[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Acetoacetic Ester-Type Cleavage by Aniline[1]

BY ROYSTON M. ROBERTS AND MARVIN B. EDWARDS

The literature contains a number of isolated references to the production of *sym*-diphenylurea[2] in reactions where a β-keto ester or a derivative of such an ester is heated with aniline.[3] Knorr[3e] showed that the initial reaction of aniline with acetoacetic ester may take place in two ways, to produce either the anilide (I) or the anil (II). Recently, Hauser and Reynolds[3h] have demonstrated that both of these reactions are reversible. Hence, one might expect the reaction of acetoacetic ester with aniline at high temperature to take place so as to produce a mixture of products by means of the several routes which are outlined in Fig. 1. Of all the experiments cited in ref. 3, the only ones in which the other product of the reaction producing DPU was isolated were those of Leuthardt and Brunner,[3f] who identified acetone; however, the isolation and analysis followed addition of water to the reaction mixture, which would bring about hydrolysis of any acetone anil (IV) present.

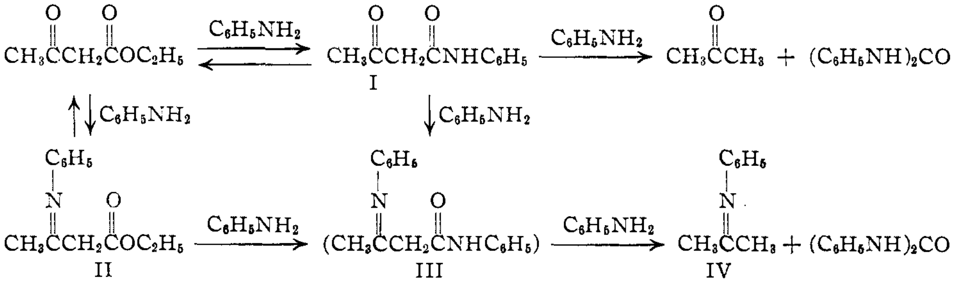

Fig. 1.

We have found that acetoacetic ester, acetoacetanilide and acetoacetic ester anil are cleaved with equal ease by excess aniline at 200° to produce DPU in yields of 83–92%. The other cleavage product from acetoacetic ester anil is acetone anil (IV).[4] It is interesting to note that this is the true anil and not the so-called "acetone anil," 2,2,4-trimethyl-1,2-dihydroquinoline, which has been obtained from acetone and aniline by a number of investigators.[5]

The products from acetoacetic ester and from acetoacetanilide were acetone, acetone anil, and DPU. The proportions of acetone and acetone anil varied widely (21–63%) in different experiments in which the yield of DPU was always about 85%. This variation in the yield of the two cleavage products depends on the comparative rates of the competing reactions outlined in Fig. 1. Apparently, at least two factors are of importance in determining the ratio of cleavage products: (1) the presence of acid in the reaction mixture and (2) the rate of removal of volatile products during the course of the reaction. Coffey, Thomson and Wilson[6] demonstrated the marked catalytic effect of small amounts of acid on the formation of anils of acetoacetic ester. We found that the amount of acid present in the reaction mixture did have a pronounced effect on the ratio of cleavage products. Since the conversion of acetoacetic ester to its anil is a reversible reaction, slower removal of water would be expected to favor acetone over acetone anil formation; this was verified.

Thus, cleavage of acetoacetic ester by aniline may be seen to be formally analogous to cleavage by dilute aqueous alkali; the products are acetone (and acetone anil) and DPU instead of acetone and carbon dioxide.

In 1909, Kötz and Merkel[7] claimed a compound with a β-lactam ring was produced by heating the β-imino compound V in aniline at 200°. Our attempt to repeat their work resulted in no product with the properties they described, but in the formation of DPU and 3-methylcyclohexanone anil (VII), *via* the anilino ester (VI). These results were corroborated by the behavior of β-aminocrotonanilide, which reacted with aniline to produce ammonia, acetone anil and DPU. The β-keto ester corresponding to V was also prepared and shown to react with aniline to produce 3-methylcyclohexanone and DPU.

The reaction of cyanoacetanilide with aniline was also investigated. DPU is produced, but the cleavage is much slower than that of acetoacet-

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(1) Presented before the Division of Organic Chemistry at The American Chemical Society Meeting in Philadelphia, April, 1950. Taken partly from the M.A. thesis of Marvin B. Edwards.

(2) This compound will hereafter be referred to as DPU.

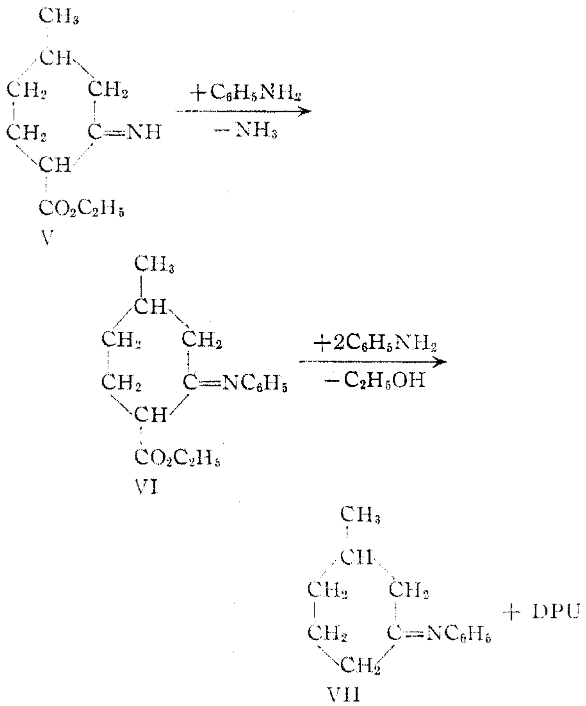
(3) (a) Oppenheim and Precht, *Ber.*, **9**, 1098 (1876); (b) Searles, THIS JOURNAL, **68**, 988 (1946); (c) Sen and Basu, *J. Ind. Chem. Soc.*, **6**, 309 (1929); (d) Thomson and Wilson, *J. Chem. Soc.*, 1262 (1933); (e) Knorr, *Ann.*, **236**, 76 (1886); (f) Leuthardt and Brunner, *Helv. Chim. Acta*, **30**, 958 (1947); (g) Conrad and Limpach, *Ber.*, **20**, 944 (1887); (h) Hauser and Reynolds, THIS JOURNAL, **70**, 2402 (1948).

(4) (a) Claisen, *Ber.*, **29**, 2932 (1896); (b) Rosser and Ritter, THIS JOURNAL, **59**, 2179 (1937); (c) I. G. Farbenind A. G., French Patent 838,434 (*C. A.*, **33**, 7817 (1939)).

(5) For evidence of the identity of this much disputed product and previous references see Reddelien and Thurm, *Ber.*, **65**, 1511 (1932).

(6) Coffey, Thomson and Wilson, *J. Chem. Soc.*, 856 (1936).

(7) Kötz and Merkel, *J. prakt. Chem.*, [2] **79**, 112 (1909).



anilide and is apparently complicated by competing reactions such as addition of aniline to the nitrile group[8] and subsequent elimination of ammonia.

Experimental[9]

Acetoacetic Ester and Aniline.—The ester (0.077 mole) and aniline (0.385 mole) were heated in a flask fitted with a thermometer having its bulb in the liquid and with a short Vigreux column; a tube from the top of the column led to a Dry Ice–ethanol condensing trap. This type of apparatus was used in the other experiments except where noted. The reaction mixture was heated by an electric mantle so that the aniline vapor condensed about half-way up the column. The temperature of the liquid was *ca.* 155° when reflux began and rose to 190° during two hours; heating was continued an additional four hours. The distillate collected was diluted with 50% ethanol and aliquots were taken for determination of the acetone by precipitation of (a), the 2,4-dinitrophenylhydrazone: 1.31 g. was obtained, m. p., 124.5–125.5°, corresponding to a 59.8% yield of acetone and (b), the acetone–mercuric oxide–mercuric sulfate complex[10]: 2.08 g. was obtained, corresponding to a 58.3% yield of acetone.

To the partly-crystalline reaction mixture was added 300 ml. of water and the mixture was distilled, using a 25-cm. Vigreux column, to hydrolyze acetone anil and remove the acetone produced. The mixture in the boiling flask was cooled and the DPU[2] was collected, washed with dilute hydrochloric acid and water; it weighed 14.17 g., or 86.8% of the theoretical amount, m. p. 241.0–242.5°. The distillate (130 ml.) was treated with concentrated hydrochloric acid and redistilled. The acetone in the second distillate was determined by the two methods used above, giving values of 23.7 and 22.4%. A blank test indicated that the maximum amount of acetone which might have come from distillation and acid hydrolysis of unchanged acetoacetic ester was 10%.

A second experiment was run in the same way but with ten times the amounts of ester and aniline, and the volatile products were removed more quickly. The acetone in the distillate amounted to 20.9% (2,4-dinitrophenylhydrazone method). The excess aniline was removed from the DPU by filtration and washing with ether; the yield was 85.3%, the melting point 242–243°. The filtrate and ether washings were combined, dried, and distilled through a small 10-plate column. Clean separation of the acetone anil from aniline was impossible with the equipment available, but a product which boiled at 80–82° (13 mm.), $n^{30}D$ 1.5424, was obtained.

Several experiments were made for the purpose of determining the effect of small amounts of acid and of rate of removal of volatile products on the ratio of acetone/acetone anil. Acetoacetic ester was kept over potassium carbonate overnight and then distilled. Aniline was distilled from a small amount of sodium *t*-butoxide. These purified reactants were allowed to react as before: the yield of acetone was 57%; DPU, 88%. In a second experiment, 2×10^{-3} mole aniline hydrochloride per mole of acetoacetic ester was added: the yield of acetone was 26%; DPU, 83%.

Experiments in which the rate of distillation of volatile products was varied showed that more rapid distillation decreased the acetone/acetone anil ratio, as expected, but this factor did not appear to be as important as the acid effect.

Acetoacetanilide and Aniline.—The molar ratio of anilide to aniline was 1:4. Apparatus and conditions were as described above. Acetone in the distillate amounted to 69.8% (2,4-dinitrophenylhydrazone), 69.7% (mercury salt complex). Acetone from hydrolysis of the reaction mixture amounted to 14.1% (2,4-dinitrophenylhydrazone), 14.5% (mercury salt complex). The maximum amount of acetone from acid hydrolysis of starting material was 3% as determined by a blank test. The yield of DPU was 87.0%.

Another experiment carried out before the effect of acid was realized gave a yield of 87% DPU, 30% acetone.

Acetoacetic Ester Anil.—The molar ratio of anil to aniline was 1:5. The distillate gave a negative test for acetone. The DPU was filtered from the cooled reaction mixture and washed with ether; yield 66.3%. The filtrate and washings were distilled; a yield of acetone anil estimated at *ca.* 28% on the basis of boiling point, refractive index and hydrolysis products was obtained. The purest fraction obtained had b. p. 80–82.5° (13 mm.), $n^{30}D$ 1.5411.

The yield of DPU in the preceding experiment was much lower than those obtained from acetoacetic ester and from acetoacetanilide. This probably was due to incomplete crystallization of the product from the excess aniline, because a second experiment which was worked up by the addition of dilute hydrochloric acid to the reaction mixture gave a yield of 90.4% of the calculated amount of DPU.

2-Carbethoxy-5-methylcyclohexanimine (V) and Aniline.—When this compound was heated with aniline at 200° as described by Kotz and Merkel,[7] the only solid product which was isolated was DPU. The odor of ammonia was noticeable almost as soon as the heating began; 2-carbethoxy-5-methylcyclohexanone anil was isolated from a mixture heated at 135° for five hours; m. p. 53–54°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.21; H, 8.30; N, 5.59.

2-Carbethoxy-5-methylcyclohexanone Anil (VI) and Aniline.—The anil (0.07 mole) was heated for six hours with aniline (0.35 mole) in the same manner as the acetoacetic acid derivatives described above. The crystals of DPU were filtered from the reaction mixture and washed with ether; they weighed 13.1 g. (88.5% of the theoretical amount). The filtrate and washings were dried and distilled through a 12-cm. Vigreux column; 6.75 g. of 3-methylcyclohexanone anil, b. p. 151–152° (18 mm.) was obtained. The anil was hydrolyzed with 10% hydrochloric acid; the 3-methylcyclohexanone was identified by means of its 2,4-dinitrophenylhydrazone and the aniline was converted to benzenesulfonanilide.

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[8] Bernthsen, *Ann.*, **184**, 329 (1877); Quenda, *Atti. d. R. Acc. d. Scienze di Torino*, XXVII [*Ber.*, **26**, ref. 326 (1892)].

[9] Melting points are corrected, boiling points are not.

[10] Van Slyke, *J. Biol. Chem.*, **32**, 480 (1917).

2-Carbethoxy-5-methylcyclohexanone and Aniline.—the keto ester (0.05 mole) and aniline (0.125 mole) were heated together in a flask equipped with an air-cooled condenser in an oil-bath at 190° for five hours. The DPU crystallized as the reaction mixture cooled; after washing with ether, it weighed 5.60 g. (52.8%). The filtrate and washings were extracted with 5% hydrochloric acid and the ether solution was dried and distilled. The residue was distilled at 90 mm. pressure, but only a small amount of material distilled so that no accurate boiling temperature could be observed. A sample of the distillate was treated with 2,4-dinitrophenylhydrazine and gave the 3-methylcyclohexanone derivative, m. p. 158–160°, after repeated recrystallization.

β-Aminocrotonanilide and Aniline.—It was found that a vigorous evolution of ammonia ensued when these reagents were heated, so the apparatus was modified so that a delivery tube led from the top of the distilling column to beneath the surface of cold standard (1.783 *N*) sulfuric acid solution. Titration of the acid solution with sodium hydroxide indicated the absorption of 92.6% of the possible amount of ammonia after the reaction mixture had been heated six hours. The yield of DPU was 91.8%.

Cyanoacetanilide and Aniline.—When cyanoacetanilide was heated with aniline in the usual way for six hours, very low yields (6–7%) of DPU were obtained along with much lower-melting material which was hydrolyzed by dilute hydrochloric acid. The small amount of distillate collected in the Dry Ice-trap was apparently ammonia.

Two 24-hour-heated runs were then made. In the first, the distillate was mixed with 30% sulfuric acid and the mixture was heated and then distilled. From the distillate, a very small amount of the *p*-nitrobenzyl ester of acetic acid was obtained in the usual way. This may have come from the hydrolysis of acetonitrile, the expected cleavage product. The yield of pure DPU obtained in this experiment was *ca.* 40%. In the second 24-hour experiment, the ammonia evolved was absorbed in standard acid solution and determined by back titration; it amounted to 36.3%: The yield of DPU was 55.5%. Some high-melting (> 310°) material was also isolated but was not identified.

Summary

It has been shown that acetoacetic ester reacts with aniline in a manner analogous to the "ketone cleavage" of this ester by dilute aqueous alkali, producing *sym*-diphenylurea and acetone. In addition, acetone anil is produced, indicating that some reaction of the keto group with aniline precedes cleavage. Acetoacetanilide and acetoacetic ester anil react with aniline under the same conditions to give *sym*-diphenylurea in comparable yields. Some other structurally related esters and anilides have been shown to undergo cleavage by aniline in similar fashion. Factors which influence the ratio of acetone/acetone anil produced are discussed.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

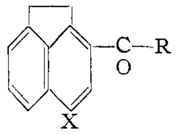
The Acylation of 5-Bromo- and 5-Chloroacenaphthene by the Friedel–Crafts Procedure[1,2]

BY DOROTHY V. NIGHTINGALE AND ROBERT M. BROOKER

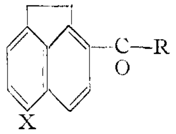
In a previous publication[3] it was stated that the reaction of 5-chloroacenaphthene with acetyl chloride in the presence of aluminum chloride as the catalyst yielded two isomeric acetylchloroacenaphthenes, but their orientation was not determined.

It has now been established that the two ketones are 3-acetyl-5-chloroacenaphthene, I-A and 3-acetyl-6-chloroacenaphthene, I-B. Acetylation of 5-bromoacenaphthene and benzoylation of both 5-chloro- and 5-bromoacenaphthene likewise yielded analogous pairs of ketones with the acyl group in the 3-position.[4]

The two acetylchloroacenaphthenes were first separated from the reaction product by fractional crystallization from ether and chloroform with high losses. In the present research it was found that oximation of the crude methyl ketones, fractional crystallization of the oximes and hydrolysis of the pure oximes to the ketones was more rapid and gave better yields.



A



B

I-A, R = CH_3, X = Cl   IB, R = CH_3, X = Cl
II-A, R = CH_3, X = Br   II-B, R = CH_3, X = Br
III-A, R = C_6H_5, X = Cl   III-B, R = C_6H_5, X = Cl
IV-A, R = C_6H_5, X = Br   IV-B, R = C_6H_5, X = Br

A comparison of the ultraviolet absorption spectra of the methyl ketones with the published spectra[5] of 3-acetylacenaphthene and 5-acetylacenaphthene indicate that the acetyl groups are in the 3-position. The spectra of the acetylhaloacenaphthenes closely resemble the spectrum of 3-acetylacenaphthene and are notably different from the spectrum of 5-acetylacenaphthene (Figs. 1, 2, 3 and 4).

The methyl ketones were oxidized to the corresponding 5-halo- and 6-halo-3-acenaphthoic acids and their ultraviolet absorption spectra closely resemble the published spectrum of 3-acenaph-

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(1) From the Ph.D. thesis of Robert M. Brooker, June, 1950.

(2) Presented in part at the St. Louis Meeting of the American Chemical Society, September, 1948.

(3) Nightingale, Ungnade and French, THIS JOURNAL, **67**, 1262 (1945).

(4) C. F. Roney (Masters Dissertation, University of Missouri, 1948) first separated 3-acetyl-5-bromo- and 3-acetyl-6-bromoacenaphthene by fractional crystallization of the crude ketones from a mixture of chloroform and ether. He converted the pure ketones to their oximes, but did not isolate pure acetylated amines from the product of the Beckmann rearrangement of the oximes.

(5) Jones, THIS JOURNAL, **67**, 2127 (1945).