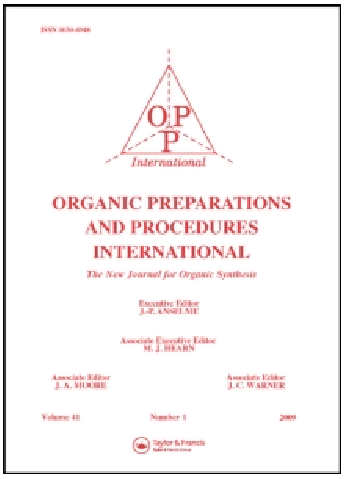

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THE PREPARATION OF DIHYDROXYDIPHENYLMETHANE DERIVATIVES CONTAINING NITRO GROUPS. I. SYMMETRICALLY SUBSTITUTED COMPOUNDS

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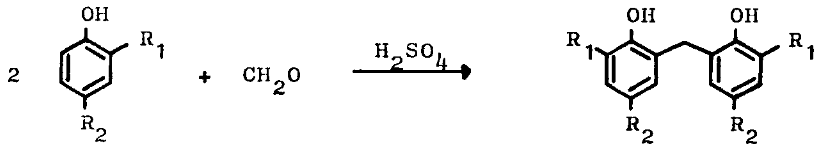
Only a few nitro-substituted dihydroxydiphenylmethane derivatives are known, although many of these compounds with other

Scheme 1

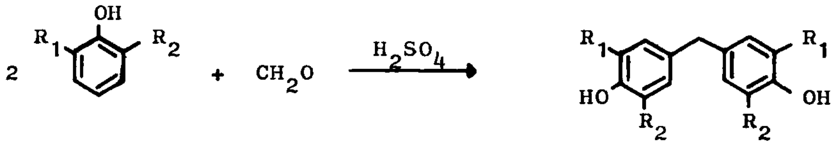


I

II

	a	b	c	d	e	f	g	h	i	j
R_1 =	NO_2	CH_3	NO_2	NO_2	CO_2H	H	H	NO_2	CH_2OH	NO_2
R_2 =	CH_3	NO_2	NO_2	CO_2H	NO_2	CH_3	NO_2	t-Bu	CH_3	H

Scheme 2



III

IV

	a	b	c	d	e
R_1 =	NO_2	NO_2	NO_2	CH_2OH	NO_2
R_2 =	CH_3	NO_2	CO_2H	CH_3	H

substituents such as halogen or alkyl groups have been synthesized. Usually, the nitro compounds are prepared by the introduction of nitro groups into dihydroxydiphenylmethane derivatives. For example, IIa has been prepared by the nitration of IIf[1] and IIc by the nitration of IIg.[2] Sometimes another substituent is displaced by the nitro group. Thus IIc can also be obtained from IIh with fuming HNO_3[3] and IVa is formed by treatment of IVd with $NaNO_2$ in acetic acid.[4] All these preparations suffer from many disadvantages; either the product is not pure or the yield is poor and the syntheses always involve too many steps.

Chattaway and Goepp[2] prepared compound IIg by the direct condensation of *p*-nitrophenol with formaldehyde and sulfuric acid. Following their procedure, we always obtained a mixture of different compounds, from which IIg could be isolated in very small amounts. This is not very surprising since IIg, like *p*-nitrophenol, still contains two reactive *ortho*-positions and therefore can undergo further condensation reactions. We therefore prefer to synthesize IIg by the condensation of chloromethylated *p*-nitrophenol with an excess of *p*-nitrophenol.

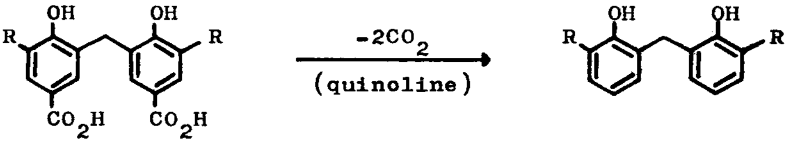
Direct condensation of nitrophenols, however, is an excellent way to prepare dihydroxydiphenylmethanes lacking further reactive *ortho*- or *para*-positions. Thus, the starting nitrophenol should not contain more than one reactive position. We recently reported the synthesis of IIa and IIb in this way[5] and pointed out that this is the best way to prepare IIa compared with the nitration of IIf or the treatment of IIi with $NaNO_2$ in acetic acid. We have now extended this reaction to other nitrophenols, using two general procedures:

a) The condensations of relatively low melting (under 120°) nitrophenols having only one nitro group were conducted in the melt with a two-fold amount of aqueous formaldehyde solution and concentrated sulfuric acid.

b) The condensation of less reactive phenols with two nitro groups or with another deactivating substituent such as carboxyl group in addition to a nitro group, was performed in concentrated sulfuric acid as the solvent and the condensation agent, using a two-fold amount of paraformaldehyde.

The known decarboxylation of substituted diphenylmethanes[6] (Scheme 3) opens a pathway to the synthesis of nitro-substituted diphenylmethanes still having free _ortho_- or _para_-positions, which cannot be obtained by the condensation of chloromethylated nitrophenols with excess nitrophenols (IIj, IVe) and of course also for compound IIg. Satisfactory yields, however, are only obtained with compound IIj.

Scheme 3



EXPERIMENTAL

Melting points were determined with a Mettler FP1. The values reported are the average of three values, differing by not more than ± 0.2°. Uncorrected values were determined by visual observation. All synthesized products are chromatographically (TLC) pure.

Preparation of IIa, IIb and IVa. A freshly prepared hot (90°) mixture of 10 ml. of 30% formalin (0.1 mole) and 10 ml. of conc. H_2SO_4 was added to 0.1 mole of the appropriate molten nitrophenol. The reaction mixture was kept at 120° for 2-3 hr. (For the preparation of IIa and IVa lower reaction temperatures of about 100° can be used). After cooling, the obtained reaction product may be purified by immediate recrystallization, but a preliminary purification by dissoluting the crude material in aqueous NaOH and reprecipitation by dropwise addition of the filtered alkaline solution to dilute (2N), aqueous HCl is preferable.

2,2'-Methylenebis(6-nitro-p-cresol) (IIa) yields 76% of yellow crystals (acetone/ethanol), mp. 183.4°, lit.[5] mp. 184°.

6,6'-Methylenebis(4-nitro-o-cresol) (IIb) yields 63% of straw colored needles (acetone), mp. 270-271° (dec.), lit.[5] mp. 270-271° (dec.).

4,4'-Methylenebis(6-nitro-o-cresol) (IVa) yields 65% of yellow crystals (ethanol), mp. 219.4°, lit.[4] mp. 217°.

Preparation of IIc, IId, IIe, IVb and IVc. A solution of 0.1 mole of the appropriately substituted nitrophenol and

0.1 mole of paraformaldehyde in 80 ml. of conc. H_2SO_4 was heated to 60° for 3 hr. The reaction mixture was kept under nitrogen atmosphere and constantly stirred. After cooling, the mixture was poured into 1 l. of water. The precipitated crude product was filtered by suction, carefully washed with water and recrystallized.

Additional remarks on the preparation of IIc. In contrast to the above mentioned general procedure, the reaction was performed in 100 ml. of conc. H_2SO_4. The reaction temperature was 100-110° and the reaction time was 5 hr. After 1, 2 and 3 hr., an additional 0.1 mole of paraformaldehyde was added.

Additional remarks on the preparation of IVb. In contrast to the general procedure, the reaction was performed in 100 ml. of conc. H_2SO_4, and the reaction temperature was 100°.

2,2'-Methylenebis(4,6-dinitrophenol) (IIc) yields 55% of pale yellow crystals (glacial acetic acid), mp. 259.5°, lit.[2,3] mp. 253°.

3,3'-Methylenebis(4-hydroxy-5-nitro-benzoic acid) (IId) yields 65% of yellow crystals (ethanol/dioxane), no definite mp., decomposition starting above 300°.

Anal. Calcd. for $C_{15}H_{10}N_2O_{10}$ C, 47.63; H, 2.66; N, 7.41;
Found C, 47.48; H, 2.85; N, 7.64;

3,3'-Methylenebis(5-nitro-salicylic acid) (IIe) yields 68% of white crystals (ethanol/dioxane), no definite mp., decomposition slowly starting above 320°.

Anal. Calcd. for $C_{15}H_{10}N_2O_{10}$ C, 47.63; H, 2.66; N, 7.41;
Found C, 47.68; H, 2.63; N, 7.42;

4,4'-Methylenebis(2,6-dinitrophenol) (IVb) yields 75% of yellow needles (glacial acetic acid), mp. 210.7° (dec.).

Anal. Calcd. for $C_{13}H_8N_4O_{10}$ C, 41.06; H, 2.12; N, 14.74;
Found C, 41.29; H, 1.99; N, 14.70;

Diacetate[7] of IVb yields white crystals (acetone/ethanol), mp. 254-256°.

Anal. Calcd. for $C_{17}H_{12}N_4O_{12}$ C, 43.97; H, 2.61; N, 12.07;
Found C, 43.72; H, 2.43; N, 11.93;

5,5'-Methylenebis(3-nitro-salicylic acid) (IVc) yields 72% of yellow crystals (ethanol/dioxane), mp. 283-286° (dec.).

Anal. Calcd. for $C_{15}H_{10}N_2O_{10}$ C, 47.63; H, 2.66; N, 7.41;
Found C, 47.73; H, 2.74; N, 7.33;

Preparation of IIg, IIj and IVe. A solution of 0.01 mole of IId, IIe or IVc in 40 ml. of quinoline was heated to 180-190° under a nitrogen atmosphere for 5 hr. After cooling, the dark solution was poured into 500 ml. of 6N aqueous HCl. The precipitated brownish black product was filtered by suction, carefully washed with water and dried. The dry material was extracted with petroleum ether (IIj) or with benzene (IVe), using a Soxhlet apparatus.

2,2'-Methylenebis(4-nitrophenol) (IIg) was only detected by TLC.

2,2'-Methylenebis(6-nitrophenol) (IIj) yields 45% of yellow needles (petroleum ether), mp. 156.0°.

Anal. Calcd. for $C_{13}H_{10}N_2O_6$ C, 53.80; H, 3.47; N, 9.65;
Found C, 54.08; H, 3.40; N, 9.73;

Diacetate[7] of IIj yields pale yellow needles (ethanol/water), mp. 126.0°.

Anal. Calcd. for	$C_{17}H_{14}N_2O_8$	C, 54.55; H, 3.77; N, 7.48;
	Found	C, 54.68; H, 3.82; N, 7.29;

4,4'-Methylenebis(2-nitrophenol) (IVe) yields 8% of yellow crystals (benzene), mp. 227.8° (dec.).

Anal. Calcd. for	$C_{13}H_{10}N_2O_6$	C, 53.80; H, 3.47; N, 9.65;
	Found	C, 54.05; H, 3.29; N, 9.36;

Diacetate[7] of IVe yields pale yellow crystals (methanol/dioxane), mp. 192.4°.

Anal. Calcd. for	$C_{17}H_{14}N_2O_8$	C, 54.55; H, 3.77; N, 7.48;
	Found	C, 54.34; H, 3.62; N, 7.70;

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