92**, 3223.

⁸ R. Huisgen and F. Bayerlein, Annalen, 1959, 630, 138. ⁹ D. B. Denney and D. Z. Denney, J. Amer. Chem. Soc., 1960,

^{82, 1389.}

L. Horner and H. Steppan, Annalen, 1957, 606, 47.
L. Horner and E. Schwenk, Annalen, 1950, 566, 69.

and Kirmse,⁵ however, found evidence against this and favoured the formation of azobenzene through radicals. The ionic mechanism will also explain the formation of benzanilides, although there are other possible ways in which these might arise.

After treatment with benzoyl peroxide at room temperature, indole was recovered largely unchanged (which was not unexpected, in view of its extremely weak basicity), although small amounts of other compounds were produced. With cumene or benzene as reaction solvent, indigo and isatin, respectively, were obtained and 2,3-dihydro-2,2-di-indol-3-yl-3-oxoindole was isolated when chloroform or benzene was used. Witkop and Patrick 12 have obtained this compound in two forms, has strong peaks at m/e 251 (shown by mass measurement to be C₁₆H₁₃NO₂) and 146 (probably C₉H₈NO). In



these solvents, as in benzene, a compound, m. p. 199-200°, was also obtained.

EXPERIMENTAL

Commercial benzoyl peroxide (containing 30% water) was shaken with chloroform, and the chloroform layer was dried overnight (MgSO₄) and diluted with methanol with

Reaction of benzoyl peroxide with amines in benzene in the presence of sodium hydroxide at 5°

	Molar ratio	Phenol			Azo-compound		Banzanilida	
				Yield	Yield		Yield	
Amine	peroxide		M. p.	(%)	М. р.	(%)	М. р.	(%)
N-Methylaniline	1.0	2-(N-Methylbenzamido)phenol	$158 - 159^{\circ}$	60	+	(707	1	(707
	3.6	2 (11 11000) 1000000000000) promot	100 100	71				
	3.6 *			21				
	4.0			73				
N-Ethylaniline	1.0	2-(N-Ethylbenzamido)phenol	$(158 - 159)^{a}$	(30) *				
	1.0		`162—163´	`50 ´				
	4.0			60				
	1.0		$(160-162)^{a}$	$(37)^{a}$				
1,2,3,4-Tetrahydro- quinoline	1.0	1-Benzoyl-1,2,3,4-tetrahydro- 8-hydroxyguinoline	180	42				
1	1.0	5 51	(174-175) ª	(16) <i>a</i>				
Aniline	2.6	2-Benzamidophenol	`168—-169 [´]	`2 ´	6566°	7	162°	15
	1.0	-		(0) ^b	(6667)	$(20)^{b}$	(160-161)	(28) ^b
<i>p</i> -Toluidine	3·0 †	6-Benzamido- <i>m</i> -cresol	(168) °	(9) •				
	3.4		172	16	140141	50	156 - 157	17
	1.0		(169) ⁴	(0) ^b	(141—142) ^b	(5) ^b	(157—158) ^b	(4) ^b
	3·0 †		(169) °	(11) °				
<i>m</i> -Toluidine	$3\cdot 4$	2-Benzamido- <i>p</i> -cresol	193	13	53 - 54	46	124 - 125	28
	1.0		(191) *	(<1) %	(53-54) *	(21) *	(125) *	(4) *
o-Toluidine	3.4	2-Benzamido- <i>m</i> -cresol	188-189	27	52	30	145	6
	1.0		(189) *	(2) °	(5153) °	(12) 0	(144145)	
0 4 37 1° 1°	3.0 †		(189) *	(9) °	140 144		140 144	
3,4-Xylidine	3.0	6-Benzamido-3,4-xylenol	156	2	143-144	34	143144	<1
· · · · · · · · · · · · · · · · · · ·	9.0.*		(195196)*	00	$(140-141)^{j}$	0.0	154	10
<i>p</i> -Anisidine	3.0 +	2-Benzamido-b-metnoxy-	108	20		33	154	12
Mathal anthro!!-+	1.0	None	(103164) 9	(0) "	$(101 - 102)^{\circ}$	(10) "	(103—104)	
metnyi anthranilat	e 2·3	none			100-101			
					101) *	3		

M. p.s and yields in parentheses are from the literature and for experiments carried out in the absence of sodium hydroxide: ^a ref. 4; ^b ref. 3; ^c ref. 5; ^d G. P. Gibson, J. Chem. Soc., 1923, 123, 1269; ^e ref. 21; ^f E. Nölting and T. Stricker, Ber., 1888, 21, 3139; ^e L. Horner and H. Steppan, Annalen, 1957, 606, 24; ^b F. Meyer and K. Dahlem, Annalen, 1903, 326, 331.

* Chloroform used instead of benzene. \dagger In chloroform at -10° .

m. p. 204 and 245°, respectively, by oxidation of indole with peracetic acid; and Young and Auld¹³ reported m. p. 244·5-245·5°. Our product had m. p. 225-227°. From the reaction in chloroform a compound, m. p. 160-161°, which may be a benzoyloxyindole, was isolated. In benzene or acetonitrile, an apparently isomeric compound, m. p. 119-120°, was obtained.

Reaction of benzoyl peroxide with 3-methylindole in chloroform, cumene, or acetonitrile afforded a compound, m. p. 207-208°, thought to be 5-benzoyloxy-3-methylindole. The mass spectrum of this compound

12 B. Witkop and J. B. Patrick, J. Amer. Chem. Soc., 1951, 73, 713. ¹³ T. E. Young and D. S. Auld, *J. Org. Chem.*, 1963, 28, 418.

stirring. The resulting crystals were dried over calcium chloride in a vacuum desiccator.

The organic layers from all reactions using benzoyl peroxide were tested as follows for the absence of peroxide before any work-up involving heat. The solution (0.2 ml.)was treated at -5° with 0.1N-methanolic sodium methoxide (5 ml.). After 5 min., ice-cold water (5 ml.) and sulphuric acid (10%; 10 ml.) were added, followed by aqueous potassium iodide (2%; 5 ml.), and freshly prepared starch solution (2 drops), which gave a blue colour if peroxide was present.

Chloroform to be used as reaction solvent was shaken twice with concentrated sulphuric acid, then successively with water, sodium hydrogen carbonate solution, and water. It was then dried overnight $(MgSO_4)$ and distilled.

Light petroleum had b. p. 40-60°.

The i.r. spectra were measured for potassium bromide discs. Mass spectra were obtained with an A.E.I. MS 9 instrument, by the direct insertion technique.

Reactions of Benzoyl Peroxide with Secondary Aromatic Amines in the Absence of Sodium Hydroxide.---(a) N-Methylaniline. A solution of benzoyl peroxide (6.0 g., 1 mol.) in benzene (40 ml.) was added during 1.5 hr. to a stirred solution of N-methylaniline (9.5 g., 3.6 mol.) in benzene (10 ml.) at 40–45°. The mixture was stirred for a further 5 hr. at $40-45^{\circ}$, kept overnight at room temperature, and then stirred with an excess of 30% sodium hydroxide solution. The violet organic layer was separated, washed with water, dried (MgSO₄), and evaporated (finally under reduced pressure from an oil-bath, to remove N-methylaniline) to give a brown residue A (2.6 g.). The aqueous layer was acidified with hydrochloric acid and the precipitate was collected, washed with sodium hydrogen carbonate solution, and dried; it gave 2-(N-methylbenzamido)phenol (1.0 g., 18%), m. p. 158-159° (from aqueous methanol). Hydrolysis of the latter by refluxing with 5N-hydrochloric acid for 2.5 hr. gave 2-methylaminophenol, m. p. 87° (from ethanol) (lit.,¹⁴ 88°).

Residue A was chromatographed on alumina. Elution with light petroleum yielded a yellow oil B (0.8 g.) and elution with benzene-light petroleum (1:4) gave p-benzovloxy-N-methylaniline (15 mg.), m. p. 126° (lit., 15 125-126°) (from benzene-light petroleum) (Found: C, 74.2; H, 5.7; N, 6·3. Calc. for $C_{14}H_{13}NO_2$: C, 74·0; H, 5·7; N, 6·2%). Rechromatography of B four times afforded an oil which gave NN'-dimethylhydrazobenzene (0.3 g.), m. p. 37.5° (from light petroleum) (Found: C, 79.2; H, 7.6; N, 13.2. Calc. for $C_{14}H_{16}N_2;\ C,\,79{\cdot}2;\ H,\,7{\cdot}5;\ N,\,13{\cdot}2\%).$ A sample of the latter prepared by Wittig's method 16 had m. p. 31.5° and showed two spots on thin-layer chromatography, but when purified as above it had m. p. and mixed m. p. 37.5°, and the same u.v. spectrum as our original sample (Wittig gives m. p. $33-33\cdot 5^{\circ}$).

Similar experiments using chloroform and acetonitrile solvents gave 2-(N-methylbenzamido)phenol (0.5 as and 0.3 g.) and NN'-dimethylhydrazobenzene (0.2 and 0.1 g.), respectively.

(b) N-Ethylaniline. A similar experiment using benzoyl peroxide (6.0 g.) and N-ethylaniline (9.0 g.) in benzene afforded 2-(N-ethylbenzamido)phenol (2.0 g., 33%), m. p. 162-163°, and NN'-dimethylhydrazobenzene, m. p. 25.5° (0.5 g.) (Found: C, 79.6; H, 7.9; N, 12.5. Calc. for $C_{16}H_{20}N_2$: C, 80.0; H, 8.3; N, 11.7%), identical with a specimen prepared by Wittig's method and purified by chromatography. This compound has been recorded as an oil 17 and as having m. p. 40-40.5°.18

Use of chloroform or acetonitrile as solvent gave 2-(Nethylbenzamido)phenol (0.6 and 0.4 g.), and NN'-diethylhydrazobenzene (0.4 and 0.1 g.), respectively.

Reactions of Benzoyl Peroxide with Primary and Secondary Aromatic Amines in the Presence of Sodium Hydroxide Solution.-(a) N-Methylaniline. A solution of benzoyl peroxide (6.0 g., 1 mol.) in benzene (45 ml.) was added during 1.5 hr. to a stirred mixture of N-methylaniline (2.6 g., 1 mol.), benzene (20 ml.), and 2N-sodium hydroxide (50 ml.)

17 H. Gilman and R. McCracken, J. Amer. Chem. Soc., 1929, **51**. 821.

at 5°. After a further 11 hr. at 5°, the mixture was worked up as before, to yield 2-(N-methylbenzamido)phenol (3.4 g., 60%).

(b) 1,2,3,4-Tetrahydroquinoline. In a similar experiment with benzoyl peroxide (6.0 g., 1 mol.) and 1,2,3,4-tetrahydroquinoline (3.4 g., 1 mol.), neutralisation of the alkaline layer afforded 1-benzoyl-1,2,3,4-tetrahydro-8-hydroxyquinoline, m. p. 180° (2.6 g., 42%). The residue from the organic layer was chromatographed on alumina. Elution with benzene-light petroleum (1:1) gave 8-benzoyloxy-1,2,3,4-tetrahydroquinoline (85 mg.), m. p. 99° (from benzenelight petroleum) (Found: C, 75.5; H, 5.6; N, 5.7. C₁₈H₁₅NO₂ requires C, 75.8; H 5.9; N, 5.5%). When this was treated with benzoyl chloride in the presence of sodium hydrogen carbonate solution it yielded 1-benzoyl-8-benzoyloxy-1,2,3,4-tetrahydroquinoline, m. p. 148° (from light petroleum) (Found: C, 77.5; H, 5.4; N, 3.8. C23H19NO3 requires C, 77.3; H, 5.3; N, 3.9%). The same compound was obtained by benzoylation of 1,2,3,4-tetrahydro-8hydroxyquinoline¹⁹ in the presence of sodium carbonate solution.

(c) p-Toluidine. The alkaline layer from benzoyl peroxide (6.0 g.) and p-toluidine (9.0 g.) yielded 6-benzamido*m*-cresol (0.9 g.), m. p. 172° (from benzene-light petroleum) (Found: C, 73.8; H 5.6; N, 6.1. Calc. for C14H13NO2: C, 74.0; H, 5.7; N, 6.1%). Chromatography of the residue from the organic layer, with light petroleum as eluent, afforded 4,4'-dimethylazobenzene (1.3 g.), m. p. 140-141°. Elution with benzene-light petroleum (1:1) gave 4'-methylbenzanilide (1.8 g.), m. p. and mixed m. p. 156-157°.

(d) Aniline. The alkaline layer from benzoyl peroxide (6.0 g.) and aniline (6.0 g.) was neutralised and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The residue yielded 2-benzamidophenol (100 mg.), m. p. 168-169° (from benzene-light petroleum). The residue from the organic layer was chromatographed on alumina. Elution with light petroleum afforded azobenzene, m. p. 65-66° (0.15 g.). Elution with benzene-light petroleum (1:4)gave the dianil of 2,5-dianilino-p-benzoquinone, m. p. and mixed m. p.20 246-247°. Elution with benzene-light petroleum (1:1) vielded benzanilide, m. p. 162° (0.7 g.).

(e) p-Anisidine. The alkaline layer from benzoyl peroxide (6.0 g.) and p-anisidine (9.5 g.) in chloroform afforded 2-benzamido-5-methoxyphenol (1.2 g.), m. p. 168° (Found: C, 68.8; H, 5.7; N, 5.8. Calc. for C₁₄H₁₃NO₃: C, 69.1; H, 5.4; N, 5.8%).

(f) 3,4-Xylidine. The alkaline layer from benzoyl peroxide (6.0 g.) and 3,4-xylidine (9.0 g.) in benzene afforded a product (0.1 g.), m. p. 156° (from benzene-light petroleum) (Found: C, 74.6; H, 6.1; N, 5.8. Calc. for C₁₅H₁₅NO₂: C, 74.7; H, 6.2; N, 5.8%). This was assumed to be 6-benzamido-3,4-xylenol, although the m. p. of the latter has been given as 195-196°.21

Reaction of Benzoyl Peroxide with Indole.---(a) In chloroform. A solution of benzoyl peroxide (6.0 g., 1 mol.) in chloroform (40 ml.) was added during 2 hr. to a stirred solution of indole (5.8 g., 2 mol.) in chloroform (20 ml.) at 5°. The mixture was kept at 5° for 6 hr., then overnight at room temperature, and worked up as usual. The brown

M. F. Capelli, A. Garzia, E. Kraushaar-Baldauf, and W. Semeria, Ann. Chim. (Italy), 1957, 47, 1225.
K. Beldall and O. Fischer, Ber., 1881, 14, 1366.

²⁰ P. Ruggli and F. Buchmeier, Helv. Chim. Acta, 1945, 28, 850. ²¹ K. v. Auwers, H. Bundesmann, and F. Wieners, Annalen, 1926, 447, 162.

¹⁴ C. K. Ingold and E. H. Ingold, J. Chem. Soc., 1926, 1310.

¹⁵ B.P. 850,394.

¹⁶ G. Wittig, Angew. Chem., 1940, 53, 241.

residue (5.8 g.) from the organic layer was chromatographed on alumina. Elution with benzene-light petroleum (1:3) gave indole (4.8 g.) and with benzene, crystals (95 mg.), m. p. 160—161°, probably a benzoyloxyindole (Found: C, 75.7; H, 4.9; H, 5.9. Calc. for $C_{15}H_{11}NO_3$: C, 75.9; H, 4.6; N, 5.9%), v_{max} , 3500 and 1740 cm.⁻¹. Elution with chloroform-benzene (1:1) afforded 2,3-dihydro-2,2-diindol-3-yl-3-oxoindole (0.3 g.) as yellow crystals, m. p. 225—227° (decomp.) (Found: C, 78.5; H, 4.7; N, 11.1. Calc. for $C_{24}H_{17}N_3O$: C, 79.3; H, 4.7; N, 11.6%). The u.v. and i.r. spectra of this compound agreed with the published spectra ¹² and the mass spectrum had strong peaks at m/e 363, 347, 334, 319, and 306.

(b) In benzene. From the alkaline layer 2,3-dihydro-2,2-di-indol-3-yl-3-oxoindole (20 mg.) was isolated The residue (5.9 g.) from the organic layer was chromatographed on alumina. Elution with light petroleum gave indole (4.8 g.) and with benzene-light petroleum (1:3) crystals (50 mg.), m. p. 119-120°, probably a benzoyloxyindole (Found: C, 75.9; H, 4.8; N, 6.0%), v_{max} 3495 and 1735 cm.⁻¹. Elution with chloroform-benzene (1:3) afforded isatin (5 mg.), m. p. 199-200°, identical with an authentic sample.

(c) In cumene. The residue (5.0 g.) from the organic layer gave indole (4.0 g.). Elution with benzene afforded indigo (0.25 g.), m. p. $338-339^{\circ}$ (decomp.), identical with an authentic sample.

(d) In acetonitrile. The benzoyloxyindole (5 mg.), m. p. 120° was isolated.

Reaction of Benzoyl Peroxide with 3-Methylindole.— (a) In chloroform. Benzoyl peroxide (1.2 g.) in chloroform (10 ml.) was added during 1 hr. to 3-methylindole (1.3 g.) in chloroform (5 ml.) at 0°. The mixture was worked up after 11 hr. at 0°. The residue (1.3 g.) from the organic layer was chromatographed on alumina. Elution with benzene gave 3-methylindole (0.3 g.), then crystals (0.2 g.), m. p. 207—208°, possibly of 5-benzoyloxy-3-methylindole (Found: C, 76·1; H, 5·4; N, 5·5. Calc. for C₁₆H₁₃NO₂: C, 76·4; H, 5·2; N, 5·6%), ν_{max} . 3495 and 1730 cm.⁻¹. Elution with chloroform-benzene (1:4) gave yellow crystals (15 mg.), m. p. 199—200° (Found: C, 77·3; H, 5·2; N, 7·2. Calc. for C₂₅H₂₄N₂O₂: C, 78·1; H, 6·2; N, 7·3%. Calc. for C₂₅H₂₀N₂O₂: C, 78·9; H, 5·3; N, 7·4%).

(b) In benzene. From the alkaline layer from a similar experiment with benzoyl peroxide (1·1 g.) and 3-methylindole (0·5 g.) in benzene at 5°, crystals (2 mg.), m. p. 224— 226° (decomp.) were isolated. The organic layer yielded (from the chloroform-benzene eluate) crystals (0·3 g.), m. p. 185—187° (decomp.), which gave three spots on t.l.c., one of which corresponded to the compound, m. p. 199— 200° obtained in (a).

(c) In cumene. As in (a), this reaction afforded the benzoyloxy-3-methylindole, m. p. $207-208^{\circ}$ (30 mg.) and the compound, m. p. $199-200^{\circ}$.

(d) In acetonitrile. This reaction afforded the same two compounds as in (c) (60 and 30 mg., respectively).

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