

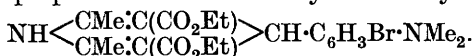
XXV.—*Condensation of 3-Bromo- and 3-Nitro-4-dimethylaminobenzaldehyde with Ethyl Acetoacetate and Ammonia.*

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ORTHO- and para-substituted aromatic dialkylamines do not react normally with nitrous acid (Würster and others, *Ber.*, 1879, **12**, 1796, 1816; Niementowski, *ibid.*, 1887, **20**, 1890; Koch, *ibid.*, p. 2459; Grimaux, *Compt. rend.*, 1891, **112**, 290, 727; Friedländer, *Monatsh.*, 1898, **19**, 627). We have observed that by the action of nitrous acid the aldehydo-group in *p*-dimethylaminobenzaldehyde is replaced by a nitroso-group, and that no action occurs with the corresponding 3-bromo- and 3-nitro-derivatives. It is to be expected, therefore, that the presence of a substituent in the ortho-position with respect to the dimethylamino-group will counteract any influence which this group may have on the reactivity of the aldehydo-group.

The behaviour of 3-bromo- and 3-nitro-4-dimethylaminobenzaldehyde in Hantzsch's pyridine synthesis has therefore been investigated, since it has been shown by one of us (*J.*, 1920, **117**, 137)

that the introduction of a *p*-dimethylamino-group into benzaldehyde exerts a marked influence upon the condensation. In this case, not only is the yield of the dihydropyridine derivative considerably reduced, but the oxidation of the latter with nitrous fumes follows an unusual course, the dimethylaminophenyl group being eliminated as *p*-nitrosodimethylaniline. The dihydropyridine derivative readily yields a methiodide and a stable hydrochloride which is insoluble in water. In the condensation with 3-bromo-4-dimethylaminobenzaldehyde the effect of the introduction of the bromine atom is strikingly shown, not only in the greatly increased yield but also in the properties and the stability of the dihydrolutidine (I),



The oxidation of this compound proceeds quite normally with nitrous fumes. The dimethylamino-group, however, no longer reacts with methyl iodide even when heated under pressure, but the compound forms a hydrochloride which is very soluble in water. In this condensation the combined effects of the bromine and the dimethylamino-group cause the aldehyde to react in a manner closely resembling that of benzaldehyde.

With 3-nitro-4-dimethylaminobenzaldehyde the condensation proceeds normally. The yield of the product is not so great as in the preceding case, nevertheless it is considerably higher than that obtained from *p*-dimethylaminobenzaldehyde (*loc. cit.*), so that the influence of the nitro-group on the dimethylamino-group, although marked, is not so great as that of bromine. The stability of the dihydrolutidine derivative appears to be between those of the compounds derived from *p*-dimethylaminobenzaldehyde and its 3-bromo-derivative, since its oxidation with nitrous fumes must be more carefully regulated in order to prevent the elimination of the nitrodimethylaminophenyl group. As in the previous condensation, the dihydrolutidine derivative does not form a methiodide, but is soluble in dilute mineral acids.

The further study of the effect of substituents in benzaldehyde upon the course of Hantzsch's pyridine synthesis is in progress.

EXPERIMENTAL.

Ethyl 4-(m-Bromo-p-dimethylaminophenyl)-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate (I).—3-Bromo-4-dimethylaminobenzaldehyde (1 mol.) dissolved in ethyl acetoacetate (2 mols.) was mixed with an alcoholic solution of ammonia (1 mol.). After remaining at the ordinary temperature for 1 hour, the mixture was heated for 7 hours in a closed flask. After removal of some of the alcohol the mixture solidified. The crude product crystallised from

alcohol in fine, yellowish-white needles (yield 82%), m. p. 133° (Found: Br, 17.5. $C_{21}H_{27}O_4N_2Br$ requires Br, 17.7%). The ester is very soluble in dilute hydrochloric acid and is not hydrolysed even in the boiling solution.

Ethyl 4-(m-Bromo-p-dimethylaminophenyl)-2:6-dimethylpyridine-3:5-dicarboxylate.—Nitrous fumes were led into a thin paste of the dihydro-ester and alcohol until a clear solution was obtained. The viscous mass obtained after removal of the alcohol slowly solidified. It crystallised from aqueous alcohol in pale yellow crystals, m. p. 91° (Found: Br, 17.7. $C_{21}H_{25}O_4N_2Br$ requires Br, 17.8%).

Hydrolysis. The ester (7 g.) was boiled for several hours with 30% alcoholic potassium hydroxide (50 c.c.). No potassium salt separated (compare J., 1920, 117, 140). The excess of potassium hydroxide was removed as carbonate, and the concentrated filtrate, after the addition of a small quantity of ether, deposited white crystals of the potassium salt.

Ethyl 4-(m-Nitro-p-dimethylaminophenyl)-2:6-dimethyl-1:4-dihydropyridine-3:5-dicarboxylate.—3-Nitro-4-dimethylaminobenzaldehyde (1 mol.), ethyl acetoacetate (2 mols.), and ammonia (1 mol. in alcohol) were heated together under the conditions previously described. After cooling, the solution was filtered from the crystals which had separated, and concentrated, a further crop being thus obtained. The product could be obtained in better yield by replacing ethyl acetoacetate and ammonia by ethyl β -aminocrotonate in alcoholic solution (yield 70%). The crude product crystallised from aqueous alcohol in deep yellow plates, m. p. 127° (Found: N, 10.3. $C_{21}H_{27}O_6N_3$ requires N, 10.1%).

Ethyl 4-(m-Nitro-p-dimethylaminophenyl)-2:6-dimethylpyridine-3:5-dicarboxylate.—The oxidation of the dihydro-ester was carried out as previously described; the nitrous fumes were, however, led in very slowly and rise in temperature prevented by external cooling with water. As soon as the dihydro-ester had dissolved, the passage of nitrous fumes was discontinued; the solution almost immediately deposited crystals, and a further crop was obtained by concentrating the mother-liquor. The base crystallised from alcohol in large, yellow crystals, m. p. 109° (Found: C, 60.6; H, 6.1; N, 10.6. $C_{21}H_{25}O_6N_3$ requires C, 60.7; H, 6.0; N, 10.1%).

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