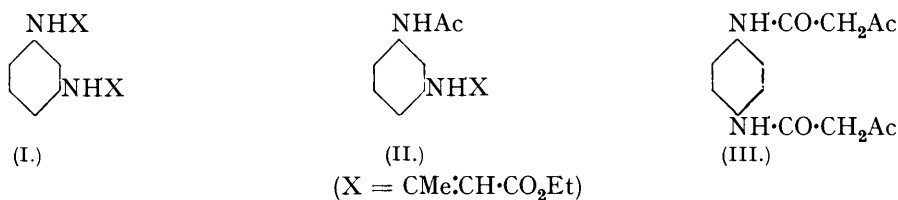


368. The Interaction between Aromatic Diamines and Ethyl Acetoacetate.

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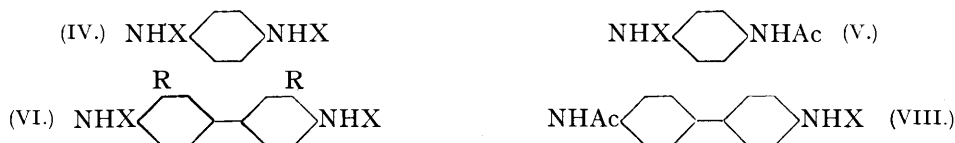
THE interaction between primary aromatic monoamines and ethyl acetoacetate produces either β -phenylaminocrotonic esters (reaction A) (Conrad and Limpach, *Ber.*, 1887, **20**, 944) or acetoacetanilides (reaction B) (Knorr, *Annalen*, 1886, **236**, 75) according to the conditions. The former compounds are converted into 4-hydroxyquinaldines by the action of heat (*loc. cit.*; Limpach, *Ber.*, 1931, **64**, 969), and the latter into 2-hydroxy-lepidines by the action of concentrated sulphuric acid (*loc. cit.*).

The reaction of *o*-phenylenediamine with ethyl acetoacetate investigated by Hinsberg and Koller (*Ber.*, 1896, **29**, 1500) is being further examined. With *m*-phenylenediamine, the product of reaction B was 5- or 7-amino-2-hydroxy-lepidine, as stated by Besthorn and Byvanck (*Ber.*, 1898, **31**, 796), but reaction A produced *ethyl m-phenylenebis- β -aminocrotonate* (I).



m-Aminoacetanilide gave *ethyl β -3-acetamidophenylaminocrotonate* (II) in reaction A, and a tarry substance in reaction B.

Knorr (*Ber.*, 1884, **17**, 545; 1886, **19**, 3303) reported that *p*-phenylenediamine reacted with ethyl acetoacetate (reaction B) to form a product (III), m. p. 176°, which he was unable to convert into a quinoline derivative. In spite of numerous attempts under widely different conditions, it was not found possible to prepare this compound; whenever a crystalline product was isolated, it always had m. p. 135° and proved to be *ethyl p-phenylenebis- β -aminocrotonate* (IV). In both reactions A and B *p*-aminoacetanilide gave *ethyl β -4-acetamidophenylaminocrotonate* (V).



Dianisidine and *o*-tolidine with ethyl acetoacetate in reaction A gave *ethyl 3:3'-dimethoxydiphenylene-4:4'-bis- β -aminocrotonate* (VI, R = OMe) and *ethyl 3:3'-dimethyldiphenylene-4:4'-bis- β -aminocrotonate* (VI, R = Me) respectively. Benzidine gave *ethyl diphenylene-4:4'-bis- β -aminocrotonate* (VI, R = H), but the main product was the substance C₃₀H₃₄O₃N₄, m. p. 128°, described by Heidrich (*Monatsh.*, 1898, **19**, 690), which appears to be a *double compound* of two molecules of ethyl 4-aminodiphenyl-4'- β -aminocrotonate with one of ethyl diphenylene-4:4'-bis- β -aminocrotonate, *i.e.*,

(VII). The presence of an amino-group in this complex was shown by its reacting instantaneously in benzene solution with acetic anhydride, forming *ethyl 4-acetamidodiphenyl-4'- β -aminocrotonate* (VIII), from which monoacetylbenzidine was readily obtained by hydrolysis. Under these conditions the crotonic esters obtained from dianisidine and *o*-tolidine did not react with acetic anhydride.

All the crotonic esters described were very readily hydrolysed to their parent bases by the action of cold dilute mineral acids, but none of them could be converted into a quinoline derivative.

EXPERIMENTAL.

(All the analyses except those marked with an asterisk were made by Pregl's micro-methods.)

Freshly purified amines and ethyl acetoacetate were used.

Reaction A.—In the case of the phenylenediamines, the reactants were heated on a water-bath for 2 hours or left at room temperature for several days; with the diphenyl compounds the reaction was best carried out in methyl- or ethyl-alcoholic solution on a water-bath.

Reaction B.—Numerous modifications of Knorr's original procedure (*loc. cit.*) have been suggested (Ewins and King, *J.*, 1913, 103, 104; Pfeiffer, *J. pr. Chem.*, 1925, 111, 240; 1926, 114, 26; Fierz-David and Ziegler, *Helv. Chim. Acta*, 1928, 11, 779; Limpach, *Ber.*, 1931, 64, 970; Naik and Thosar, *J. Indian Chem. Soc.*, 1932, 9, 127), but they all have the disadvantage that consistent yields are not obtained, and sometimes, for no apparent reason, the yields are very poor. The following modification of Limpach's method gave excellent yields with monoamines, and was used by the author (*J.*, 1933, 1031) but not described. The amine (1 mol.) was heated to about 200° and rapidly added to boiling ethyl acetoacetate (4 mols.); the vigorous reaction was completed by 2—3 minutes' boiling. On cooling, the acetoacetanilide separated (more could be obtained from the mother-liquor by concentration under diminished pressure) and was pure after being washed with ether. The yield decreased if more than 10 g. of amine were used at a time.

Ethyl m-Phenylenebis-β-aminocrotonate (I).—5 G. of *m*-phenylenediamine (1 mol.) and 11.6 c.c. of ethyl acetoacetate (2 mols.) were heated on a water-bath for 2 hours. The viscous product was dissolved in alcohol and precipitated with water three times and then dried over phosphoric oxide (Found: C, 65.2; H, 7.1. $C_{18}H_{24}O_4N_2$ requires C, 65.1; H, 7.2%). The same product was obtained from reaction B after removal of the excess of ethyl acetoacetate, and to obtain the lepidine derivative described by Besthorn and Byvanck (*loc. cit.*) it was necessary to heat the reactants in a sealed tube as described by these authors.

Ethyl β-3-Acetamidophenylaminocrotonate (II).—2 G. of *m*-aminoacetanilide (1 mol.) and 1.7 c.c. of ethyl acetoacetate (1 mol.) were heated on a water-bath for ½ hour and then left for several days over phosphoric oxide. The product (2.1 g.) crystallised from dilute methyl alcohol in small colourless needles, m. p. 92° (Found: C, 63.8; H, 6.6. $C_{14}H_{18}O_3N_2$ requires C, 64.1; H, 6.9%).

Ethyl p-Phenylenebis-β-aminocrotonate (IV).—5 G. of *p*-phenylenediamine (1 mol.) and 12 c.c. of ethyl acetoacetate (2 mols.) were heated on a water-bath for 2 hours. After cooling, the melt solidified completely, the yield being quantitative. The solid crystallised from alcohol in colourless plates, m. p. 135° [Found: C, 65.0; H, 7.2; N, 8.5; *M* (Rast), 320.4. $C_{18}H_{24}O_4N_2$ requires C, 65.1; H, 7.2; N, 8.4%; *M*, 332]. An aqueous suspension of (IV) gave no colour with ferric chloride, but with an alcoholic solution an intense dark-red coloration was produced. The compound was insoluble in caustic soda solution, and in alcoholic solution gave with hydrochloric acid a crystalline precipitate of *p*-phenylenediamine hydrochloride (compare Knorr, *loc. cit.*) (Found: * HCl, 40.1. Calc. for $C_6H_8N_2 \cdot 2HCl$: HCl, 40.3%). Under the conditions described by Knorr (170° for 4 hours), a crystalline material could not be obtained. If, however, the tube was heated at 150° for ½ hour, the product was (IV); this compound, too, was formed in reaction B.

Ethyl β-4-Acetamidophenylaminocrotonate (V).—10 G. of *p*-aminoacetanilide (1 mol.) and 8 c.c. of ethyl acetoacetate (1 mol.) were heated on a water-bath for ½ hour; the homogeneous melt solidified suddenly after 10 minutes. Crystallised from alcohol, the product formed large colourless plates, m. p. 185°. It was very readily hydrolysed by boiling with dilute alcohol (Found: C, 64.4; H, 6.5. $C_{14}H_{18}O_3N_2$ requires C, 64.1; H, 6.9%). Reaction B formed the same product, but heating the reactants in a sealed tube at 140° for 5 hours gave 3 g. of a finely divided, crystalline, colourless residue (after removal of tarry decomposition products by extraction with alcohol), which was insoluble in the ordinary organic solvents and in mineral acids, except concentrated sulphuric acid, charred above 300°, and proved to be *NN'*-diacetyl-*p*-phenylenediamine (Found: C, 62.2; H, 6.0. Calc. for $C_{10}H_{12}O_2N_2$: C, 62.5; H, 6.25%).

Ethyl 3 : 3'-Dimethoxydiphenylene-4 : 4'-bis-β-aminocrotonate (VI, R = OMe).—3.3 G. of dianisidine (1 mol.) and 3.5 c.c. of ethyl acetoacetate (2 mols.) were refluxed in methyl-alcoholic solution for 6 hours. After 12 hours, 4.2 g. of a cream-coloured solid had separated, which crystallised from ethyl alcohol in small plates, m. p. 132—134° (Found: C, 66.7; H, 7.2; N, 6.25. $C_{26}H_{32}O_6N_2$ requires C, 66.7; H, 6.8; N, 6.0%).

Ethyl 3 : 3'-Dimethyldiphenylene-4 : 4'-bis-β-aminocrotonate (VI, R = Me).—7 G. of tolidine (1 mol.) and 8.5 c.c. of ethyl acetoacetate (2 mols.) were refluxed in methyl-alcoholic solution

for 7 hours. After 12 hours, a yellow solid had separated (10 g.); twice recrystallised from ethyl alcohol, in which it was fairly readily soluble, it was obtained as small colourless plates, m. p. 129—130° (Found : C, 71.9; H, 7.7; N, 6.9. $C_{26}H_{32}O_4N_2$ requires C, 71.6; H, 7.3; N, 6.4%).

The Reaction between Benzidine and Ethyl Acetoacetate.—The yellow compound (VII) was best prepared by refluxing benzidine (1 mol.) with the ester (2 mols.) in methyl-alcoholic solution for 2 hours. The product had a constant m. p. 134° after two recrystallisations from methyl alcohol [Found : C, 71.9, 71.95, 72.1; H, 6.7, 6.7, 7.0; N, 8.5, 8.5; *M* (Rast), 324. $C_{60}H_{68}O_8N_6$ requires C, 72.0; H, 6.8; N, 8.4%; *M*, 1000). The molecular weight was further determined by hydrolysing a weighed quantity of (VII) and estimating the benzidine as sulphate (compare van Loon, *Rec. trav. chim.*, 1904, 23, 62); the sulphuric acid content of the sulphate so obtained was also estimated. Under these conditions the double compound (VII) would be expected to yield three molecules of benzidine [Found : * *M*, 330.5, 331; H_2SO_4 , 34.7, 35.1. (VII) requires *M*, 333 if dissociated; $C_{12}H_{12}N_2, H_2SO_4$ requires H_2SO_4 , 34.75%]. Numerous unsuccessful attempts were made to convert (VII) into the bis-crotonic ester (VI, R = H) by prolonging the reaction, raising the temperature, or using excess of ethyl acetoacetate; further, it was not found possible to separate the double compound into its constituents, although its reaction with acetic anhydride (see below), as well as the molecular weight determinations, indicates that it is readily dissociated.

Ethyl Diphenylene-4 : 4'-bis-β-aminocrotonate (VI, R = H).—To isolate this compound from the above reaction, the following modified procedure was adopted : After the separation of (VII) had commenced ($\frac{1}{2}$ hour), methyl alcohol was added in small quantities from time to time to keep the product in solution; refluxing was then continued for an hour. The solution was rapidly cooled with vigorous shaking, (VII) filtered off, and the filtrate kept over-night; colourless needles of (VI, R = H) had then separated, m. p. 99.5—100° after two recrystallisations from methyl alcohol (Found : C, 70.8; H, 6.9; N, 6.9. $C_{24}H_{28}O_4N_2$ requires C, 70.6; H, 6.9; N, 6.9%).

Ethyl 4-Acetamidodiphenyl-4'-β-aminocrotonate (VIII).—5 G. of (VII) were dissolved in benzene, and 3 c.c. of acetic anhydride added to the cold solution. 3.5 G. of a solid separated which, after filtration and washing with ether, had m. p. 201° (Found : C, 70.9; H, 6.7; N, 8.45. $C_{20}H_{22}O_3N_2$ requires C, 71.0; H, 6.5; N, 8.3%). When hydrochloric acid was added to a cold alcoholic solution of (VIII), a white precipitate of acetylbenzidine hydrochloride was formed; this dissolved when made alkaline with ammonia, and on addition of water and stirring, acetylbenzidine, m. p. 202° after crystallisation from dilute alcohol, separated (Found : C, 73.8; H, 6.4; N, 12.4. Calc. for $C_{14}H_{14}ON_2$: C, 74.3; H, 6.2; N, 12.4%).

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