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

BY NORMAN H. CROMWELL AND NORVAL G. BARKER

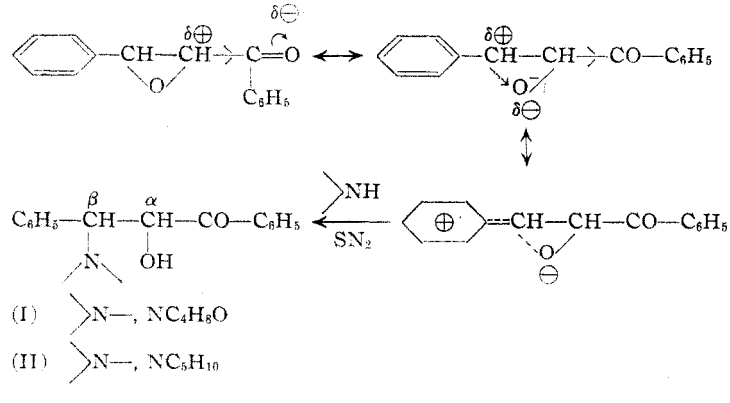
This study was undertaken as a companion research of that reported in the preceding paper.[1] Although no previous investigation of the reaction of an amine with an epoxyketone has been reported it seemed reasonable that such experiments should result in the formation of either α-hydroxy-β-aminoketones 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.



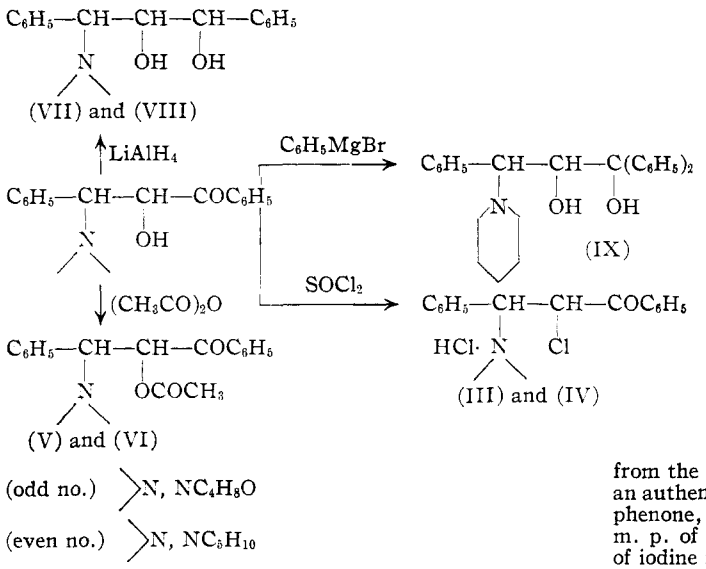
The partial positive charge at the β-position should be more favored by resonance than at the α-position. A more detailed discussion of this mechanism must await further experimental results.

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).



were identical with the acetoxyaminobenzylacetophenones produced from the reactions of α-bromo-β-aminobenzylacetophenones with acetate salts was established. Thus these two parallel investigations served to establish the structures of the products from these latter reactions.[1]

The α-hydroxy-β-aminoketones were readily reduced to the corresponding aminopropyleneglycols (VII) and (VIII). The product (VIII) had been reported previously.[1] α-Hydroxy-β-piperidinobenzylacetophenone (II) reacted readily with excess phenylmagnesium bromide to produce 1,1,-3-triphenyl-3-piperidinopropanediol-1,2 (IX) which was identical with that obtained by the reaction of the same Grignard reagent with α-acetoxy-β-piperidinobenzylacetophenone.[1]

Acknowledgment.—This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service.

Experimental[4]

α-Hydroxy-β-aminobenzylacetophenones (I) and (II).—A mixture of 4.48 g. (0.02 mole) of epoxybenzylacetophenone[5] and 0.04 mole of the corresponding amine in 20 ml. of methanol was warmed slightly to obtain solution and allowed to stand at room temperature. The reaction mixture containing morpholine was concentrated by partial evaporation of the solvent under vacuum, after standing for two days, to give 5.0 g. (80% yield) of (I), m. p. 155–156°; recrystallized from absolute alcohol.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.28; H, 6.80; N, 4.50. Found: C, 73.23; H, 6.96; N, 4.61.

The solution containing piperidine was best concentrated by evaporation of part of the methyl alcohol under vacuum, after standing for only one day. Further reaction time reduced the yield and produced a tar. The yield of colorless needles (II) was 4.18 g. (68%), m. p. 139–140°; recrystallized from 95% alcohol.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49; N, 4.53. Found: C, 77.50; H, 7.51; N, 4.61.

(4) Microanalyses for carbon, hydrogen and nitrogen were determined by the Clark Microanalytical Laboratory, Urbana, Ill.

(5) Kohler, Richtmyer and Hester, THIS JOURNAL, **53**, 213 (1931).

α-Chloro-β-aminobenzylacetophenone Hydrochlorides (III) and (IV).—A 0.1 mole sample of the α-hydroxy-β-aminoketone was dissolved in 25 ml. of chloroform and treated with 6 ml. of thionyl chloride. The solution was refluxed for one-half hour, cooled to room temperature, and diluted with about 200 ml. of dry ether. The precipitate was washed with ether several times and recrystallized from a mixture of methyl alcohol and acetone.

Compound (I) gave 2.2 g. (61% yield) of (III), m. p. 146–148°, identical with an authentic sample of α-chloro-β-morpholinobenzylacetophenone hydrochloride.[3] This product (I) released 96.2% of one equivalent of iodine from an acidified potassium iodide solution in twenty minutes.[3] A sample of (III) was converted to the free base by shaking it with a mixture of benzene and saturated aqueous sodium bicarbonate solution. Two products, in nearly equal amounts, were obtained from the benzene layer. One of them was identical with an authentic sample of α-chloro-β-morpholinobenzylacetophenone, m. p. 126–127°.[3] The second product had a m. p. of 114–116° and released 90.2% of one equivalent of iodine in twenty minutes.

Anal. Calcd. for $C_{19}H_{20}NO_2Cl$: C, 69.19; H, 6.11. Found: C, 69.01; H, 6.32.

These two products are apparently different racemic mixtures of α-chloro-β-morpholinobenzylacetophenone. The α-hydroxy-β-piperidinobenzylacetophenone (II) produced 1.26 g. (34%) of a colorless crystalline product, m. p. 140–142°, identical with an authentic sample of α-chloro-β-piperidinobenzylacetophenone hydrochloride[3]; iodine release in twenty minutes was 87%.

α-Acetoxy-β-aminobenzylacetophenones (V) and (VI).—On warming slightly with a small amount of acetic anhydride 0.5 g. of (I) gave 0.45 g. (80% yield) of colorless crystals (V), m. p. 187–188°, identical with the previously prepared compound.[1] In a similar experiment 0.1 g. of (II) produced 0.09 g. (80% yield) of (VI), m. p. 160–161°, identical with the compound prepared by Cromwell and Starks.[1]

1,3-Diphenyl-3-amino-1,2-propanediols (VII) and (VIII).—A sample of the α-hydroxy-β-aminoketone was placed in the cup of a Soxhlet extraction apparatus and refluxed for four hours with a dry ether solution of four molar equivalents of lithium aluminum hydride. The reaction mixture was decomposed with water and the product isolated from the ether layer by evaporation of the solvent. The products were recrystallized from methanol. In this way 3.37 g. of (I) gave 1.64 g. (50% yield) of (VII), m. p. 165–166°.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.71; H, 7.21; N, 4.66.

The α-hydroxy-β-aminoketone (II) (0.5 g.) produced 0.36 g. (72% yield) of (VII), m. p. 150–151°, identical with 1,3-diphenyl-3-piperidinopropanediol-1,2 reported by Cromwell and Starks.[1]

1,1,3-Triphenyl-3-piperidinopropanediol-1,2 (IX).—A mixture of 100 ml. of dry ether and 50 ml. of dry benzene containing 5.0 g. (0.016 mole) of (II) was added over a period of one-half hour to a dry ether solution containing 0.065 mole of phenylmagnesium bromide. After refluxing for forty-five minutes the reaction mixture was cooled and decomposed with an ice and ammonium chloride mixture. Evaporation of the dried ether solution gave a yellow oil which was crystallized from absolute alcohol; m. p. 173–174°; wt. 2.0 g. (32% yield). This product was identical with that reported by Cromwell and Starks.[1]

Summary

1. Epoxybenzylacetophenone has been found to react with the amines, morpholine and piperidine, to produce α-hydroxy-β-aminobenzylacetophenones. A tentative mechanism has

been proposed for these reactions.

2. The α-hydroxy-β-aminoketones are readily converted to the corresponding α-chloro and α-acetoxy-β-aminobenzylacetophenones. The latter are identical with the products from the reactions of α-bromo-β-aminobenzylacetophenones with acetate salts.[1]

3. The α-hydroxy-β-aminobenzylacetophenones react with lithium aluminum hydride and with phenylmagnesium bromide to produce aminopropyleneglycols.

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An Experimental Study of Chromatography on Silicic Acid–Celite. The Applicability of the Theory of Chromatography[1,2]

BY KENNETH N. TRUEBLOOD[3] AND EARL W. MALMBERG[4]

Introduction

Although the theory of the simple adsorption chromatogram has been discussed extensively during the past decade,[5-10] comparatively few experimental tests of the predictions of the proposed theories have been reported. Furthermore, those experimental studies which have been described present a somewhat incomplete and conflicting picture. The importance of the simple adsorption chromatogram, not only as a practical laboratory tool in its own right, but also as the fundamental chromatographic experiment, prompted the present investigation, which was designed to provide quantitative experimental data suitable for testing the various theories which may be applied to the simple Tswett chromatogram, in particular in their application to chromatograms on columns of silicic acid–Celite.

The first careful experimental study of the fundamental factors involved in simple adsorption chromatography was made by Weil-Malherbe[11] who investigated a few simple systems on alumina and silica gel by means of analyses of the filtrate from the column and found in general fairly good agreement with the theory proposed by Weiss.[7] Likewise, DeVault[6] was able to explain reasonably well on the basis of his theory the rather limited data of Cassidy and Wood[12] on the development of lauric acid on carbon. On the other hand, LeRosen[13] could obtain no more than partial qualitative agreement with theory in his experiments with *o*-nitroaniline in benzene on silicic acid, and similarly Thomas[10] found at best only rough qualitative agreement with his kinetic theory of chromatography in experiments with anthracene in cyclohexane on alumina. Jacobs and Tompkins[14] encountered some difficulty in reconciling with theory the results of their studies of the development of certain inorganic ions on alumina, but the more recent experiments of Glueckauf and Coates have almost completely resolved these difficulties. Indeed, as a result of the excellent work of the latter investigators and of Boyd and his coworkers,[15] and Mayer and Tompkins,[16] the theoretical treatment of the special field of ion-exchange chromatography now rests on a firm experimental foundation. Similarly, the theories which have been developed for the special adsorption analysis techniques of Tiselius have been tested extensively and found entirely adequate.[17] Although much of the theory applicable to ion-exchange columns may be considered to apply also to the closely analogous Tswett adsorption chromatogram, the theories of frontal analysis and displacement development[17] are of no direct aid in consideration of the simple adsorption chromatogram; however, their success does demonstrate that straightforward reasoning on the basis of measured adsorption isotherms can for many systems lead to the correct predictions of the chromatographic behavior of mixtures under particular conditions. Several earlier attempts[18] to find a correlation between the adsorption isotherms and relative

(1) Presented in part before the Division of Physical and Inorganic Chemistry at the 115th National Meeting of the American Chemical Society in San Francisco, April 1, 1949.

(2) Aided by a grant from the National Foundation for Infantile Paralysis.

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(11) H. Weil-Malherbe, *J. Chem. Soc.*, 303 (1943).

(12) H. G. Cassidy and S. E. Wood, THIS JOURNAL, **63**, 2628 (1941).

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(16) S. W. Mayer and E. R. Tompkins, *ibid.*, **69**, 2866 (1947).

(17) S. Claesson, *Arkiv. Kemi Mineral. Geol.*, **23A**, No. 1 (1946).

(18) See for example (a) A. Lottermoser and K. Edelmann, *Koll. Z.*, **83**, 262 (1938); (b) H. G. Cassidy, THIS JOURNAL, **62**, 3073, 3076 (1940).