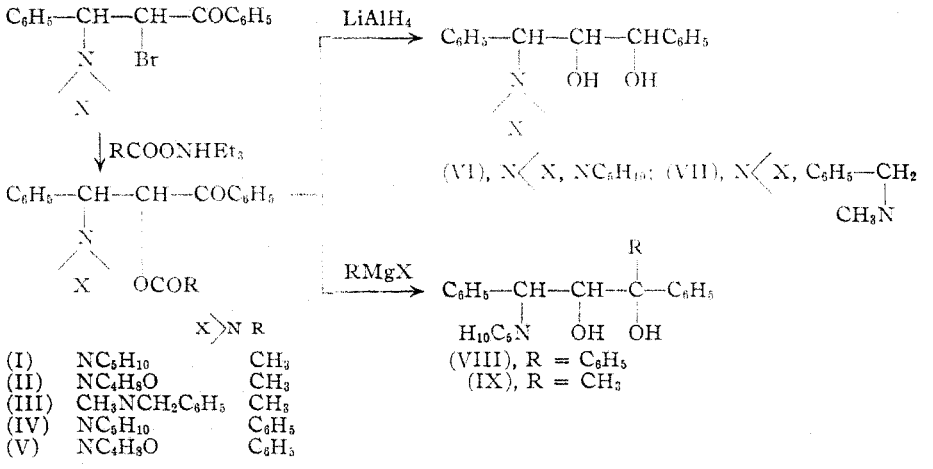
[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Synthesis and Reactions of α-Acetoxy and α-Benzoxy-β-amino Ketones

BY NORMAN H. CROMWELL AND FRED W. STARKS[1]

Dufraisse and Moureu[2] found that α-bromobenzalacetophenone reacted with piperidine to give an addition compound to which they assigned the structure of α-bromo-α-piperidinobenzylacetophenone. It has since been shown that such addition compounds of amines with α-bromo-α,β-unsaturated ketones are actually α-bromo-β-amino ketones.[3,4,5]

Dufraisse and Moureu[2] also found that the bromopiperidinobenzylacetophenone, obtained from the reaction of piperidine with α-bromobenzalacetophenone, reacted with potassium acetate to give a product to which they assigned the structure, α-acetoxy-α-piperidinobenzylacetophenone. In view of our recent investigations[3,4,5] it seemed more probable that this compound was either α-piperidino-β-acetoxybenzylacetophenone or α-acetoxy-β-piperidinobenzylacetophenone (I). The present investigations have served to establish this latter structure, to improve the method of preparing such substances, to extend the improved method to the preparation of several other related compounds, and to develop the chemistry of the compounds.



(I)	NC_5H_{10}	CH_3
(II)	NC_4H_8O	CH_3
(III)	$CH_3NCH_2C_6H_5$	CH_3
(IV)	NC_5H_{10}	C_6H_5
(V)	NC_4H_8O	C_6H_5

In connection with another problem being investigated in this laboratory, β,β′-dihydroxyisopropylamines were required. Hydrogenation of α-amino-β-acetoxyketones might be expected to yield such diols.[6]

α - Acetoxy - β - piperidinobenzylacetophenone, identical with the product reported by Dufraisse and Moureu[2], was obtained in a 70% yield when α - bromo - β - piperidinobenzylacetophenone was treated with triethylammonium acetate in benzene solution. These are conditions which might be expected to favor a direct bimolecular replacement of the bromine ion by the acetate ion. Other conditions including those described previously[2] which employed more basic conditions gave larger amounts of the side product, α-piperidinobenzalacetophenone.

The analogous compounds, α-acetoxy-β-morpholinobenzylacetophenone (II), α-acetoxy-β-(N-methylbenzylamino)-benzylacetophenone (III), α-benzoxy-β-piperidinobenzylacetophenone (IV), and α-benzoxy-β-morpholinobenzylacetophenone (V) were obtained in fair to poor yields. The preparation of the analogous α-acetoxy- and α-benzoxy-β-aminobenzylacetones was not realized.

The structures of the α-acetoxy-β-aminobenzylacetophenones (I) and (II) were definitely established by showing them to be identical with the acetolysis products of the corresponding α-hydroxy-β-aminobenzylacetophenones.[7] The direct relationship between the positions of the acetoxy and benzoxy groups in the two series of compounds was established by reduction of (I) and (IV) with lithium aluminum hydride. In both instances the product was 1,3-diphenyl-3-piperidinopropanediol-1,2 (VI) which also results from the lithium aluminum hydride reduction of α-hydroxy-β-piperidinobenzylacetophenone.[6] The diol (VI) readily formed a diacetate (X). Reduction of (III) gave 1,3-diphenyl-3-[N-methylbenzylamino]-propanediol-1,2 (VII).

As the yields in Table I would indicate, steric difficulties are encountered in the introduction of the larger benzoxy groups into these molecules. Also the presence of an amino group with greater steric requirements than piperidino or morpholino, such as the N-methylbenzylamino group, offers hindrance to the introduction of even the acetoxy group. If the replacement reaction is slowed by steric hindrance the formation of the α-

(1) Abstracted from the Ph.D. thesis of F. W. Starks, University of Nebraska Regents Fellow 1948–49.

(2) Dufraisse and Moureu, *Bull. soc. chim.*, **41**, 457 (1927).

(3) Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943).

(4) Cromwell and Witt, *ibid.*, **65**, 308 (1943).

(5) Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(6) For another attempt to obtain such diols see the following paper, Cromwell and Barker, THIS JOURNAL, **72**, 4110 (1949).

(7) In the following paper, ref. 6, it is shown that epoxybenzylacetophenone reacts with morpholine and piperidine to give β-morpholino- and β-piperidino-α-hydroxybenzylacetophenone, respectively.

TABLE I

PHYSICAL AND ANALYTICAL DATA[d]

No.	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
II	10[a] 63[b]	186–187	$C_{21}H_{23}NO_4$	71.36	71.16	6.56	6.66	..	..
III	20[b]	127–128	$C_{25}H_{25}NO_3$	77.49	77.56	6.51	6.33	3.61	3.69
IV	24[a] 13[b] 29[c]	163–164	$C_{27}H_{27}NO_3$	78.42	78.67	6.58	6.58	3.39	3.49
V	7[a] 9[b]	199–200	$C_{26}H_{25}NO_4$	75.19	75.27	6.06	6.26	3.36	3.31
VI	63[e] 63[f]	149	$C_{20}H_{25}NO_2$	77.13	77.18	8.09	8.28	4.49	4.58
VII	45	118–119	$C_{23}H_{25}NO_2$	79.50	79.62	7.25	7.33	4.03	4.05
VIII	60[g] 63[h]	174	$C_{26}H_{29}NO_2$	80.58	80.44	7.54	7.46	3.62	3.58
IX	46	147	$C_{21}H_{27}NO_2$	77.50	77.74	8.36	8.69	4.30	4.33
X	58	103	$C_{24}H_{29}NO_4$	73.14	72.87	7.42	7.55	3.54	3.69

[a] Method 1. [b] Method 4. [c] Method 3. [d] Microanalyses for C, H, N by the Clark Microanalytical Laboratories, Urbana, Ill. [e] From (I). [f] From (IV). [g] Using C_6H_5MgBr. [h] Using C_6H_5Li.

amino-α,β-unsaturated ketone, which is less affected by such factors, becomes the predominant reaction.

α-Acetoxy-β-piperidinobenzylacetophenone reacted readily with phenylmagnesium bromide or phenyl lithium to give 1,1,3-triphenyl-3-piperidinopropanediol-1,2 (VIII), and with methylmagnesium iodide to produce 2,4-diphenyl-4-piperidinobutanediol-2,3 (IX).

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Experimental

Preparation of α-Acetoxy-β-piperidinobenzylacetophenone, (I).—Method 1.—The conditions used were similar but not identical with those reported previously.[2] To a suspension of 24.0 g. (0.065 mole) of α-bromo-β-piperidinobenzylacetophenone[2] in 100 ml. of absolute alcohol was added 8.4 g. (0.085 mole) of potassium acetate. The mixture was stirred for four hours and then stored at room temperature for three days. During this time the solution slowly developed a red color. The reaction mixture was cooled to 0° for four hours. The precipitate was removed by filtration and completely washed with the following sequence of solvents: 85% alcohol, water, 85% alcohol, and finally with ether. This product was recrystallized from absolute alcohol. The yield from this experiment was 5.5 g. (0.0157 mole) or 24%, m. p. 159–160°.[2]

Method 2.—A solution of potassium acetate in absolute alcohol was prepared and the *p*H adjusted to 8.0 by adding glacial acetic acid (checked with a Beckman *p*H meter). This solution was added to a suspension of 0.663 equivalent of α-bromo-β-piperidinobenzylacetophenone in absolute alcohol and the mixture allowed to stand at room temperature for three days. A 29.5% yield of product melting at 159–160° and identical with the product of method 1 resulted from this experiment.

Method 3.—Conditions similar to those of method 1, but employing acetone as a solvent and a stirring time of fourteen hours followed by three days of storing at room temperature gave a 41% yield of product identical with that previously obtained.

Method 4.—A mixture of 5.7 g. (0.0153 mole) of α-bromo-β-piperidinobenzylacetophenone and 150 ml. of benzene was prepared. To this suspension was added 1.68 g. (0.028 mole) of glacial acetic acid and then 2.32 g. (0.023 mole) of triethylamine. The clear, pale yellow solution was stored at room temperature for two days. During this time the solution developed an orange color and a colorless precipitate formed which was removed by filtration and shown to be 2.5 g. of triethylamine hydrobromide. This indicated at least a 90% removal of the bromine available in the starting material. The orange colored filtrate was concentrated by evaporation of the benzene, and petroleum ether added to induce crystallization. A colorless product resulted, wt. 3.76 g. (0.0107 mole) or 70%. This product was identical with the products obtained from the above-described procedures.

By these various methods, as indicated in Table I, (II) was obtained from α-bromo-β-morpholinobenzylacetophenone,[8] and (III) from α-bromo-β-(N-methylbenzylamino)-benzylacetophenone.[4] These were both recrystallized from absolute alcohol.

Preparation of α-Benzoxy-β-aminobenzylacetophenones.—These compounds were prepared by the various methods outlined for the acetoxy compounds as indicated in Table I. Potassium benzoate and triethylammonium benzoate were used in place of the acetate salts. In this way (IV) was obtained from α-bromo-β-piperidinobenzylacetophenone and (V) from α-bromo-β-morpholinobenzylacetophenone. The products were recrystallized from absolute alcohol.

Hydrolysis of α-Acetoxy-β-piperidinobenzylacetophenone.—a. Action of sodium methoxide:[2] A methyl alcohol solution of sodium methoxide reacted rapidly with this compound (I) to produce phenylbenzyldiketone, which was identified as its *o*-phenylenediamine derivative, benzylphenylquinoxaline, m. p. 98–99°.[9]

b. Aqueous Sulfuric Acid.—Six hours of refluxing of (I) with 15% sulfuric acid did not change this compound.

c. Alcohol and Morpholine.—In an attempt to replace the acetoxy group with an amino group, an alcohol solution of (I) and three equivalents of morpholine was refluxed for twenty hours. The starting material was recovered unchanged.

d. Alcoholic Hydrogen Chloride.—One gram of (I) was refluxed for five hours with a mixture of 25 ml. of alcohol and 10 ml. of 35% hydrochloric acid. From this experiment 0.45 g. of phenylbenzyldiketone identified as the quinoxaline[9] was obtained. Also recovered was 0.05 g. of the starting material (III).

Reduction of α-Acetoxy and α-Benzoxy-β-aminobenzylacetophenones.—Several attempts were made to reduce the acetoxy compound (I) by the usual catalytic methods using hydrogen at 45 lb./sq. in. and employing as catalysts Raney nickel, platinum oxide and palladium on charcoal. Both acid and neutral solvents were used. In no case was a reduction of pressure observed and all of the starting material was recovered.

These compounds were readily reduced by refluxing them for thirty minutes with an ether solution containing two molar equivalents of lithium aluminum hydride. The excess reducing agent was destroyed by the dropwise addition of water to the reaction mixture. The ether layer was washed with water, dried and concentrated. Addition of petroleum ether caused white crystalline products to

(8) Cromwell, THIS JOURNAL, 62, 2897 (1940).

(9) Widman, *Ber.*, 49, 484 (1916).

form which were purified by recrystallization from alcohol–water solutions. In this way the diol (VI) was obtained from both (I) and (IV) and the diol (VII) from (III).

A 1.5-g. sample of the diol (VI) was refluxed for thirty minutes with 4 ml. of acetic anhydride. The reaction mixture was cooled and poured into 200 ml. of saturated sodium bicarbonate solution. The oily precipitate was removed and crystallized from a mixture of ether and petroleum ether to give 1,3-diphenyl-1,2-diacetoxy-3-piperidinopropane (X).

Preparation of 1,1,3-Triphenyl-3-piperidinopropanediol-1,2 (VIII).—(a) A suspension of 5.0 g. of the acetoxy compound (I) in 200 ml. of dry ether was added to a dry ether solution containing eight molar equivalents of phenylmagnesium bromide. After refluxing for two hours the reaction mixture was decomposed with ice and ammonium chloride. The product was separated as the hydrochloride from the dried ether solution. The free base was liberated in sodium bicarbonate solution and recrystallized from a mixture of ether and petroleum ether, wt. 3.66 g., colorless crystals.

(b) Five grams of (I) reacted with eight molar equivalents of phenyl lithium in a dry ether solution to give 3.80 g. of (VIII). The procedure for isolating the product was the same as in (a) above.

Preparation of 2,4-Diphenyl-4-piperidinobutanediol-2,3 (IX).—This product was obtained from the reaction of (I) with eight equivalents of methylmagnesium iodide in dry ether solution. The procedure was the same as in method (a) for the preparation of (VIII) as given above.

Summary

Methods have been devised for the synthesis of α-acetoxy and α-benzoxy-β-aminobenzylacetophenones. Some of these have been converted into various new types of aminopropyleneglycols by the action of lithium aluminum hydride, Grignard reagents and phenyl lithium.

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α-Hydroxy-β-amino Ketones and Derivatives

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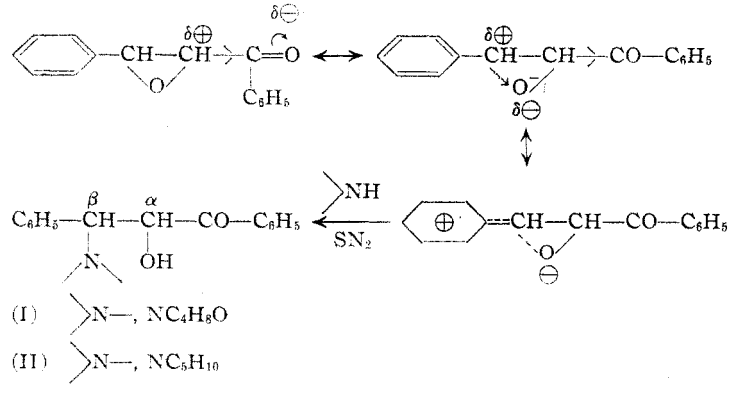
This study was undertaken as a companion research of that reported in the preceding paper.[1] Although no previous investigation of the reaction of an amine with an epoxyketone has been reported it seemed reasonable that such experiments should result in the formation of either α-hydroxy-β-aminoketones or α-amino-β-hydroxyketones or both. Such products on acetylation might then be expected to give acetoxyaminoketones either identical with or position isomers of those obtained from α-bromo-β-aminobenzylacetophenone as reported in the preceding paper.[1]

Fourneau and Billeter[2] have reported that aniline and *p*-phenetidine react with phenyl glycidic ester to give the α-amino products, but with ammonia and aliphatic amines to form the β-amino-α-hydroxy esters.

Our preliminary investigations have now shown that the major products resulting from the reaction of epoxybenzylacetophenone with morpholine and piperidine are the α-hydroxy-β-aminoketones (I) and (II), respectively. The reactions in non-polar solvents such as benzene or ether were extremely slow giving low yields of products. In the absence of solvents these reactions proceeded very rapidly but produced a considerable amount of decomposition products. The best conditions discovered involved the use of methyl alcohol as a solvent at room temperature.

The location of the hydroxy group in these molecules was established by converting them to the corresponding α-chloro-β-aminoketone hydrochlorides (III) and (IV) which have been reported previously.[3] The position of the chlorine was checked through the use of the iodine release method which has been described.[3]

A kinetic study of the reaction of epoxyketones with amines has been undertaken in this laboratory. The above observed effect of solvent change on the speed of the reaction as well as the established structure of the products points to the mechanism.



The partial positive charge at the β-position should be more favored by resonance than at the α-position. A more detailed discussion of this mechanism must await further experimental results.

The acetylation of the α-hydroxy-β-aminoketones (I) and (II) gave the α-acetoxy-β-aminoketones (V) and (VI). The fact that these products

(1) Cromwell and Starks, THIS JOURNAL, **72**, 4108 (1950).

(2) Fourneau and Billeter, *Bull. soc. chim.*, [5] **7**, 593 (1940).

(3) Cromwell and Wankel, THIS JOURNAL, **70**, 1320 (1948).