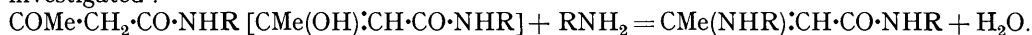


24. Arylamides of β -Arylamino-crotonic Acids. Part II.

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HAVING shown previously (J., 1933, 1262) that most of Jadhav's so-called β -arylamino-crotonoarylamides (*J. Indian Chem. Soc.*, 1930, 7, 669) are the corresponding *s*-diarylureas, we have now prepared the real β -arylamino-crotonoarylamides; we have also found that the appearance and melting point of β -*p*-nitroanilino-crotono-*p*-nitroanilide as described by Jadhav are incorrect.

Arylamides of β -arylamino-crotonic acids should result from one molecule of ethyl acetoacetate and two molecules of arylamine: $\text{CMe(OH):CH}\cdot\text{CO}_2\text{Et} + 2\text{RNH}_2 = \text{CMe(NHR):CH}\cdot\text{CO}\cdot\text{NHR} + \text{H}_2\text{O} + \text{EtOH}$. Control of this reaction was difficult and the yields of β -arylamino-crotonoarylamides (diarylamides) were poor, intermediate and degradation products such as ethyl β -arylamino-crotonates, acetoacetylarylamides, and diarylureas being usually obtained. As the acetoacetyl derivatives of the arylamines examined were easily accessible, the conditions governing the following reaction were investigated:



When the acetoacetylarylamide and the corresponding arylamine were heated in an inert organic solvent under strictly neutral conditions, the reaction as judged by the appearance of water in the condensate proceeded, if at all, very slowly. The addition of a very small quantity of the arylamine hydrochloride, dilute hydrochloric acid, or iodine considerably shortened the time necessary to complete the reaction.

The above method (Method I) gave satisfactory yields in practically every case. In all cases, except with the nitroanilines, a method (Method II), which consisted in heating the β -aminocrotonoarylamide with the corresponding arylamine in an inert organic solvent, gave a slightly enhanced yield of crude product of better quality: $\text{CMe(NH}_2\text{):CH}\cdot\text{CO}\cdot\text{NHR} + \text{RNH}_2 = \text{CMe(NHR):CH}\cdot\text{CO}\cdot\text{NHR} + \text{NH}_3$.

In both methods the solvent should as far as possible fulfil the following conditions: (1) the boiling point should be as low as possible consistent with the rapid production of water or ammonia; if the temperature is too high, decomposition products make their appearance; (2) it should be immiscible with water; (3) at the boiling point a homogeneous mixture of the reactants should result and at the end of the reaction the diarylamide should separate on cooling.

All the β -arylamino-crotonoarylamides were easily hydrolysed by dilute hydrochloric acid in the cold (β -*p*-nitroanilino-crotono-*p*-nitroanilide requires to be heated to 30°) to

the corresponding acetoacetarylamides in yields between 80 and 90% of the theoretical, the loss being due to the slight solubility of the acetoacetarylamides in dilute hydrochloric acid.

EXPERIMENTAL.

The apparatus used for the preparation of β -arylaminoacrotonoarylamides by Method I consisted of a 250 c.c. round-bottomed flask fitted with an inverted V-shaped air-condenser. The limb attached to the flask acted as a reflux condenser, the rate of heating being adjusted so that the condensing vapour just reached the bend in the condenser. The condensate from the free limb was collected in a small measuring cylinder; the water given off during the reaction, together with the water from the added aqueous acid, separated from the immiscible solvent on standing and gave an approximate measure of how far the reaction had proceeded. Heating was stopped when the distillate ceased to be turbid.

The apparatus used in Method II consisted of a 250 c.c. round-bottomed flask fitted with an ordinary air-condenser. Heating was continued till the evolution of ammonia ceased.

The β -aminocrotonoarylamides from *m*- and *p*-nitroaniline, *p*-anisidine, *o*- and *p*-chloroaniline were described by Jadhav (*loc. cit.*). These compounds and also the β -aminocrotonoarylamides from *p*-phenetidine, *p*-xylylidine, *m*-4-xylylidine, and *m*-chloroaniline have been prepared as follows: The acetoacetarylamide (20 g.) was ground to a paste with alcohol (50 c.c.), aqueous ammonia (50 c.c., *d* 0.88) added, and the solution filtered immediately from any impurity and unaltered acetoacetarylamide. On standing over-night (in a freezing mixture in the case of the *m*-chloroaniline derivative, which would otherwise tend to separate as an oil), the crystalline β -aminocrotonoarylamide was deposited; this was collected, thoroughly drained, pressed on porous tile, dried in a vacuum desiccator, and then recrystallised if necessary from warm alcohol to which some aqueous ammonia had been added. The alcoholic ammonia mother-liquors should not be concentrated, as slight decomposition may occur, but should be diluted with water and made just acid with hydrochloric acid with stirring and cooling. The amino-compound is thereby hydrolysed to the acetoacetarylamide, which is precipitated and can be collected and crystallised if necessary. The yield calculated on the acetoacetarylamide consumed in the reaction is almost theoretical. Estimations of the nitrogen in these compounds were carried out by the Dumas method, the carbon dioxide being generated externally and dried by sulphuric acid before entering the combustion tube, as otherwise low results due to hydrolysis of the amino-compound in the early stages of the estimation were obtained.

β -*m*-Nitroanilinocrotono-*m*-nitroanilide, $\text{CMe}(\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2)_2\cdot\text{CH}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$.—Acetoacet-*m*-nitroanilide (11.1 g.), *m*-nitroaniline (6.9 g.), toluene (70 c.c.), and 2*N*-hydrochloric acid (0.1 c.c.), Method I, 50 minutes. At the end of this time 40 c.c. of distillate were collected, from which 0.7 c.c. of water due to the reaction (theory, 0.9 c.c.) separated. The yellow mass deposited on cooling was boiled with 50 c.c. of absolute alcohol; the residue of β -*m*-nitroanilinocrotono-*m*-nitroanilide was washed with absolute alcohol and dried; further quantities were obtained by concentration of the toluene and alcohol mother-liquors. Yield, 79%.

β -Aminocrotono-*m*-nitroanilide (11.05 g.), *m*-nitroaniline (6.9 g.), and toluene (75 c.c.), Method II, 7 hours; the evolution of ammonia was slow. The substance (yield, 39%) crystallised from absolute alcohol in short yellow prisms, *m. p.* 152—153° (Found: C, 56.1; H, 4.2. $\text{C}_{16}\text{H}_{14}\text{O}_5\text{N}_4$ requires C, 56.1; H, 4.1%). Tars resulted when attempts were made to obtain this substance by Jadhav's method.

β -*p*-Nitroanilinocrotono-*p*-nitroanilide.—Acetoacet-*p*-nitroanilide (16.1 g.), *p*-nitroaniline (10 g.), *p*-nitroaniline hydrochloride (0.01 g.), and chlorobenzene (50 c.c.), Method I, 30 minutes. A red solid separated from the boiling mixture, and more on cooling; this was collected and treated with successive small quantities of warm alcohol till free from arylamine and monoarylamide. The mother-liquor on concentration yielded a further small quantity of β -*p*-nitroanilinocrotono-*p*-nitroanilide. The product (yield, 94%), consisting of small, bright red prisms, *m. p.* 220—221°, was free from thermal decomposition products such as *s*-diarylurea. Yield, 94%. On crystallisation from a large quantity of 90% alcohol and drying at 60° a similar red material was obtained, which shrank considerably at about 200° and finally melted sharply at 221—222°; it was a monohydrate of β -*p*-nitroanilinocrotono-*p*-nitroanilide (Found: N, 15.6; loss at 115—120°, 5.3. $\text{C}_{16}\text{H}_{14}\text{O}_5\text{N}_4\cdot\text{H}_2\text{O}$ requires N, 15.6; loss, 5.0%). There was no change in appearance on prolonged heating at 120°, neither was the melting point changed, though the shrinkage at 200° was rather less pronounced; heated at 140—150° in air, the compound decomposed completely (Found for substance dried at 115—120°: C, 55.6, 55.7; H, 4.1, 4.2; N, 16.3, 16.3. $\text{C}_{16}\text{H}_{14}\text{O}_5\text{N}_4$ requires C, 56.1; H, 4.1; N, 16.4%). Method II, β -aminocrotono-

p-nitroanilide (4.8 g.), *p*-nitroaniline (3.0 g.), chlorobenzene (50 c.c.), 10 hours. The evolution of ammonia was very slow and the quality of the product was inferior; yield, 70%. The quality and yield of the substance obtained by Jadhav's method were poor.

β -*p*-Anisidinocrotono-*p*-anisidide.—Method I, acetoacet-*p*-anisidide (10.35 g.), *p*-anisidine (6.15 g.), petroleum (b. p. 100—120°) (50 c.c.), and 2*N*-hydrochloric acid (0.1 c.c.), 1 hour; 0.6 c.c. of water (theory requires 0.9 c.c.) was given off in the reaction. The solvent was evaporated till the temperature of the mixture reached 125°; sufficient benzene was then added to give a homogeneous solution, from which colourless prisms separated on cooling, a further amount being obtained by concentration of the mother-liquors. The substance after recrystallisation from benzene melted at 116—117° (yield, 69%). The same substance was obtained in 83% yield by Method II, β -aminocrotono-*p*-anisidide (10.3 g.), *p*-anisidine (6.15 g.), petroleum (b. p. 100—120°) (50 c.c.), 4 hours, the solution being worked up as before [Found: (micro) C, 69.5; H, 6.5; N (macro), 9.1. $C_{18}H_{20}O_3N_2$ requires C, 69.2; H, 6.5; N, 9.0%].

β -*p*-Aminocrotono-*p*-phenetidide was prepared from acetoacet-*p*-phenetidide [plates, m. p. 104—105°. Found: N, 6.4. $C_{12}H_{15}O_3N$ requires N, 6.3%. Limpach (*Ber.*, 1931, 64, 970) does not give melting point or analysis] with alcohol and ammonia as already described; it formed rectangular plates, m. p. 123—124° (Found: N, 12.8. $C_{12}H_{16}O_2N_2$ requires N, 12.7%).

β -*p*-Phenetidinocrotono-*p*-phenetidide was prepared by Method I from acetoacet-*p*-phenetidide (11.05 g.), *p*-phenetidine (6.9 g.), petroleum (b. p. 100—120°) (50 c.c.), and 2*N*-hydrochloric acid (0.1 c.c.); 45 minutes. 0.8 c.c. (theory, 0.9 c.c.) of water was produced. Benzene was added to the warm reaction mixture; on cooling, colourless prisms, m. p. 105—106° after being washed with petroleum, were deposited (yield, 65%). It was also prepared by Method II, β -aminocrotono-*p*-phenetidide (11.0 g.), *p*-phenetidine (6.9 g.), petroleum (b. p. 100—120°) (50 c.c.), 90 minutes, the reaction mixture being worked up as before (yield, 96%). The m. p. of the crude washed substance was not altered by recrystallisation from absolute alcohol or benzene [Found: (micro) C, 70.3; H, 7.1; N (macro), 8.2. $C_{20}H_{24}O_3N_2$ requires C, 70.5; H, 7.1; N, 8.2%].

β -Aminocrotono-*m*-4-xylidide, prepared in the usual way from the acetoacet-*m*-4-xylidide, formed long colourless prisms, m. p. 124—125° (Found: N, 13.7. $C_{12}H_{16}ON_2$ requires N, 13.7%).

β -*m*-4-Xylidinocrotono-*m*-4-xylidide was prepared by Method I, from the acetoacet-*m*-xylidide (10.25 g.), *m*-xylidine (6.05 g.), petroleum (b. p. 100—120°) (50 c.c.), and 2*N*-hydrochloric acid (0.1 c.c.), 50 minutes; 0.85 c.c. of water (theory, 0.9 c.c.) was formed. On cooling, the substance was deposited as colourless prismatic needles (yield, 92%), m. p. 115—120° after being washed with petroleum and 126—127° after recrystallisation from absolute alcohol or benzene. The same substance was also obtained by Method II, β -aminocrotono-*m*-4-xylidide (10.2 g.), *m*-4-xylidine (6.05 g.), petroleum (b. p. 100—120°) (50 c.c.), 3 hours. A little benzene was added to the warm reaction mixture and the prismatic needles which separated (m. p. 118—120° after washing with petroleum) were purified as before, a further amount being obtained by concentrating the reaction mother-liquors [Found: (micro) C, 77.5; H, 8.0; N (macro), 9.1. $C_{20}H_{24}ON_2$ requires C, 77.8; H, 7.9; N, 9.1%].

β -Aminocrotono-*p*-xylidide was prepared in the usual way from acetoacet-*p*-xylidide [long prisms, m. p. 98—99°. Found: N, 7.0. $C_{12}H_{15}O_2N$ requires N, 6.8%. Limpach (*loc. cit.*) does not give m. p. or analysis]; it formed long prisms, m. p. 136—137° (Found: N, 13.7. $C_{12}H_{16}ON_2$ requires N, 13.7%).

β -*p*-Xylidinocrotono-*p*-xylidide was obtained by Method I, acetoacet-*p*-xylidide (10.25 g.), *p*-xylidine (6.1 g.), petroleum (b. p. 100—120°) (50 c.c.), and 2*N*-hydrochloric acid (0.05 c.c.), 60 minutes; 0.85 c.c. of water (theory, 0.9 c.c.) was formed in the reaction. A further 50 c.c. of petroleum ether were added to the hot reaction mixture, which, on cooling, deposited long prisms; more was obtained on concentration. They melted at 106—108° after being washed with petroleum (yield, 89%) and 107—108° after recrystallisation from absolute alcohol. The same compound was obtained in 91% yield by Method II, β -aminocrotono-*p*-xylidide (10.2 g.), *p*-xylidine (6.1 g.), petroleum (b. p. 100—120°) (50 c.c.), 4 hours, the reaction mixture being worked up as before [Found: (micro) C, 77.8; H, 7.9; N (macro), 9.2. $C_{20}H_{24}ON_2$ requires C, 77.8; H, 7.9; N, 9.1%].

β -*o*-Chloroanilinocrotono-*o*-chloroanilide was prepared by Method I, acetoacet-*o*-chloroanilide (8.3 g.), *o*-chloroaniline (5.0 g.), petroleum (b. p. 100—120°) (50 c.c.), and 2*N*-hydrochloric acid (0.1 c.c.), 1 hour; 0.3 c.c. of water (theory, 0.7 c.c.) was formed. Varying the amount of acid and the time of heating had little effect on the yield of water. After almost complete evaporation of the solution the stiff oily residue was dissolved in dry ether and this solution was slowly

evaporated in a current of dry air. Large needles of the monoarylamide and large dense crystals of the desired substance separated; the latter crystals were picked out and again subjected to the same treatment with ether. The substance formed colourless, almost rectangular prisms with pyramidal ends, m. p. 99—100° (yield, 14%). The same substance was also obtained (yield, about 35%) by Method II, β -aminocrotono-*o*-chloroanilide (8.3 g.), *o*-chloroaniline (5.0 g.), petroleum (b. p. 100—120°) (50 c.c.), 6 hours, the reaction mixture being worked up as before [Found: (micro) C, 59.7; H, 4.6; N, 8.6; Cl, 22.2. $C_{16}H_{14}ON_2Cl_2$ requires C, 59.8; H, 4.4; N, 8.7; Cl, 22.1%]. The yields are poor owing to the laborious and wasteful method of purification. A solvent which will retain the acetoacetylarnide in solution while allowing the β -chloroanilinocrotono-*o*-chloroanilide to crystallise has not yet been found.

β -Aminocrotono-*m*-chloroanilide prepared from acetoacet-*m*-chloroanilide by the usual method, formed long prisms, m. p. 81—82° (Found: N, 13.1. $C_{10}H_{11}ON_2Cl$ requires N, 13.3%).

β -*m*-Chloroanilinocrotono-*m*-chloroanilide cannot be satisfactorily prepared by Method I, oils which are very difficult to solidify and work up being obtained. It was obtained by Method II, β -aminocrotono-*m*-chloroanilide (10.5 g.), *m*-chloroaniline (6.4 g.), petroleum (b. p. 100—120°) (50 c.c.), 90 minutes. On cooling, an oily layer separated; sufficient *isopropyl* ether (about 1 c.c.) to give a homogeneous solution at 25° was added and seed crystals of the substance were introduced. The solution on very slow cooling deposited a mass of small prisms, which was collected, washed with petroleum (b. p. 80—100°), and dried in a vacuum (yield, 51%). The seed crystals were obtained by keeping a solution of the oil in petroleum and ethyl ether at a low temperature for a prolonged time. The substance on recrystallisation first from a small quantity of *isopropyl* ether and then from a large quantity of petroleum (b. p. 80—100°) melted at 86—87° [Found: (micro) C, 60.0; H, 4.6; N (macro), 8.7. $C_{16}H_{14}ON_2Cl_2$ requires C, 59.8; H, 4.4; N, 8.7%].

β -*p*-Chloroanilinocrotono-*p*-chloroanilide was prepared by Method I, acetoacet-*p*-chloroanilide (8.3 g.), *p*-chloroaniline (5.0 g.), chlorobenzene (50 c.c.), and 2*N*-hydrochloric acid (0.15 c.c.), 40 minutes. The solution was then evaporated till the temperature of the residue reached 145°; the oily residue solidified when cooled and scratched. On crystallisation from benzene-petroleum (b. p. 100—120°), colourless prisms, m. p. 123—124°, were obtained (yield, 33%). The same compound was obtained in 43% yield by Method II, β -aminocrotono-*p*-chloroanilide (8.3 g.), *p*-chloroaniline (5.0 g.), petroleum (b. p. 100—120°) (50 c.c.), 5 hours. Benzene was added to the mixture after it had been slightly cooled; prisms of the substance separated on standing, and further amounts were obtained by addition of petroleum to the mixture [Found: (micro) C, 59.8; H, 4.5; N (macro), 8.7. $C_{16}H_{14}ON_2Cl_2$ requires C, 59.8; H, 4.4; N, 8.7%].

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