The Addition of Ketones to Schiff Bases

A. H. BLATT AND NORMA GROSS

Department of Chemistry, Queens College of the City University of New York, New York, New York

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The uncatalyzed addition of ketones to Schiff bases reported in the literature could not be repeated. The addition of a number of ketones to Schiff bases can be brought about by small amounts of hydrochloric acid but the reaction is of limited applicability. Probable reasons are given for the limited scope of the addition reaction, some inaccuracies in the earlier literature are corrected, and a brief description of the chemistry of the adducts is presented.

A wide variety of reactive methylene compounds adds to Schiff bases in a way that is formally analogous to aldolization. The addition of one group of reactive methylene compounds, ketones that contain α-hydrogen atoms, has been studied by Francis,[1] by Mayer,[2] and by Snyder, Kornberg, and Romig.[3] Their results, together with information on the few other reported additions of ketones to benzalaniline and related Schiff bases, are collected in Table I.

Francis and Mayer used no added catalyst to bring about addition; Snyder, Kornberg, and Romig used boron trifluoride etherate. We took up the study of the addition of ketones to Schiff bases because we were unable to duplicate the results reported by Francis and by Mayer and because of the observation that a typical addition (eq. 1) was catalyzed by hydrochloric acid.[4]

$$C_6H_5COCH_3 + C_6H_5CH{=}NC_6H_5 \longrightarrow \underset{\text{I}}{C_6H_5COCH_2CH(C_6H_5)NHC_6H_5} \quad (1)$$

The details of our experiments, designed to determine the most effective catalysts and procedures for the addition and the description of our preferred procedures, are given in the Experimental section. Our results with benzalaniline are given in Table I. These results, together with those of earlier workers shown in the same table, permit two conclusions.

The first conclusion is that our procedure is generally superior to earlier procedures in yield or convenience or in both respects. When our yields are compared with those of Snyder, Kornberg, and Romig it should be kept in mind that they used a 300% excess of ketone as reactant and solvent, while we used equimolar amounts of reactants. We found that an excess of acetophenone or benzalaniline increased the yield of adduct, but not sufficiently to make the excess worthwhile. Their procedure gave an adduct with pinacolone while ours did not; by contrast, our procedure worked with diethyl ketone, methyl benzyl ketone, and propiophenone, whereas theirs did not. A comparison of our results with those of Francis is difficult for he did not report yields and we could not repeat his work. Our procedure gave poor results with desoxybenzoin and dibenzyl ketone. With methyl benzyl ketone we obtained an adduct in 80% yield, but its properties are different from those reported by Francis for the same adduct.

We established the structure of our adduct as II by deaminating it to an unsaturated ketone and identifying the ketone as III.

$$\underset{\text{II}}{C_6H_5CH_2COCH_2CH(C_6H_5)NHC_6H_5} \qquad \underset{\text{III}}{C_6H_5CH_2COCH{=}CHC_6H_5}$$

Our results generally parallel those of Mayer,[2] but a comparison is again difficult for Mayer reported yields for only two reactions. We repeated one of these reactions, the addition of methyl *n*-butyl ketone, and obtained a 63% yield instead of the 7% yield reported by Mayer. Our procedure is more convenient (requiring an 18-hr. reaction period rather than several weeks) and is more reliable than Mayer's procedure proved to be in our hands. Thus in two experiments with acetophenone and benzalaniline which we ran according to Mayer's directions, deposition of adduct began after 63 and 132 days, respectively.

Francis and Mayer, as we stated earlier, used no added catalyst. From our experiments with acid-free reagents and glassware and very small amounts of hydrochloric acid added as catalyst, it seems probable that Francis and Mayer did have traces of acid present in their reactions. The smallest amount of hydrochloric acid that we found to be effective was 0.002 mole %, which corresponds to 7.3 γ of hydrogen chloride in a reaction mixture containing 0.01 mole each of acetophenone and benzalaniline. The presence of small and varying amounts of acid of this order of magnitude would account for the long reaction times reported by Francis and by Mayer and for our difficulty in repeating their work.

The second conclusion from the data in Table I is that the addition of ketones to benzalaniline by any of the procedures so far developed is a reaction of limited applicability, limited for practical purposes to cyclanones and to methyl ketones CH_3COR where R is a primary or secondary alkyl group or an aryl group unsubstituted in the *ortho* positions. The exceptions so far are diethyl ketone, ethyl *n*-propyl ketone, and propiophenone which appear to be limiting cases. The reasons for the limitations are the other reactions, competing and consecutive, that can take place.

Ethanol solutions of benzalaniline containing hydrochloric acid develop a blue-green color on standing. Heat or exposure to air accelerates the changes involved. Although no pure colored products could be isolated, the development of color may be rationalized by reactions that consume benzalaniline and lead to products related to Doebner's violet.[5]

Another serious interfering reaction is that leading to unsaturated ketones. From a typical reaction between

(1) (a) F. E. Francis, *J. Chem. Soc.*, **75**, 865 (1899); (b) *ibid.*, **77**, 1191 (1900); (c) *ibid.*, **81**, 441 (1902); (d) F. E. Francis and E. B. Ludlum, *ibid.*, **81**, 956 (1902).

(2) (a) C. Mayer, *Bull. soc. chim. France*, [3] **31**, 953 (1904); (b) *ibid.*, **31**, 985 (1904); (c) *ibid.*, **33**, 157 (1905); (d) *ibid.*, **33**, 395 (1905); (e) *ibid.*, [4] **19**, 427 (1916); (f) *ibid.*, **19**, 452 (1916).

(3) H. R. Snyder, H. A. Kornberg, and J. R. Romig, *J. Am. Chem. Soc.*, **61**, 3556 (1939).

(4) A. Rosenoff, report on undergraduate research problem, Queens College, June 1956.

(5) Farbwerke Meister Lucius and Brünig, German Patent 106,497 (1899).

TABLE I

ADDITION OF KETONES TO SCHIFF BASES[a]

Ketone	Mayer[b]	Snyder, Kornberg, and Romig[c,d]	Other reports	This article[e]
Acetone	Piperidone —[f,g]	67	—[h]	70
($C_6H_5CH{=}NC_6H_4CH_3$-*o*)	0[i]			
($C_6H_5CH{=}NC_6H_4CH_3$-*m*)	Piperidone —[i,j]			
($C_6H_5CH{=}NC_6H_4CH_3$-*p*)	—[i]		—[k]	
($C_6H_5CH{=}CHCH{=}NC_6H_5$)				
Methyl ethyl	—[l]	66		69
Methyl *n*-propyl	—[l]			58
Methyl isopropyl	—[m]			58
Diethyl		0		33
Cyclopentanone		42		40
Methyl *n*-butyl	7[m]			63
Methyl isobutyl		61		
Methyl *t*-butyl		71		0
Ethyl *n*-propyl				20
Mesityl oxide		0		0
Cyclohexanone		0		40
Methyl *n*-amyl		38		62
Methyl isoamyl		38		
Di-*n*-propyl				0
Diisopropyl				0
Cycloheptanone				63
Methyl *n*-hexyl	—[l]			
($C_6H_5CH{=}NC_6H_4CH_3$-*p*)	10[l]			
Acetophenone	Good[l]	62		79
($C_6H_5CH{=}NC_6H_4CH_3$-*p*)	—[l]			
($C_6H_5CH{=}NC_{10}H_7$-β)	—[l,n]			
p-Nitroacetophenone				94
Methyl *n*-heptyl	—[l]			
Methyl benzyl		0	—[o,p]	80
m-(and *p*)-Methylacetophenone	—[m]			48
p-Methoxyacetophenone				48
Propiophenone	—[l]			11
Di-*n*-butyl		0		
Benzalacetone	Piperidone —[f,q]			
Methyl phenethyl		26		
Ethyl benzyl			—[o,p]	
α-Tetralone		0		0
Methyl *n*-nonyl	—[l]			
($C_6H_5CH{=}NC_6H_4CH_3$-*m*)	—[r]			
Acetomesitylene		0		
n-Propyl benzyl			—[o,p]	
Desoxybenzoin			—[o,s,t,u]	0
Dibenzyl			—[o,s,u]	0
Di-*n*-nonyl		0		

[a] The Schiff base is benzalaniline and the addition product is a β-arylamino ketone unless otherwise noted. The numbers represent percentage yields. A dash indicates that no yield was reported. [b] Mayer kept ethanol solutions of equimolar amounts of reactants at room temperature without added catalyst for several days to weeks. [c] Ref. 3. [d] Snyder, Kornberg, and Romig added 0.65 mole of boron fluoride etherate to the cold (ice–water bath) solution of 1.0 mole of benzalaniline in 4.0 moles of the ketone and poured the reaction mixture on ice and water after about 5 min. [e] With the exception of the acetone adduct for which no satisfactory method of purification could be found, these yields represent products of reasonable but not analytical purity. [f] The product is 1,2,6-triphenyl-4-piperidone formed presumably either by addition of the acetone adduct to a second molecule of benzalaniline and subsequent ring closure by elimination of a molecule of aniline, or by cyclization of the benzalacetone adduct. [g] Ref. 2a. [h] E. Macovski and A. Silberg, *J. prakt. Chem.*, [2] **37,** 131 (1933). An acetone solution of benzalaniline was heated with 30% aqueous hydrogen peroxide. [i] Ref. 2f. [j] The product is 1-*m*-tolyl-4,6-diphenyl-4-piperidone formed presumably as described in footnote *f*. [k] E. Macovski, S. Pop, and A. Lepădatu, *Ber.*, **74,** 1725 (1941). The reactants were heated with 30% aqueous hydrogen peroxide. [l] Ref. 2c. [m] Ref. 2d. [n] Potassium hydroxide was used as a catalyst in this reaction. [o] Francis warmed the reactants without solvent or added catalyst. [p] Ref. 1d. [q] Ref. 2b. [r] Ref. 2e. [s] Ref. 1a. [t] Ref. 1b. [u] Ref. 1c.

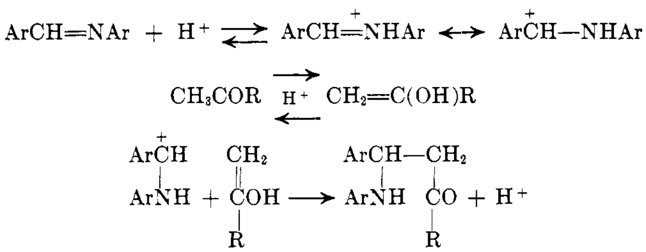
benzalaniline and acetophenone, after isolation of the adduct in about an 80% yield, we were able to obtain pure benzalacetophenone (IV) in about 7% yield. The unsaturated ketone can result from deamination of the adduct I (a reaction that is brought about by acids or heat) or by reaction between acetophenone and the benzaldehyde formed by hydrolysis of benzalaniline. Deamination seems to us the more likely path.

$$C_6H_5COCH_2CH(C_6H_5)NHC_6H_5 \xrightarrow{H^+} C_6H_5COCH{=}CHC_6H_5 + C_6H_5NH_2$$
IV

Our attempts to extend the applicability of the addition reaction met with little success. The use of an anhydrous medium should suppress hydrolysis. With glacial acetic acid in benzene we did observe much less development of color, but the addition was much slower and the yield was no better than in the standard proce-

dure. The addition was slower in absolute ethanol than in 95% ethanol. Another possibility is the use of a Schiff base that either hydrolyzes less readily or forms colored condensation products less readily than benzalaniline. We examined the behavior of anisalaniline, *p*-nitrobenzalaniline, benzalanisidine, and benzal-*p*-nitroaniline in ethanol containing hydrochloric acid, and the addition of several ketones to these Schiff bases. The results, which were not significantly better than those with benzalaniline, are collected in Table III in the Experimental section.

Our results give no specific information about the mechanism of addition, but the acid catalysis can be rationalized in the following way.

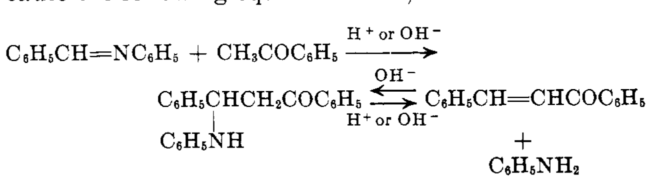


The formal analogy between aldolization and the addition of ketones to Schiff bases suggested the use of a basic catalyst. However, the yield of impure adduct from acetophenone and benzalaniline with 8 mole % sodium hydroxide was less than 40% in 7 days. With 1 equiv. of sodium hydroxide, no adduct could be isolated. Instead a nitrogen-free product of undetermined structure was obtained.

Attempts to extend the acid-catalyzed addition reaction (1) to other azomethines than Schiff bases were unsuccessful. No adducts were obtained from acetophenone and the following azomethines: $CH_2{=}NC(CH_3)_3$, $n\text{-}C_3H_7CH{=}NC(CH_3)_3$, $C_6H_5CH{=}NC(CH_3)_3$, $C_6H_5CH{=}NC_4H_9\text{-}n$, $C_6H_5CH{=}NC_{13}H_{27}\text{-}n$, $C_6H_5CH{=}NCH_2C_6H_5$, and $C_2H_5OCH{=}NC_6H_5$.

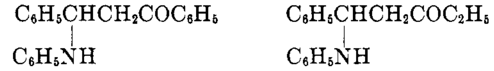
We also examined the behavior of a representative group of ten reactive methylene compounds, *e.g.*, acetoacetic ester, malonic ester, acetylacetone, toward benzalaniline in the presence of about 10 mole % hydrochloric acid. Many of the reactions had been studied by earlier workers with results that formed no clear pattern. Since the reactive methylene compounds are themselves acids and could catalyze the addition, we hoped that the presence of hydrochloric acid would lead to more consistent results. This did not prove to be the case.

Finally, it should be noted that many of the reaction mixtures develop a characteristic odor similar to that of phenyl isocyanide. The same odor develops when some azomethines are stored. The odor appears whether the reaction mixtures are alkaline or acid. It also develops in reaction mixtures in which an adduct is the organic reactant. The isonitrile-like odor is more pronounced after exposure of the reaction mixtures to air. Because the odor appears in so many reactions and because the following equilibria exist, we could not relate



the isonitrile-like odor to any single precursor. We did show that, when benzalaniline was treated with peracetic acid or with sodium peroxide, an isonitrile-like odor developed rapidly and polymeric material that resembled carbon was formed.

We examined the chemical behavior of the β-arylamino ketones obtained by adding ketones to Schiff bases, using principally the adducts I and V but including others when it was desirable.

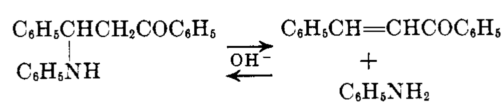


I V

The adducts as a group are deaminated to yield α,β-unsaturated ketones on solution in glacial acetic acid or concentrated sulfuric acid as reported by Mayer.[2] Acetic acid is to be preferred for the deamination of adducts from substituted acetophenones, *e.g.*, I, and sulfuric acid for adducts from dialkyl ketones, *e.g.*, V. The yields of α,β-unsaturated ketones ranged from 83% to quantitative, except for the adducts from benzalaniline with diethyl ketone, propiophenone, or cycloheptanone which did not deaminate satisfactorily. Preparation of an adduct followed by deamination is less satisfactory than a Claisen condensation for the preparation of benzalacetophenone and its analogs. However, the two-step procedure may be preferable for the preparation of some alkyl styryl ketones as it was for the preparation of benzyl styryl ketone (45% yield as compared with less than 10% by direct condensation).

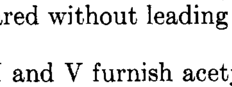
The adducts I and V do not deaminate cleanly with hydrochloric acid. They form hydrochlorides which could not be purified but from which the adducts could be regenerated by treatment with base.

The adduct I is deaminated by heating in methanol with sodium methoxide, completely if the hot solution is poured on ice and water and partially if the solution is allowed to cool. The reaction involved appears to be the reversal of the addition of aniline to benzalacetophenone. (The adduct I and a few of its analogs can be prepared in excellent yield by addition of an arylamine to an α,β-unsaturated ketone in the presence of sodium hydroxide or methoxide, but the addition is not a general reaction.)[6]



The adduct V was unchanged on brief heating in methanol with sodium methoxide, and on extended heating disappeared without leading to any identifiable products.

The adducts I and V furnish acetyl derivatives with acetic anhydride. The acetyl derivative VI yields



VI

benzalacetophenone and acetanilide on treatment with base. It is unaffected by solution in glacial acetic acid but is deaminated by solution in concentrated sulfuric acid.

(6) Tambor and Wildi, *Ber.*, **31**, 349 (1898).

Experimental

The experiments with benzalaniline and acetophenone, done to establish a procedure for the addition, do not require individual descriptions. In a typical experiment 5.4 g. (0.03 mole) of benzalaniline was dissolved in 3.6 g. (0.03 mole) of acetophenone by warming the mixture to room temperature. The solution was made ~1.2 *M* in each reactant by the addition of 16.5 ml. of 95% ethanol. Then 0.25 ml. (10 mole %) of concentrated hydrochloric acid was added and the reaction mixture was left stoppered for 18 hr. during which time a cake of adduct formed. The product was separated by filtration and washed with cold ethanol to furnish 7.1 g. (79%) of β-anilino-β-phenylpropiophenone (I), m.p. 166–168°.

Variations of these conditions showed the following.

(1) Increasing the temperature favors side reactions and the formation of deeply colored products. At 40° the yield of adduct drops to 70%, and from reactions run at the boiling point of the reaction mixture no adduct can be obtained.

(2) Decreasing the temperature decreases the rate of addition, but decreases the rates of side reactions even more. At 8° (refrigerator temperature) the yield of adduct is 80% after 67 hr., but the color of the reaction mixture is less than that in a run at room temperature after 16 hr.

(3) Increasing the amount of hydrochloric acid increases the extent of side reactions and decreases the yield of adduct. With 1 equiv. of hydrochloric acid no adduct is obtained.

(4) Decreasing the amount of hydrochloric acid decreases the rate of addition and decreases the rates of side reactions even more. As the amount of hydrochloric acid is reduced from 20 mole % to 0.02 mole %, the length of time required for the appearance of the adduct increases from about 1 hr. to about 145 hr. When the amount of hydrochloric acid is reduced to 0.002 mole %, the addition is erratic (27 days were required in one experiment and 45 days in a second for the appearance of adduct) but this may have been the consequence of our failure to measure accurately the small quantities of acid. With 20, 10, or 5 mole % acid, the concentrated acid and 6 *N* acid were equally effective.

(5) Methanol, tetrahydrofuran, dimethylformamide, and absolute ethanol are less satisfactory solvents than 95% ethanol.

(6) Other hydrogen acids can be used but we have found none that is superior to hydrochloric acid. Acetic, hydrobromic, and hydriodic acids give no better yields than hydrochloric acid. With acetic acid and with hydriodic acid there is less development of color. Addition is slower with acetic acid and with hypophosphorous acid. Sulfuric acid gives lower yields.

These experiments led to the following preferred procedure. Concentrated hydrochloric acid (10 mole %) is added to a solution of equimolar amounts of ketone and Schiff base, each about 1.2 *M*, in 95% ethanol. The reaction mixture is kept at room temperature for 18 hr. and the adduct is then removed by filtration.

The addition is sufficiently slow under the most favorable conditions so that neither the amount of hydrochloric acid, nor the temperature, nor the reaction time is sharply critical. Five mole per cent of acid can be used if the time is increased to 24 hr.; reactions can be run at 8°, rather than at room temperature, if the time is increased to about 64 hr.; and reactions can be run at 8° with 5 mole % acid, if the time is increased to about 114 hr. Finally, even for a reaction with 20 mole % of acid at room temperature the time can be increased or decreased by 1 hr. without significantly affecting the yield. Observation of a reaction mixture usually gives sufficient information to enable one to modify the experimental procedure. Thus the evolution of heat or the formation of a precipitate at the beginning of an experiment indicates that the reaction mixture should be chilled, and the development of color during an experiment indicates that the reaction should be worked up promptly. The development of color is critical. Although the yield of crude adduct does not decrease markedly as the reaction mixture becomes colored, the adduct can be obtained pure only with difficulty and in poor yield.

Addition of Ketones to Benzalaniline.—The description of a typical addition reaction given above will also serve as a general description of the addition of ketones to benzalaniline. Details of the individual reactions are given in Table II.

The adducts, which are sparingly soluble in 95% ethanol, were purified by crystallization from that solvent unless otherwise noted. The recovery in the crystallizations from ethanol was between 75 and 85%, except for the adducts from diethyl ketone, cyclopentanone, ethyl *n*-propyl ketone, cyclohexanone, and cycloheptanone. Each of these adducts, which contains two asymmetric centers, can exist in two racemic forms. We isolated only a single isomer, but in every case a low yield in the addition, or a low melting point of the crude adduct, or a large loss in purification was an indication of the presence of a second, more soluble, racemate.

TABLE II

Ketone	Temp., °C.	Time, hr.	Crude yield, %; m.p., °C.
Acetone	8	2.5	70; 60[a]
Methyl ethyl	8	19	69; 118–119
Methyl *n*-propyl	8	19	58; 81–82
Methyl isopropyl	20	43	58; 116–117
Diethyl	8	70	33; 122–124[b]
Cyclopentanone	8	1.5	80; 140–142[c]
Methyl *n*-butyl	20	19	63; 76
Ethyl *n*-propyl	8	11 days	30; 97–100[d]
Cyclohexanone	8	18	73; 113–115[e]
Methyl *n*-amyl	20	17	62; 70–72
Cycloheptanone	20	18.5	85; 125–132[f]
Acetophenone	20	18	79; 169–171[g]
p-Bromoacetophenone	20	16	80; 143–145[h]
p-Nitroacetophenone	20	21	94; 167–168[i]
p-Methoxyacetophenone	20	22	49; 128–130[j]
Methyl benzyl	20	24	79; 115–118[k]
Propiophenone	8	14 days	17; 110–113[l]

[a] Five mole per cent acid was used. The adduct could not be purified satisfactorily. [b] The analytical sample melted at 122.5–123°. *Anal.* Calcd. for $C_{18}H_{21}NO$: C, 80.89; H, 7.86. Found: C, 81.11; H, 8.08. [c] The crude product is always contaminated with gummy material. Crystallization from acetone (6 ml./g.) by adding ethanol (3 ml./g.) and concentrating the solution to half of its original volume furnishes the pure adduct, m.p. 164–165°, with a 50% recovery. [d] The recovery on purification was only 60%. The analytical sample melted at 101–102°. *Anal.* Calcd. for $C_{19}H_{23}NO$: C, 81.14; H, 8.18. Found: C, 80.44; H, 8.07. [e] Two recrystallizations from ethanol (60% recovery) are necessary in order to obtain the pure adduct, m.p. 139–140°. [f] The analytical sample, obtained by crystallization from benzene, melted at 145°. *Anal.* Calcd. for $C_{20}H_{23}NO$: C, 81.90; H, 7.85. Found: C, 82.23; H, 7.71. [g] This very sparingly soluble adduct was crystallized from toluene (10 ml./g.) with 90% recovery. Our purest samples melted at 180–181°, lit. m.p. 173°[2c] and 166–167°.[3] [h] The very sparingly soluble adduct was crystallized from acetone plus ethanol. The analytical sample melted at 144.5–145°. *Anal.* Calcd. for $C_{21}H_{18}BrNO$: C, 66.3; H, 4.73. Found: C, 66.9; H, 4.72. [i] The very sparingly soluble, bright orange adduct was crystallized from ethyl acetate (~20 ml./g.) with an 80% recovery. The pure adduct melted at 173°. *Anal.* Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.8; H, 5.20. Found: C, 72.9; H, 5.35. [j] The adduct was crystallized from ethanol (20 ml./g.) with a 72% recovery. The analytical sample melted at 133°. *Anal.* Calcd. for $C_{22}H_{21}NO_2$: C, 79.76; H, 6.34. Found: C, 80.17; H, 6.52. [k] The adduct, purified by crystallization from ethanol (20 ml./g.) with a 90% recovery, melted at 123–123.5°. *Anal.* Calcd. for $C_{22}H_{21}NO$: C, 83.81; H, 6.67. Found: C, 83.90; H, 6.61. [l] Five mole per cent hydrochloric acid was used.

Pinacolone gave no adduct; desoxybenzoin and dibenzyl ketone gave very small yields of adducts and the addition reactions were not consistently reproducible.

The adducts were vacuum dried at room temperature before analysis. Adducts that had been dried under vacuum at 80 or 100° gave erratic results on analysis, probably as the result of partial deamination (see below).

1,4-Diphenyl-4-anilinobutan-2-one.—The adduct we obtained from benzalaniline and methyl benzyl ketone melted at 123–123.5° instead of 173° as reported by Francis and Ludlum.[1d] When 5.0 g. (0.016 mole) of the adduct was added during 15 min. to 25 ml. of concentrated sulfuric acid, the solid dissolved to form an orange solution. After 45 min. the solution, which was very dark red, was poured onto 300 g. of ice and water. The precipitate, after it had been washed with 1% aqueous sodium carbonate and dried, weighed 2.83 g. and melted at 63–66°. It was dissolved in ether and the solution was washed with 1% aqueous sodium carbonate. (It is important to remove traces of acid

TABLE III[a]

Reactants	Reaction time, hr.	Crude yield, %; m.p., °C.
$C_6H_5CH{=}NC_6H_4Br$-p		
$CH_3COC_6H_5$	19	85; 178–180[b]
$C_6H_5CH{=}NC_6H_4NO_2$-p		
$C_2H_5COC_2H_5$	19	33; 158–160[c]
$CH_3COC_6H_5$	18	80; 183–185[d]
$CH_3COC_6H_4NO_2$-p	22	56; 164–168[e]
$CH_3COC_6H_4OCH_3$-p	21	70; 139–141[f]
$C_2H_5COC_6H_5$	48	12; 171–175[g]
$C_6H_5CH{=}NC_6H_4OCH_3$-p		
$CH_3COC_6H_5$	18	30; 143–145[h]
$CH_3COC_6H_4NO_2$-p	21	Oil[i]
$CH_3COC_6H_4OCH_3$-p	20	Unreacted material[j]
p-$O_2NC_6H_4CH{=}NC_6H_5$		
$CH_3COC_6H_5$	21	Unreacted material[k]
$CH_3COC_6H_4NO_2$-p	22	Impure adduct[l]
$CH_3COC_6H_4OCH_3$-p	24	Gummy material
p-$CH_3OC_6H_4CH{=}NC_6H_5$		
$CH_3C_6OCH_5$	17	52; 146–148[m]
$CH_3C_6OCH_4NO_2$-p	18	Mixture[n]
$CH_3COC_6H_4OCH_3$-p	18	0

[a] Reactions were run at room temperature with 10 mole % concentrated hydrochloric acid as catalyst except when otherwise noted. [b] The very sparingly soluble adduct was crystallized from benzene to furnish an analytical sample, m.p. 183°. *Anal.* Calcd. for $C_{21}H_{18}BrNO$: C, 66.3; H, 4.73. Found: C, 66.88; H, 4.84. [c] The yield increased to 49% after 1 week. The adduct crystallized from ethanol as a bright yellow solid that melted at 163°. *Anal.* Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.23; H, 6.41. Found: C, 69.71; H, 6.83. [d] The yield was 95% after 10 days. The adduct, crystallized from acetone by adding an equal volume of ethanol, was obtained as bright yellow crystals, m.p. 186–187°. *Anal.* Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.83: H, 5.20. Found: C, 73.08; H, 5.59. [e] The yellow adduct, crystallized from acetone by addition of ethanol, melted at 170–171°. *Anal.* Calcd. for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.34. Found: C, 64.36; H, 4.50. [f] The crude yellow adduct was crystallized by solution in acetone and addition of ethanol, m.p. 145–146°. *Anal.* Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.21; H, 5.32. Found: C, 70.68; H, 5.60. Attempts to crystallize the adduct from ethanol led to partial decomposition. [g] The yield was 37% after 5 days. The adduct crystallized from aqueous acetone as bright yellow crystals, m.p. 181–181.5°. *Anal.* Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.3; H, 5.56. Found: C, 73.4; H, 5.46. [h] The very sparingly soluble adduct was crystallized by solution in acetone and addition of an equal volume of ethanol as pale yellow crystals, m.p. 150–151°. *Anal.* Calcd. for $C_{22}H_{21}NO_2$: C, 79.76; H, 6.34. Found: C, 80.08; H, 6.11. [i] In this reaction, 8 mole % hydrochloric acid was used as catalyst. When the reaction was left for 5 days, the unsaturated ketone, $C_6H_5CH{=}CHCOC_6H_4NO_2$-$p$, identified by comparison with an authentic specimen, was obtained in 92% yield. [j] In this reaction, 8 mole % hydrochloric acid was used as catalyst. When the reaction was left for 5 days, the crude adduct, m.p. 120–125°, was obtained in a 35% yield. The second crop of crystals consisted of the unsaturated ketone, $C_6H_5CH{=}CHCOC_6H_4OCH_3$-$p$, identified by comparison with an authentic specimen. The pure adduct, obtained by crystallization from ethanol, melts at 133°. *Anal.* Calcd. for $C_{23}H_{23}NO_3$: C, 76.45; H, 6.37. Found: C. 76.87; H, 6.71. [k] When the reaction was run at 40° for 5 hr., the unsaturated ketone, p-$O_2NC_6H_4CH{=}CHCOC_6H_5$, identified by comparison with an authentic specimen, was obtained in quantitative yield. Experiments run for extended periods of time at room temperature gave mixtures of products that apparently contained some of the adduct but from which we were unable to obtain any pure adduct. [l] Reactions run for 5 days gave an impure product that corresponded in weight to more than 90% yield of adduct. Attempts to obtain the pure adduct from the crude product were not successful, for the material on repeated crystallization furnished only the unsaturated ketone, p-$O_2NC_6H_4CH{=}CHCOC_6H_4NO_2$-$p$, m.p. 213°, which was identified by comparison with a sample prepared by condensing p-nitrobenzaldehyde and p-nitroacetophenone. The analytical sample, purified by crystallization from acetone, melted at 213°. *Anal.* Calcd. for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.36. Found: C, 60.10; H, 3.57. [m] The sparingly soluble adduct, crystallized from ethanol or acetone, melted at 148°. *Anal.* Calcd. for $C_{22}H_{21}NO_2$: C, 79.75; H, 6.34. Found: C, 80.25; H, 6.28. [n] The product was a mixture of unsaturated ketone, p-CH_3O-$C_6H_4CH{=}CHCOC_6H_4NO_2$-$p$, and, presumably, adduct. On attempted purification by crystallization the mixture was converted to the unsaturated ketone, identified by a mixture melting point.

from the crude unsaturated ketone before attempting to purify it.) The solid obtained after evaporation of the ether was crystallized from methanol (5 ml./g.) to furnish 1.8 g. (55%) of benzyl styryl ketone, m.p. 69–70°. The melting point was not depressed by admixture with an authentic sample of benzyl styryl ketone, m.p. 67–68°, prepared in 7% yield from benzaldehyde and methyl benzyl ketone.[7] The adduct can also be deaminated by warming its solution in glacial acetic acid.

Benzalaniline, Acetophenone, and Sodium Hydroxide.—One milliliter of 10% sodium hydroxide (8 mole %) was added to a solution of 5.4 g. (0.03 mole) of benzalaniline and 3.6 g. (0.03 mole) of acetophenone in 16.5 ml. of ethanol. The colorless solution did not deposit any solid during 18 hr. but did turn bright yellow. After 4 days, 2.65 g. of waxy white solid, m.p. 155–164°, had separated. The filtrate deposited small additional amounts of solid on standing and developed an isonitrile-like odor. The solid, after crystallization from ethanol, proved to be identical (melting point and mixture melting point) with β-anilinobenzylacetophenone. Minor variations in the experimental procedure did not change the results significantly.

Quite different results were obtained when 1 equiv. of sodium hydroxide was used. In a typical experiment 27 g. (0.15 mole) of benzalaniline and 18 g. (0.15 mole) of acetophenone were dissolved in 100 ml. of 95% ethanol, and a solution of 6.0 g. (0.15 mole) of sodium hydroxide in 10 ml. of water was added. After 24 hr., a heavy oil had formed at the bottom of the orange solution. After 48 hr., particles of solid had formed in the oil. After 8 days the lower layer, which was now solid, no longer increased in amount. The mixture was filtered and the sticky solid was triturated with ethanol and with acetone. The filtrate had an isocyanide-like odor.

The crude washed solid, whose weight varied with the effectiveness with which the adhering oil had been removed, was crystallized by dissolving it in 100 ml. of acetone and concentrating the solution to about half its volume. This furnished about 6 g. of a colorless solid that melted at 200–205°. Further purification was effected by crystallization from acetone to constant melting point, 207–208°.

Anal. Found: C, 85.00, 84.99; H, 5.96, 5.90; O, 9.24.

The very sparingly soluble material does not contain nitrogen. However, it is not formed when benzalaniline is omitted from the reaction mixture.

Reactions of the Anilino Ketones.—β-Anilinobenzylacetophenone (I) and ethyl β-anilinophenethyl ketone (V) can be distilled at pressures below 1 mm., but at higher pressures they eliminate aniline to form benzalacetophenone and ethyl styryl ketone, respectively. Preparative deamination of I and its analogs is most conveniently effected using glacial acetic acid. Thus 3.0 g. (0.01 mole) of the adduct I was dissolved by warming with 15 ml. of glacial acetic acid. After 10 min. the solution was left to cool to room temperature and poured into 60 ml. of water. The precipitate of benzalacetophenone, m.p. 50–52°, m.m.p. 51–53°, weighed 2.0 g., 95%. The analogs, $C_6H_5CH(NHC_6H_5)$-$CH_2COC_6H_4Br$-p, p-$CH_3OC_6H_4CH(NHC_6H_5)CH_2COC_6H_5$, and p-$CH_3OC_6H_4CH(NHC_6H_5)CH_2COC_6H_4NO_2$-$p$, furnished the corresponding unsaturated ketones in 90% yield.

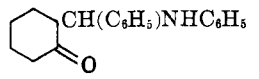
Preparative deamination of V and its analogs is most conveniently effected by concentrated sulfuric acid. The adduct V (20 g.) was added in small portions to 100 ml. of concentrated sulfuric acid. After 1 hr. the deep red solution was poured into 450 g. of ice and water. The light tan precipitate (11.7 g., 91%) was crystallized from ligroin (30–60°) to furnish 7.5 g. (58%) of pure ethyl styryl ketone, m.p. 33°. When the crude product was washed with 1% aqueous sodium carbonate and distilled (117–120° at 3 mm.) the yield of unsaturated ketone was 70%.

(7) Goldschmiedt and Knöpfer, *Monatsh.*, **18**, 437 (1897); Goldschmiedt and Krczmar, *ibid.*, **22**, 667 (1901).

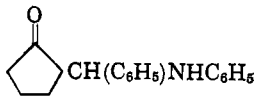
The identity of the deamination product as ethyl styryl ketone was established by adding aniline to it to furnish the adduct V. Piperidine (0.2 ml., 10 mole %) was added to a soution of 3.2 g. (0.02 mole) of the deamination product and 1.8 g. (0.02 mole) of aniline in 11 ml. of ethanol, and the yellow solution was left overnight. The first crop of the adduct V (m.p. 116–118°) was 3.2 g. (64%) and a second crop raised the yield to 76%. The melting point of this sample of the adduct was not lowered by admixture with a sample prepared from benzalaniline.

The following analogs of the adduct V, which are not deaminated efficiently by acetic acid, are deaminated by sulfuric acid.

$C_6H_5CH(NHC_6H_5)CH_2COC_5H_{11}$-$n$
(quantitative)



83%



88%

The adducts from benzalaniline and propiophenone, diethyl ketone, and cycloheptanone were destroyed on attempted deamination.

The adducts I and V are not deaminated by hydrochloric acid. When concentrated hydrochloric acid is added to hot ethanol suspensions of these adducts and the resulting solutions are cooled quickly, colorless crystalline hydrochlorides can be isolated. The hydrochlorides, which could not be crystallized, gave poor results on analysis.

Anal. Calcd. for $C_{21}H_{19}NO\cdot HCl$: Cl, 10.5. Found: Cl, 8.92. Calcd. for $C_{17}H_{19}NO\cdot HCl$: Cl, 12.27. Found: Cl, 11.03.

No products could be obtained when the hydrochlorides were heated alone or in solution in ethanol or acetic acid. Addition of 10% aqueous sodium carbonate to freshly prepared solutions of the hydrochlorides in ethanol or acetone regenerated the adducts.

When 1 equiv. of 1 *M* sodium methoxide in methanol was added to a suspension of the adduct I in boiling methanol, the solid dissolved after 10 min. of heating. When the hot solution was poured into ice and water, benzalacetophenone was formed in quantitative yield. When the solution was allowed to cool to room temperature and poured into water, benzalacetophenone (80%) and unchanged adduct (17%) could be isolated. The adduct V on similar treatment is unaffected, and on longer heating furnishes no definite products.

The adducts I and V formed acetyl derivatives in 90% yield when they were dissolved by heating with acetic anhydride and the solutions were left overnight, then poured into water. The acetyl derivatives were purified by crystallization from ethanol.

Anal. of $C_6H_5COCH_2CH(C_6H_5)N(COCH_3)C_6H_5$ (VI). Calcd. for $C_{23}H_{21}NO_2$: C, 80.46; H, 6.12. Found: C, 80.58; H, 6.38.

Anal. of $C_2H_5COCH_2CH(C_6H_5)N(COCH_3)C_6H_5$. Calcd. for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12. Found: C, 77.38; H, 7.52.

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Rotatory Dispersion Studies. IV.[1a] Substituted Cyclohexanone Oximes[1b]

GLORIA G. LYLE AND RENÉE MESTRALLET BARRERA

Department of Chemistry, University of New Hampshire, Durham, New Hampshire

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The base-catalyzed stereoselective Beckmann rearrangement of the isomeric oximes of (+)-3-methylcyclohexanone gave products permitting characterization of the α-oxime as having the *syn*-methyl configuration and the β-oxime as the *anti*-methyl isomer. A comparison of the optical rotatory dispersion curves of several cyclic ketone oximes, benzoyl derivatives of the oximes, and the lactams produced by their Beckmann rearrangements is described.

The absolute configuration of an oxime may be determined by the stereospecific Beckmann rearrangement of the oxime if only a single product (amide or lactam) is obtained from a reaction in which the configuration of the oxime is not altered. Brown and co-workers[2] found that the two isomers of isobutyrophenone oxime gave different products on treatment with benzenesulfonyl chloride in basic solution but that the use of hydrogen chloride in acetic acid produced the same amide from both oximes, the product of phenyl migration. It was apparent that the acidic medium promoted equilibration thus leading to the product resulting from the rearrangement of the group with the higher migratory aptitude.

Acid sensitivity has been observed in a number of oximes whose configuration could not be established under the usual Beckmann conditions. One such pair of oximes is that from (+)-3-methylcyclohexanone (I). (+)-Pulegone was isolated from oil of pennyroyal[3] and converted to I[4] from which the mixture of diastereomeric oximes II was prepared. The oximes II consisted of a mixture that contained approximately 65% of the α-oxime IIa, lit.[5] m.p. 60°, and 35% of the β-oxime IIb, lit.[5] m.p. 47°, the percentages being based on rotation data (*vide infra*). A partial separation of the mixture could be effected by chromatography on basic alumina. Acid-washed alumina catalyzed the Beckmann rearrangement of the oxime mixture.

The oximes were separated more satisfactorily by fractional crystallization of the O-benzoyl derivatives III as described by Hückel[5] when chromatography of the benzoates on florisil or alumina was unsuccessful. Careful hydrolysis of the benzoates gave the crystalline oximes. Heat or trace amounts of acid promoted the rapid interconversion of the oximes. The infrared absorption spectra of the isomeric benzoates III were quite similar but showed small differences in the finger-

(1) (a) Part III: G. G. Lyle and W. Gaffield, *Tetrahedron Letters*, **No. 21**, 1371 (1963). (b) This work was supported in part by a National Science Foundation Grant, G 9489. A summary of the results was presented before the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960.

(2) (a) R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955); (b) N. H. P. Smith [*J. Chem. Soc.*, 4209 (1961)] reported that the *syn*- and *anti*-oximes of 2-bromo-5-nitroacetophenone could be stereospecifically rearranged to the corresponding amides with the use of polyphosphoric acid. These oximes are much less labile than those reported in this paper.

(3) O. Wallach, *Ann.*, **289**, 337 (1896).

(4) F. Nerdel, B. Gnauck, and G. Kresze, *ibid.*, **580**, 35 (1953).

(5) W. Hückel and M. Sachs, *ibid.*, **498**, 166 (1932).