from the mother liquor to give an oil. This was dissolved in 4 ml. of concentrated sulfuric acid and heated on the steam-bath for 5 minutes. It was poured on ice and extracted 5 times with ether. The ethereal solution was washed with saturated sodium chloride and dried. The solvent was distilled. The residue was dissolved in 10 ml. of 10% sodium hydroxide and methylated in the usual way with methyl *p*-toluenesulfonate.[13] The product was crystallized from methanol to give 0.25 g. of yellow crystals, m.p. 84–86°, alone or when mixed with an authentic sample of 1-keto-2-methyl-9-methoxy-1,2,3,4-tetrahydrophenanthrene.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H. 6.71. Found: C, 79.96, 80.07; H, 6.64, 6.70.

Pure samples of the crystalline cyclic keto-ester hydrolyzed with alcoholic potash and then treated with sulfuric acid or treated with sulfuric acid directly did not cyclize to the tetrahydrophenanthrene.

3-Carboxy-2-hydroxy-3-methyl-6-phenylcyclohexan-1-acetic Acid.—The cyclic keto-ester (III, 1.0 g.) was hydrogenated in 100 ml. of ether with 1.0 g. of Adams platinum oxide catalyst at 3 atm. The product was hydrolyzed in 30 ml. of methanol and 2.5 ml. of 45% potassium hydroxide by refluxing for 30 minutes. The solution was filtered, diluted with water, acidified and extracted with ether. After the usual treatment, the product was crystallized from ethyl acetate, m.p. 163–165° (dec.).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.90; H, 6.88.

PHILADELPHIA, PENNA. RECEIVED[22] FEBRUARY 7, 1951

(22) Original manuscript received April 14, 1950.

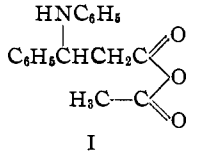
[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Action of Acetic Anhydride on Benzalaniline. A Reinvestigation

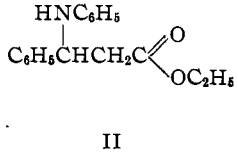
BY ALBERT W. BURGSTAHLER[1]

It is verified that the reaction of acetic anhydride with benzalaniline leads to the formation of N-(α-acetoxybenzyl)-acetanilide (III), which ethanol converts to N-(α-ethoxybenzyl)-acetanilide (IV). Both of these products yield N-ethyl-N-phenylbenzylamine when reduced with lithium aluminum hydride.

Recently it has been proposed[2] that the previously observed[3] product formed by the action of acetic anhydride on benzalaniline under mildly acidic conditions is acetic β-anilinohydrocinnamic anhydride (I), postulated to arise as the first-stage of a Perkin type addition of acetic anhydride to the >C=N— system in benzalaniline. Among the considerations adduced in support of this view were: (i) the nearly quantitative reversion of the product to benzalaniline and acetic anhydride on heating, or to benzaldehyde and acetanilide (or aniline) under acidic hydrolytic conditions; (ii) the ready reaction of the adduct with ethanol to form an ethoxy derivative, considered to be ethyl β-anilinohydrocinnamate (II); and (iii) the conversion of the adduct to ethyl cinnamate (or cinnamic acid) on treating with sodium ethoxide.

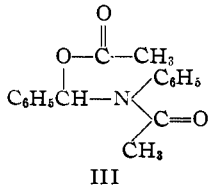


I

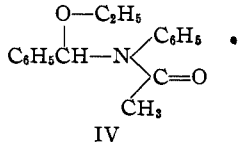


II

All of these transformations, however, are in accord with those which might be anticipated from the isomeric formulation III, proposed earlier by Ekeley, *et al.*[3b] Thus, N-(α-acetoxybenzyl)-acetanilide (III), is a structure closely related to an acetal and should therefore be easily convertible with aqueous acid to the parent aldehyde (benzaldehyde), acetic acid and acetanilide, as observed.[2] The reformation of benzalaniline and acetic anhydride on heating is also readily explicable in terms of formula III. Moreover, the formation of an ethoxy derivative by reaction with ethanol, rather than necessarily indicating the presence of an anhydride system in the adduct, is interpretable on the basis of III as a solvolytic cleavage by the alcohol present in excess, leading to N-(α-ethoxybenzyl)-acetanilide (IV) and acetic acid.[4] This product (IV), like III, would be expected to undergo the observed[2] facile reversion to benzaldehyde and acetanilide when treated with acid. Lastly, the reaction of the addition product with excess sodium ethoxide to form ethyl cinnamate (or cinnamic acid) along with acetanilide and a small amount of benzaldehyde and aniline, is a foreseeable result on the basis of formula III through the intermediate generation of benzaldehyde and ethyl acetate, which then react by a normal Claisen condensation in the presence of the strong base to yield ethyl cinnamate and thence cinnamic acid by partial hydrolysis from the water formed in this latter reaction. Partial hydrolysis of the acetanilide produced accounts for the aniline observed.[2] The fact that benzaldehyde is also isolated[2] is further evidence in support of this interpretation.



III



IV

In confirmation of these deductions, conclusive verification of structures III and IV for the respective products can now be reported. The infrared spectra of these compounds have been determined, and the following relevant features may be considered. The absence of any definite absorption in the >N–H (or –O–H) region (2.9–3.0μ) places the formulations I and II in immediate

(1) National Institute of Health Predoctoral Fellow, Harvard University, 1950–1951.

(2) H. S. Angel and A. R. Day, THIS JOURNAL, **72**, 3874 (1950).

(3) (a) M. Passerini and M. P. Macentelli, *Gass. chim. ital.*, **58**, 641 (1928); (b) J. B. Ekeley, M. C. Swisher and C. C. Johnson, *ibid.*, **62**, 81 (1932); (c) H. R. Snyder, R. H. Levin and P. F. Wiley, THIS JOURNAL, **60**, 2025 (1938).

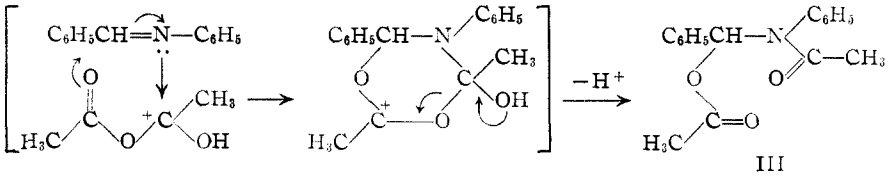
(4) The almost quantitative formation of acetic acid and not ethyl acetate in this reaction (*cf.* Experimental) is in agreement with this proposed mechanism and clearly indicates that the process is actually a solvolysis and not a simple ester exchange.

question, since both contain such a grouping. Formulas III and IV, on the other hand, lack either of such functions and therefore would not be anticipated to absorb in this region. Equally serious is the absence of the typical anhydride double absorption bands around 5.4 and 5.6μ in the spectrum of the addition product, expected to appear if formula I were correct. There is present, however, strong absorption in the ester and amide carbonyl region (5.8 and 6.0μ) of the spectrum of this material, as would be expected from III. Finally, the absence of any ester carbonyl absorption (expected at about 5.8μ) in the spectrum of the ethoxy derivative of the addition product definitely excludes structure II for this substance.[5,6]

Chemical evidence corroborating these considerations was afforded by the reduction of the addition product and its ethoxy derivative with lithium aluminum hydride. From the reduction of the former, N-ethyl - N - phenylbenzylamine (ethylbenzylaniline) was recovered in low yield (8%), along with a considerable quantity of N-ethylaniline (79%) and benzyl alcohol. The ethoxy derivative, on the other hand, was reduced in high yield (88%) to N-ethyl-N-phenylbenzylamine by lithium aluminum hydride, without the attendant formation of N-ethylaniline. The isolation of N-ethyl-N-phenylbenzylamine, along with N-ethylaniline in the first case, is readily explicable on the basis of formulas III and IV for the adduct and ethoxy derivative, respectively, but is in no way derivable from the formulations I and II. As a supplementary experiment, N-ethylbenzanilide was reduced by lithium aluminum hydride to the same two amines in about equal yields (40–45%),[7] a finding which lends further support to the conclusion just drawn.

Final proof that the ethoxy derivative of the benzalaniline addition product does not have the structure of ethyl β-anilinohydrocinnamate (II) has now also been established by direct comparison of the ethoxy derivative with this ester, prepared by the esterification of the known[8] β-anilinohydrocinnamic acid: on admixture the two substances gave depressed melting points. And, contrary to the suggestion of Angel and Day[2] that a primary ester of this structure (II) should be resistant to the action of aqueous alkali, the basic hydrolysis of ethyl β-anilinohydrocinnamate was found to take place quite smoothly. The resistance of an N-substituted acetanilide to alkaline hydrolysis is undoubtedly enhanced by steric hindrance in the case of IV which therefore accounts for the relative stability of this latter material to base.

With respect to the manner of the formation of the adduct, mild acid catalysis appears to be involved.[2,3c] One mechanism for the formation of the adduct (as III), proposed by Snyder and co-workers,[3c] postulates initial C-acetoxylation, followed by N-acylation. While this suggestion accommodates the known features of the reaction, there is an alternative possibility involving initial N-acylation, followed successively or accompanied simultaneously by an internal C-acetoxylation



III

Experimental[9]

Acetic Anhydride Addition Product of Benzalaniline.—The procedure of Angel and Day[2] for the preparation of this adduct was modified by gently refluxing for one hour the equimolar mixture of benzalaniline, m.p. 52°,[10] and acetic anhydride, together with the specified one-third molar equivalent of glacial acetic acid. In this manner reproducible yields of colorless addition product, m.p. 130–131° as reported,[2,3] corresponding to 80% conversion, were obtained on cooling the reaction mixture and recrystallizing the filtered product from a 3:1 benzene–petroleum ether (30–60°) mixture. Without the addition of acetic acid the yield of product by this procedure decreased to 30–40%, as found by earlier workers.[3a] In the cold the compound is readily soluble in chloroform, slightly soluble in benzene, and sparingly soluble in ether and water. After standing in air at room temperature for several hours the odors of acetic acid and benzalaniline (or benzaldehyde?) become readily detectable, and the melting point likewise is somewhat depressed. The infrared spectrum of material that has stood for a day at room temperature possesses rather pronounced absorption at 2.9 and 5.9 μ, wholly absent in fresh samples and indicating the presence of considerable quantities of free acetic acid in such partially decomposed material.

The Action of Alcohol on the Addition Product of Benzalaniline and Acetic Anhydride.—Treatment of the above adduct with absolute ethanol according to the description of Angel and Day[2] yielded the reported product as large, colorless, beautifully-formed prism clusters, m.p. 80–81°, crystallizing readily from petroleum ether (30–60°) containing a small quantity of benzene.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.93, 75.65; H, 7.02, 7.01; N, 5.08.[11]

Two determinations of the molecular weight of this substance by the Rast method gave values of 262, 270; $C_{17}H_{19}NO_2$ totals 269.33. In another experiment, 2.833 g. (0.010 mole) of freshly prepared and recrystallized addition product was refluxed for 45 minutes with 2.5 ml. of absolute ethanol and the filtrate from the benzene–petroleum ether-washed product titrated at 0° with 0.2085 *N* sodium hydroxide to the phenolphthalein end-point, 44.90 ml. of the

(5) Likewise, the ionic formulation, $\left[C_6H_5CH{=}N\begin{matrix}C_6H_5\\COCH_3\end{matrix}\right]^+ CH_3COO^\ominus$, proposed by Passerini and Macentelli (ref. 3a) for the adduct itself, would not be expected to possess its acetoxyl function absorption at the observed low wave length (5.78μ) but as a broader band at 6.3μ, the region of carboxylate anion absorption in the infrared.

(6) After this paper was submitted it was learned that Dr. H. R. Snyder, D. B. Bright and J. C. Lorenz of the University of Illinois had arrived at these same conclusions from an examination of the infrared spectra of these compounds and also further chemical evideuce; *cf.* their paper, THIS JOURNAL, **73**, 1836 (1951).

(7) R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948), record the reduction of N,N-diethylbenzamide by this reagent as leading exclusively to diethylamine and benzyl alcohol. The failure to isolate N,N-diethylbenzylamine, in contrast to the results obtained here, may be due to variation of procedure or to inherent differences in the properties of the two systems involved.

(8) (a) E. Fourneau and J. R. Billeter, *Bull. soc. chim.*, [5e] **7**, 602 (1940); (b) P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2532 (1949).

(9) Microanalyses by Mr. S. M. Nagy and associates.

(10) "Organic Syntheses," Coll. Vol. I, p. 80.

(11) Angel and Day (ref. 2) report the following analytical data for this compound: "*Anal.* Calcd. for $C_{17}H_{19}NO_2$: C, 78.84; H, 7.06; N, 4.95. Found: C, 78.78; H, 7.01; N, 5.04." Snyder, *et al.*, (ref. 6) also have noted this discrepancy.

base being required. This amount corresponds to 0.0094 mole of acetic acid (identified by its benzylthiuronium salt, m.p. 134°,[12] undepressed when mixed with an authentic specimen) in the filtrate, and indicates a 94% conversion in the reaction from which 80–85% yields of ethoxy derivative melting at 80–81° are isolated.

The substance obtained by refluxing 10 ml. of absolute *methanol* with 7.1 g. (0.025 mole) of the addition product (III) for one hour, followed by cooling and scratching, could not be induced to crystallize. The crude reaction mixture was therefore shaken with an excess of 10% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were dried over sodium sulfate, the solvent removed on the steam-bath, and the colorless product purified by distillation *in vacuo*. A single fraction, weighing 5.5 g. (86%) and forming the entire distillate, was collected at 135–140° (0.9 mm.), $n^{23}D$ 1.5580, d^{23}_4 1.084. The infrared spectrum of this material is very nearly the same as that of the ethoxy homolog (IV), with a pronounced amide carbonyl function absorption at 6.0 μ and no other absorption in the carbonyl region.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.08; H, 6.50.

Lithium Aluminum Hydride Reductions.—Into a solution of 0.75 g. of lithium aluminum hydride dissolved in 80 ml. of anhydrous ether was added with stirring over a five-minute period 1.4 g. (0.0052 mole) of the ethoxy derivative (IV) dissolved in 20 ml. of the same solvent. After one hour 5 ml. of a saturated aqueous sodium sulfate solution was added dropwise to decompose the excess reagent. Then 20 g. of anhydrous sodium sulfate was added, the resulting ethereal suspension filtered and the salt cake washed several times with ether. The ether filtrates were extracted with dilute hydrochloric acid (10%) and the aqueous layer neutralized with alkali and re-extracted with ether. After evaporation of the solvent from the basic extract, the product was distilled *in vacuo;* the sole fraction was a colorless liquid, b.p. 125–127° (0.8 mm.), weighing 0.97 g., $n^{23}D$ 1.5943. This material was seen from the infrared spectrum to lack the amide carbonyl function (absorption at 6.0 μ) present in the starting material. By warming with a saturated ethanolic picric acid solution and then cooling, the substance produced a deposit of bright yellow crystals melting at 117–118°, which on recrystallization from ethanol melted at 119–120° (mixed m.p. with picric acid 95–115°). These were identified as the picrate of N-ethyl-N-phenylbenzylamine (ethylbenzylaniline), the melting point remaining unchanged on admixture with the picrate (m.p. 119–120°, lit.[13] 120–121°) of an authentic sample of this amine.[14] With nitrous acid in the cold, the basic reduction product formed a green nitroso derivative, m.p. 61–62°,[15] also undepressed when mixed with an authentic sample. The 0.97 g. yield of amine in the reduction of IV corresponds to 88% conversion.

Reduction of 2.2 g. (0.0086 mole) of the liquid methoxy derivative of the benzalaniline addition product by the same procedure gave 1.5 g. (83%) of N-ethyl-N-phenylbenzylamine, picrate m.p. 119–120°.

In the reduction of the original addition product (III), it was found necessary to employ benzene as a co-solvent because of the sparing solubility (*vide supra*) of the material in ether. By adopting this expedient, 7.1 g. (0.025 mole) of freshly prepared addition product, m.p. 130–131°, was reduced with excess lithium aluminum hydride (3.0 g., 0.08 mole) in the manner described above. Fractional distillation of the basic extracts gave as the major component 2.4 g. of N-ethylaniline, b.p. 90–95° (14 mm.), characterized by its N-acetyl derivative, m.p. 54°, undepressed on admixture with a specimen prepared by the acetylation of N-ethylaniline. N-Ethyl-N-phenylbenzylamine, distilling at 170–180° (14 mm.), $n^{22}D$ 1.5938 (lit. b.p. 185.5–186.5° (22 mm.)[15]; $n^{20}D$ 1.5950[16]), was collected as the minor constituent, yield 0.45 g. (8.5%); m.p. of the picrate 118–120°, undepressed when mixed with authentic material. Benzyl alcohol was identified as the major component of the residual neutral fraction from the extracts (*ca.* 2.3 g.) by its 3,5-dinitrobenzoate, m.p. 112–113°.

From the reduction of 11.3 g. (0.05 mole) of N-ethylbenzanilide (prepared by the Schotten–Baumann benzoylation of N-ethylaniline), these same last-mentioned products were obtained. The basic extracts yielded 2.5 g. (41%) of distilled N-ethylaniline and 4.8 g. (45%) of distilled N-ethyl-N-phenylbenzylamine, characterized as above. Benzyl alcohol was identified in the neutral extracts, which weighed 2.6 g.

Esterification of β-Anilinohydrocinnamic Acid.—This acid, m.p. 135–136°,[8] was prepared according to the directions of Southwick and Seivard[8b] by the alkaline hydrolysis of its β-lactam[17] in the yield recorded. For the formation of its ethyl ester, 2.0 g. (0.0083 mole) of the acid was dissolved in 50 ml. of absolute ethanol, 3 ml. of concd. sulfuric acid added, and the resulting solution allowed to stand two days at 35°. At the end of this period the reaction mixture was poured into 400 ml. of water and the clear solution slowly neutralized with 10% aqueous sodium carbonate to *p*H 10. After thorough cooling (ice-bath), the deposited material was collected and dried; it weighed 2.1 g. (94%), and on recrystallization from 95% ethanol 1.9 g. (85%) of colorless, fine needle clusters, m.p. 76°, was obtained. On admixture with the ethoxy derivative (IV) from the benzalaniline addition product, these melted at 68–74°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.60; H, 7.03.

By substituting methanol in place of ethanol in the above esterification reaction, the same procedure gave an 87% yield of pure methyl ester, crystallizing similarly as fine needle clusters from methanol, m.p. 106.5–107°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.00; H, 6.72.

Hydrolysis of the β-Anilinohydrocinnamate Esters.—Hydrolysis of the above ethyl and methyl esters to free β-anilinohydrocinnamic acid was accomplished by refluxing 1.0 g. of each of them for one hour with an excess of 10% aqueous potassium hydroxide containing sufficient alcohol to maintain a single phase at the reflux temperature. The cooled hydrolysis mixtures were poured into 50 ml. of water and the acid recovered by acidification to *p*H 4 as described in the procedure for the above noted lactam hydrolysis.[8b] The yield of acid melting at 134–136° after one crystallization from 50% ethanol[8a] was in each case 0.7 g. (*ca.* 75–80%). When mixed with the original β-anilinohydrocinnamic acid preparation, this hydrolysis product gave an undepressed mixed m.p. 135–136°; with cinnamic acid, m.p. 133°, the m.p. was depressed to 104–118°.[8a]

Acknowledgments.—The author is gratefully indebted to Professor R. B. Woodward and Dr. David Taub for occasioning this work and offering helpful suggestions, and to Professor Gilbert Stork for discussions of the problem and assistance in the preparation of the manuscript.

CAMBRIDGE 38, MASS. RECEIVED DECEMBER 26, 1950

(12) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(13) R. Râscanu, *Ann. Sci. univ. Jassy*, Pt. I, **25**, 395 (1939); *C. A.*, **34**, 394 (1940). *Cf.* also ref. 15.

(14) P. Friedländer, *Ber.*, **22**, 588 (1889).

(15) G. Schultz, G. Rhode and E. Bosch, *Ann.*, **334**, 235 (1904).

(16) R. Raw, *J. Soc. Chem. Ind.*, **66**, 452 (1947).

(17) H. Gilman and M. Speeter, THIS JOURNAL, **65**, 2255 (1943).