197. *Ethyl Esters of β-Arylaminocrotonic Acids.*

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The following types of compound can be obtained directly from ethyl acetoacetate and a primary arylamine according to the experimental conditions : (1) esters of β-arylaminocrotonic acids, $CMe(NHR){:}CH{\cdot}CO_2Et$, (2) arylamides of acetoacetic acid, $Me{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}NHR$, (3) arylamides of β-arylaminocrotonic acids, $CMe(NHR){:}CH{\cdot}CO{\cdot}NHR$, (4) *s*.-diarylureas, $CO(NHR)_2$, (5) derivatives of 2-hydroxylepidine.

A considerable number of ethyl esters of β-arylaminocrotonic acids have been prepared by various investigators by the reaction $Me{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et + R{\cdot}NH_2 = Me{\cdot}C(NHR){:}CH{\cdot}CO_2Et + H_2O$. Varied conditions are described for the preparation and in many instances different products are obtained on repetition. Knorr (*Ber.*, 1883, **16**, 2593) obtained ethyl β-anilinocrotonate by reaction at the ordinary temperature, Conrad and Limpach (*ibid.*, 1887, **20**, 944; 1888, **21**, 523, 1649; 1891, **24**, 2990) prepared a number of such esters by the same method but preferred to carry out the reaction on the water-bath, as the separation of water is accelerated thereby. Gibson, Harihan, Menon, and Simonsen (J., 1926, 2247), however, on attempting to prepare ethyl β-1-naphthylaminocrotonate by Conrad and Limpach's method obtained instead acetoaceto-1-naphthalide, as would be expected from our results; the reaction went, however, in the desired direction in the cold in the presence of a few drops of diethylamine as catalyst. Nair and Simonsen (*ibid.*, p. 3140) used piperidine as catalyst. In a patented method, Limpach (*Ber.*, 1931, **64**, 969) prepared ethyl β-anilino-, -*p*-phenetidino-, and -1-naphthylaminocrotonates at the ordinary temperature. Many of these esters have not been definitely characterised or analysed. Pellizzari (*Gazzetta*, 1891, **21**, 340), in preparing ethyl β-*m*-carboxyanilinocrotonate, used boiling alcohol as solvent. According to I.G. patents (F.P., 1930, 680, 384, Hung. P., 1930, 101, 504) ethyl β-dehydrothiotoluidinocrotonate is prepared by heating the reactants on the water-bath for 10 hours. Jadhav (*J. Indian Chem. Soc.*, 1930, **7**, 669) prepared ethyl β-*p*-phenetidino-, and -*p*-chloroanilino-crotonates by reaction at the ordinary temperature and claimed to have obtained ethyl β-*p*-nitroanilinocrotonate by refluxing ethyl acetoacetate with *p*-nitroaniline. We could not confirm the latter observation, the only reference in the literature to a β-nitroarylaminocrotonic ester, and we regard his product as acetoaceto-*p*-nitroanilide. Other ethyl β-arylaminocrotonates described in the literature are usually prepared at the ordinary temperature; in many instances it is recorded that warming on the water-bath accelerates the reaction.

It is therefore not obvious what conditions facilitate the reaction. One of us found that, although commercial ethyl acetoacetate reacted with aniline in the cold in the course of a few days as described by Knorr, no reaction occurred for a prolonged period, often 20 days, if carefully purified ester was used. It was discovered that the Knorr reaction could be accelerated by the addition of acid catalysts; thus a mixture of ester and aniline which remained unchanged for nearly a month gave ethyl β-anilinocrotonate in 5 minutes on addition of a small quantity of aniline hydrochloride, heat being evolved; the speed of the reaction was roughly proportional to the strength of the acid. Alkalis (sodium hydroxide, sodium carbonate, ammonia, borax, piperidine) had only a slight catalytic effect; solvents had little if any effect. It appeared that the reaction was very sensitive to acids, but was not inhibited by alkalis.

Further work on the influence of catalysts on the general reaction has confirmed these conclusions. We prepared the following esters by Knorr's method (ordinary temperature, no catalyst), using carefully purified ethyl acetoacetate: ethyl β-anilino-, -*p*-anisidino-, -*p*-phenetidino-, -*m*-4-xylidino-, -p-*xylidino*-, -*p*-chloroanilino-, -p-*phenylaminoanilino*-crotonates; the rate of reaction, as judged by the separation of water, varied from a few hours to many days. These esters, and ethyl β-o-*chloroanilino*- and -m-*chloroanilino-crotonates*, were also prepared under the same conditions as before, but with addition of a very small quantity of the corresponding arylamine hydrochloride or iodine; the reaction was so much accelerated that water commenced to separate in a few minutes. The β-*o*- and -*m*-chloroanilinocrotonic esters have not yet been obtained without the use of a catalyst. In a number of instances traces of alkalis (sodium hydroxide, ammonia, pyridine, diethylamine, etc.) were tried, but in general they did not accelerate or inhibit the reaction. All attempts to prepare ethyl β-arylaminocrotonates from *o*-, *m*-, and *p*-nitroanilines, *m*-nitro-*p*-toluidine, *p*-chloro-*o*-nitroaniline, and 2 : 4-dinitroaniline failed; the addition of ether, alcohol or in some instances excess of ester did not have any effect even on gentle warming and in presence of acid or iodine as catalyst.

It was thought that β-arylaminocrotonoarylamides, for which two of us (Thomson and Wilson, J., **1935**, 111) had already worked out general methods of preparation, might be obtained from ethyl β-arylaminocrotonates by heating with arylamine, $\mathrm{Me{\cdot}C(NHR){:}CH{\cdot}CO_2Et + R{\cdot}NH_2 = Me{\cdot}C(NHR){:}CH{\cdot}CO{\cdot}NHR + EtOH}$. The experiment was carried out by heating equivalent amounts of the reactants for about 5 hours in a solvent of suitable boiling point such as petroleum (b. p. above 120°) or chlorobenzene. In only two instances were small quantities of the desired products, β-*p*-xylidinocrotono-*p*-xylidide and β-*o*-chloroanilinocrotono-*o*-chloroanilide, obtained, the latter compound once only. It is concluded that in the preparation of β-arylaminocrotonoarylamides these esters are not intermediate compounds.

EXPERIMENTAL.

The ethyl acetoacetate was purified by keeping over-night with anhydrous sodium carbonate and after filtration was fractionally distilled at a pressure of not more than 6 mm.; the refractive index always corresponded within the limits of experimental error with the values given by Meyer and Schoeller (*Ber.*, 1920, **53**, 1410).

Ethyl β-anilinocrotonate was prepared by mixing equimolecular quantities of aniline (18·6 g.) and ethyl acetoacetate (26 g.) with addition of approximately 0·05 g. of aniline hydrochloride; in about 6 minutes water began to separate and the temperature rose slightly.

After 12 hours, the water was removed by centrifuging and absorption by filter-paper; the pale greenish-yellow oil, after being dried with sodium sulphate, distilled almost wholly at 135—139°/6—7 mm. except for a little unchanged ester and aniline and a very small residue. On redistillation it had b. p. 137—139°/6 mm. (Décombe, *Ann. Chim.*, 1932, **18**, 118, gives 142—145°/5 mm.) (Found: C, 70·3; H, 7·6; N, 6·8. Calc.: C, 70·2; H, 7·4; N, 6·8%). Iodine as a catalyst is as efficient as aniline hydrochloride, and one drop of hydrochloric acid caused the appearance of water in about 1 minute.

Ethyl β-*p*-anisidinocrotonate (Conrad and Limpach, *Ber.*, 1888, **21**, 1649) was prepared by gently warming a mixture of equimolecular quantities of ethyl acetoacetate (6·5 g.) and *p*-anisidine (6·15 g.) until the latter had dissolved, removing it from the water-bath, adding a trace of catalyst, and then shaking thoroughly. In these experiments the amount of solid catalyst was about 0·01—0·02 g., the amount of liquid catalyst was a small drop from the end of a capillary tube. The times which elapsed before the appearance of water were: (1) with no catalyst, about 1 hour; (2) iodine, about 1½ minutes; (3) hydrochloric acid, ½ minute; (4) pyridine, about 1 hour. The combined products after removal of water in an evacuated desiccator and recrystallisation from *iso*propyl ether gave prisms, m. p. 45—45·5° (Found: N, 6·1. Calc.: N, 6·0%); yield, about 90%.

Ethyl β-*p*-phenetidinocrotonate is first referred to by Riedel (D.R.-P. 76798; Frdl., **4**, 1199), who gave m. p. 52·5—53°. It was prepared but not purified by Limpach (*loc. cit.*) and was later described by Jadhav (*loc. cit.*) as melting at 60—61°. To a mixture of equimolecular quantities of ethyl acetoacetate (6·5 g.) and *p*-phenetidine (6·85 g.), a catalyst was added. The times which elapsed before turbidity appeared were: (1) with no catalyst, over-night; (2) *p*-phenetidine hydrochloride, 14—20 minutes; (3) iodine, 4—12 minutes; (4) diethylamine, no reaction over-night, but on keeping in a vacuum crystals of the substance appeared after several days. The products from (1), (2), and (3) solidified over-night; the crystals after drying on porous tile and recrystallisation from dilute alcohol or *iso*propyl ether melted at 54—54·5°; yield, 85% (Found: C, 67·4; H, 7·5; N, 5·7. Calc.: C, 67·5; H, 7·6; N, 5·6%).

Ethyl β-o-*chloroanilinocrotonate* was prepared from ethyl acetoacetate and *o*-chloroaniline with addition of a trace of *o*-chloroaniline hydrochloride; in about 20 minutes water commenced to separate: without a catalyst, there was no apparent reaction after 1 week. After removal of the water in an evacuated desiccator the product was distilled at 2—3 mm.; about 25% (unaltered reactants) distilled below 80°; the remainder, consisting of the desired substance, passed over at 141—143°/2 mm., leaving a negligible residue (Found: N, 6·0; Cl, 14·8. $C_{12}H_{14}O_2NCl$ requires N, 5·9; Cl, 14·8%).

Ethyl β-m-*chloroanilinocrotonate* was prepared in the same way with a trace of iodine or *m*-chloroaniline hydrochloride as catalyst; water appeared in about 20 minutes: without a catalyst, there was no appearance of reaction in 1 week. The ester, an almost colourless oil, boiled at 145—148°/1—1·5 mm. with only a trace of decomposition (*s*-di-*m*-chlorophenylurea); yield, 83% (Found: N, 5·9; Cl, 14·6. $C_{12}H_{14}O_2NCl$ requires N, 5·9; Cl, 14·8%). Ethyl β-*p*-chloroanilinocrotonate, described by Jadhav (*loc. cit.*), was prepared by dissolving *p*-chloroaniline in ethyl acetoacetate with gentle warming and when cold adding a trace of catalyst. The turbid mixture crystallised in a vacuum over sulphuric acid; the product, dried on porous tile and recrystallised from alcohol, formed needles, m. p. 55° (Found: N, 5·9. Calc.: N, 5·9%). The times which elapsed before turbidity appeared were: (1) with no catalyst, 20 minutes; (2) hydrochloric acid, 1—2 minutes; (3) iodine, 9 minutes; (4) diethylamine, no action over-night but the mixture crystallised after several days in a vacuum over sulphuric acid.

Ethyl β-*m*-4-xylidinocrotonate was described but not purified or analysed by Conrad and Limpach (*Ber.*, 1888, **21**, 523) and by Späth (*Monatsh.*, 1919, **40**, 93). It was prepared from *m*-4-xylidine as a non-crystallisable oil, b. p. 123—124°/2 mm. (Found: N, 6·1. Calc.: N, 6·0%); yield, almost quantitative. The times which elapsed before water appeared in the reaction mixture were: (1) with no catalyst, over-night; (2) iodine, 5—10 minutes; (3) *m*-4-xylidine hydrochloride, 1—2 hours; (4) diethylamine, over-night.

Ethyl β-p-*xylidinocrotonate* was prepared from *p*-xylidine with a catalyst (no catalyst, over-night; iodine, 42 minutes; *p*-xylidine hydrochloride, about 1 hour; diethylamine, over-night). After drying in a vacuum over sulphuric acid, the non-crystallisable oil had b. p. 132—133°/2—3 mm.; yield, 95%. At higher pressures there was considerable formation of the urea (Found: N, 6·1. $C_{14}H_{19}O_2N$ requires N, 6·0%).

Ethyl β-p-*phenylaminoanilinocrotonate*, $CMe(NH\cdot C_6H_4\cdot NHPh){:}CH\cdot CO_2Et$, was prepared by gently warming an equimolecular mixture of ethyl acetoacetate and *p*-aminodiphenylamine till solution took place and then adding a catalyst after removal from the water-bath (no catalyst, over-night; hydrochloric acid, 3 minutes; iodine, 17 minutes; diethylamine, about 2 hours). The mixture solidified in a vacuum over sulphuric acid; the crystalline product had m. p. 77—78° after recrystallisation from petroleum (b. p. 100—120°); yield, nearly quantitative (Found: N, 9·6. $C_{18}H_{20}O_2N_2$ requires N, 9·5%).

β-p-*Xylidinocrotono*-p-*xylidide*.—Ethyl β-*p*-xylidinocrotonate (5·85 g.) and *p*-xylidine (3·05 g.) were refluxed in petroleum (b. p. above 120°) under a fractionating column for 5 hours; a small quantity of alcohol appeared at the top of the column. The cold solution after filtration from a small quantity of the urea was distilled at 2 mm.; solvent and unaltered reactants passed over. The residue was dissolved in a little petroleum (b. p. 100—120°); the solution on nucleation and standing for several days deposited a small clump of crystals, m. p. 107—108°, identical with β-*p*-xylidinocrotono-*p*-xylidide as shown by comparison with an authentic specimen; yield, 17%.

β-*o*-Chloroanilinocrotono-*o*-chloroanilide was obtained by a similar method on one occasion only in a yield of 3%. The other ethyl β-arylaminocrotonates did not give β-arylaminocrotonoarylamides.

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