[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FACULTY OF SCIENCE, HOKKAIDO UNIVERSITY]

Synthesis of 1-Phenylpropane Derivatives. I[1]

BY TAKESHI MATSUMOTO AND KUNIO HATA

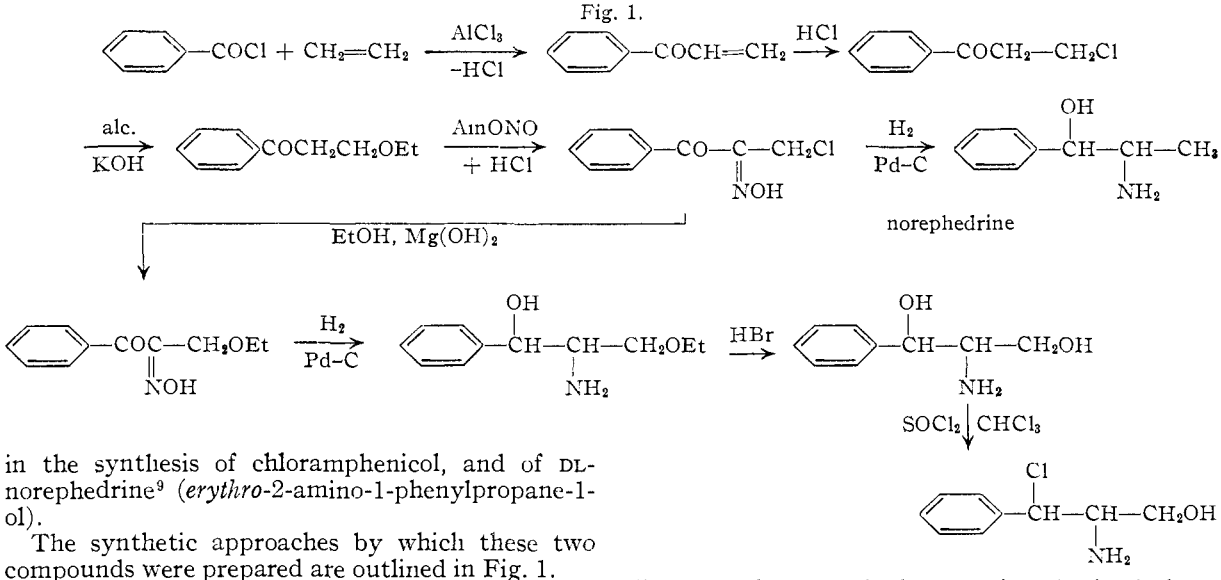
RECEIVED MAY 11, 1957

A novel stereospecific route for DL-*threo*-2-amino-1-phenyl-1-chloro-propane-3-ol and DL-norephedrine has been developed.

A number of synthetic routes[2-7] have been devised for the preparation of the antibiotic chloramphenicol. However, in view of its remarkable therapeutic properties, it seems still desirable to develop a novel synthetic approach to this compound. Synthesis of a number of 1-phenylpropane derivatives, which are structurally related to chloramphenicol, was therefore attempted. As Part I of this series of investigation, the writers wish to report a new synthesis of DL-*threo*-2-amino-1-phenyl-1-chloropropane-1-ol, a well-known key compound[8] in the synthesis of chloramphenicol, and of DL-norephedrine[9] (*erythro*-2-amino-1-phenylpropane-1-ol).

The synthetic approaches by which these two compounds were prepared are outlined in Fig. 1.

Fig. 1.



Phenyl vinyl ketone was prepared by the method of Norris and Couch[10] by condensing ethylene and benzoyl chloride in presence of anhydrous aluminum chloride. The yield was raised to 70% by a modified procedure that makes use of tetrachloroethane as the solvent. The oily product was then condensed with hydrogen chloride in dry ether to give rise to crystalline β-chloropropiophenone[11] which in turn was converted to α-isonitroso-β-chloropropiophenone, by means of amyl nitrite and hydrochloric acid in alcoholic solution. Attempts to prepare the isonitroso compound by condensation with amyl nitrite in presence of sodium ethoxide resulted in the formation of resinous products, and the desired product was not obtained. The isonitroso compound also is obtained by treating β-ethoxypropiophenone, derived from the β-chloro compound by Kohler's method[11] with amyl nitrite and ethanolic hydrogen chloride. Since β-ethoxypropiophenone is obtained from phenyl vinyl ketone and ethanolic hydrogen chloride,[11] similar treatment of phenyl vinyl ketone itself with amyl nitrite and ethanolic hydrogen chloride should, and in fact does, lead to α-isonitroso-β-chloropropiophenone. By this simplified procedure the isonitroso compound was obtained in excellent yield. Reduction of this isonitroso compound with hydrogen in the presence of palladium–charcoal was effected by the use of Hartung's[12] general procedure for the preparation of alkamines. As a result of the reduction the chlorine atom in the β-position was hydrogenolyzed, and norephedrine was obtained in excellent yield. The reaction followed a stereospecific course as noted by Hartung[13] in other similar instances, and the possible by-product, nor-ψ-ephedrine, could not be isolated. Replacement of the chlorine atom in α-isonitroso-β-chloropropiophenone by an ethoxyl group presented considerable difficulty. The isonitroso compound readily gave a resinous product by the action of

(1) Presented before the 8th annual meeting of the Chemical Society of Japan, April, 1955.

(2) J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., THIS JOURNAL, **71**, 2463 (1949); L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469 (1949); M. C. Rebstock, *J. Org. Chem.*, **19**, 851 (1954).

(3) G. Carrara and his collaborators, *Gazz. chim. ital.*, **79**, 856 (1949); **81**, 142 (1951); **82**, 325, 674 (1952); *C. A.*, **44**, 7268 (1950); **45**, 9029 (1950); **47**, 9300 (1953); **48**, 5148 (1954).

(4) S. Tatsuoka and his collaborators, *J. Pharm. Soc. Japan*, **71**, 604, 608, 612, 774, 776, 778, 781 (1951), and references cited therein.

(5) J. Kollonitsch, *Experientia*, **13**, 476 (1954).

(6) M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953).

(7) T. Taguchi, M. Tomoeda and T. Ishida, *J. Pharm. Soc. Japan.*, **75**, 666 (1955).

(8) S. Ikuma and M. Nagawa, *ibid.*, **72**, 310 (1952); S. Ikuma, *ibid.*, **72**, 947 (1952).

(9) L. Reti, "Ephedra Bases," in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. III, Academic Press, Inc., Publishers, New York, N. Y., 1953, pp. 339–362.

(10) H. B. Couch and J. F. Norris, THIS JOURNAL, **42**, 2329 (1920).

(11) E. P. Kohler and B. M. Coll, *Am. Chem. J.*, **42**, 375 (1909).

(12) W. H. Hartung and F. Crossley, *Org. Syntheses*, **16**, 44 (1936).

(13) Y. C. Chang and W. H. Hartung, THIS JOURNAL, **75**, 89 (1953).

alkaline reagents, hence the usual method involving the use of this type of reagents could not be employed. However, the difficulty was solved by the use of colloidal magnesium hydroxide suspended in ethanol. By this method, the desired α-isonitroso-β-ethoxypropiophenone was obtained in good yield. Attempts to prepare this compound from β-ethoxypropiophenone and amyl nitrite in presence of hydrogen chloride resulted in the formation of α-isonitroso-β-chloropropiophenone, as noted above.

The ethoxyisonitroso derivative thus obtained was then hydrogenated in the presence of palladium–charcoal, again by the use of Hartung's[12] procedure. The ethoxyisonitroso compound absorbed the expected 3 moles of hydrogen, but the hydrochloride of the resultant base, as well as the base itself, could not be obtained crystalline, although the 3,5-dinitrobenzoic acid salt crystallized. These results suggested that the reduction did not entirely follow the stereospecific course and gave rise to a mixture of *threo*- and *erythro*-isomers. The crude hydrochloride was therefore hydrolyzed without further purification with constant boiling hydrobromic acid. The product, which seemed to consist largely of *threo*- and *erythro*-2-amino-1-phenylpropane-1,3-diol again was not obtained crystalline, although its dinitrobenzoic acid salt crystallized and showed correct elemental composition. According to Ikuma,[8] both the *threo*- and *erythro*-2-amino-1-phenylpropane-1,3-diol give rise to *threo*-2-amino-1-phenyl-1-chloropropane-3-ol when treated with thionyl chloride regardless of the molecular configuration of the starting materials. The above oily product should therefore afford *threo*-1-chloro derivative by this method and in fact did so in satisfactory yield. The key intermediate in the chloramphenicol synthesis has thus been obtained in good over-all yield.

Experimental[14]

Phenyl Vinyl Ketone.—A mixture of benzoyl chloride (0.22 mole) and aluminum chloride (0.22 equivalent) was heated gently to give an adduct.[15] The adduct, obtained as orange crystals, was dissolved in tetrachloroethane. Ethylene was then passed through the solution for 30 hours at 2–5° with vigorous stirring. The ethylene was generated by the catalytic dehydration of ethanol and purified by washing successively with aqueous sodium hydroxide, a saturated solution of mercuric chloride in 3 *N* hydrochloric acid and then with concentrated sulfuric acid. The resultant viscous, reddish brown solution was poured carefully into a mixture of ice and dilute hydrochloric acid. The mixture was extracted with ether, and the extract was evaporated under reduced pressure. The residue was then distilled *in vacuo*, and a fraction boiling at 115–117° (18 mm.), was collected. The product contains small amounts of β-chloropropiophenone and unreacted benzoyl chloride. To remove these impurities, the product was washed with aqueous sodium hydroxide and redistilled; yield 70%. On treating this compound with phenylhydrazine in ethanol, yellow crystals of 1,3-diphenylpyrazoline[10,11,16] were obtained. The pyrazoline was recrystallized from alcohol in the form of needles, m.p. 152–153°.

β-Chloropropiophenone.—This compound was prepared from phenyl vinyl ketone according to Kohler's procedure.[11] The product, which melted at 53–55°, was obtained in 90% yield.

α-Isonitroso-β-chloropropiophenone.—β-Chloropropiophenone (1 part) was dissolved in ethanol (10 parts) saturated with hydrogen chloride and to this solution one equivalent of amyl nitrite was added under ice cooling. After the addition was completed, the mixture was set aside at room temperature for 2 days. The resulting red solution was evaporated *in vacuo*, and the residue was extracted with benzene–petroleum ether (1:1). Evaporation of the extract left crude α-isonitroso-β-chloropropiophenone in large plates. Recrystallization from petroleum ether gave pure product, melting at 113–114°; yield 85%.

Anal. Calcd. for $C_9H_8ClNO_2$: N, 7.12. Found: N, 6.87.

On processing β-ethoxypropiophenone by the same procedure, crystals melting at 113° were obtained along with brown resinous products. The product m.p. 113° showed no melting point depression on admixture with α-isonitroso-β-chloropropiophenone prepared by the above method. Treatment of phenyl vinyl ketone in the same manner afforded a 70% yield of α-isonitroso-β-chloropropiophenone.

α-Isonitroso-β-ethoxypropiophenone.—To an ethanolic solution of α-isonitroso-β-chloropropiophenone an excess amount of gelatinous, wet magnesium hydroxide (freshly precipitated by addition of ammonia to an aqueous solution of magnesium sulfate) was added and the solution was stirred for several hours at room temperature. The pale yellow solution was filtered from excess magnesium hydroxide along with the magnesium chloride formed. Evaporation of the solution under reduced pressure left crude α-isonitroso-β-ethoxypropiophenone as a yellow solid. The product was recrystallized from carbon tetrachloride in white needles, m.p. 84.5°; yield 85%. The product showed a positive ferrous sulfate color test[17] for the isonitroso group and the presence of the ethoxyl group was indicated by a micro Zeisel test.

Anal. Calcd. for $C_{11}H_{13}NO_3$: N, 6.76. Found: N, 6.96.

Catalytic Hydrogenation of α-Isonitroso-β-chloropropiophenone.—Absolute methanol, saturated with hydrogen chloride, was employed as the solvent. As catalyst, 30% Pd–C, prepared by Pfau–Plattner's[18] technique was used. The α-isonitroso-β-chloropropiophenone absorbed 4 moles of hydrogen after shaking 4 hours in the presence of catalyst. The solution was filtered from the catalyst, evaporated under reduced pressure and the pale yellow residue was crystallized from methanol–ether. The crude norephedrine hydrochloride product was recrystallized from methanol–ether in white plates, m.p. 188–190°; yield 90%.

Anal. Calcd. for $C_9H_{14}ClNO$: N, 7.42. Found: N, 7.41.

This hydrochloride was added to a concentrated solution of sodium hydroxide and the solution was extracted with ether. After drying, the solution was evaporated and crude norephedrine was obtained as white crystals. The product was recrystallized from ether, m.p. 102–103°. This melting point is identical with that recorded in the literature.[19]

Anal. Calcd. for $C_9H_{13}NO$: C, 71.47; H, 8.68. Found: C, 71.42; H, 8.43.

On heating the base with acetic anhydride at 100° for 30 minutes, an N-acetyl derivative was formed. After removal of the solvent under reduced pressure, the product, N-acetylnorephedrine, was recrystallized from ether, m.p. 134–135°, identical with the melting point reported in the literature.[19]

2-Amino-1-phenyl-3-ethoxypropane-1-ol Hydrochloride.—α-Isonitroso-β-ethoxypropiophenone was hydrogenated as described for α-isonitroso-β-chloropropiophenone. In this case, 3 moles of hydrogen was absorbed. After the removal of catalyst by filtration, the filtrate was evaporated *in vacuo*, to leave 2-amino-1-phenyl-3-ethoxypropane-1-ol hydrochloride as a colorless glass. All attempts to crystallize this product from various solvents were unsuccessful. To obtain the free base, concentrated sodium hydroxide was added to the hydrochloride and the resulting solution was extracted with ether. The ether extract was dried and evaporated. The base was obtained as a pale yellow oil. The yield of the base from the isonitroso compound was about 90%. On addition of a solution of 3,5-dinitrobenzoic

(14) All the melting points are uncorrected.

(15) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, pp. 192–194.

(16) F. Ramirez and A. F. Kirby, THIS JOURNAL, **75**, 6026 (1953).

(17) M. A. Whiteley, *J. Chem. Soc.*, 44 (1903).

(18) A. St. Pfau and Pl. A. Plattner, *Helv. Chim. Acta*, **23**, 781 (1940).

(19) N. Nagai, *J. Pharm. Soc. Japan*, **47**, 102 (1927).

acid in chloroform to a solution of the base in the same solvent, the salt, m.p. 117–119°, was precipitated.

2-Amino-1-phenylpropane-1,3-diol.—2-Amino-1-phenyl-3-ethoxypropane-1-ol (1 g.) was dissolved in hydrobromic acid (48%, 7 ml.) and the solution was refluxed for one and a quarter hours. After cooling, the solution was separated by filtration from a small amount of resinous product which was formed and concentrated under reduced pressure. Water was then added to the residue and the solution was again concentrated under reduced pressure. This process was repeated three times to remove hydrobromic acid as completely as possible. Crude 2-amino-1-phenylpropane-1,3-diol hydrobromide was obtained as a reddish orange sirup. The product was then dissolved in concentrated sodium hydroxide and the solution was extracted with ethyl acetate. The extract was dried with anhydrous magnesium sulfate and evaporated to remove the solvent. Crude 2-amino-1-phenylpropane-1,3-diol was obtained as an oil in good yield. This base also could not be induced to form crystals. However, on addition of a solution of the base in chloroform to a solution of 3,5-dinitrobenzoic acid in the same solvent, the salt separated as a white precipitate which crystallized from an alcohol–ether mixture in white plates, m.p. 175–177°.

Anal. Calcd. for $C_{16}H_{17}N_3O_8$: N, 11.06. Found: N, 10.90.

2-Amino-1-phenyl-1-chloropropane-3-ol.—The oily 2-amino-1-phenylpropane-1,3-diol, prepared as described above was reconverted to sirupy hydrochloride through the addition of alcoholic hydrogen chloride followed by removal of the solvent. The hydrochloride was suspended in chloroform, and a slight excess of thionyl chloride in the same solvent was added. After standing overnight, the solution was evaporated *in vacuo* at room temperature to give a pale yellow solid. The solid was dissolved in absolute methanol and to this solution absolute ether was added. On keeping at room temperature, the 2-amino-1-phenyl-1-chloropropane-3-ol hydrochloride separated out as colorless plates in good yield. A sample was recrystallized from methanol ether and analyzed, m.p. 192–193°.

Anal. Calcd. for $C_9H_{13}Cl_2NO$: N, 6.37. Found: N, 6.43.

SAPPORO, HOKKAIDO, JAPAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Aminolysis Products of 1-Chloro-2-hydroxy-3-butene, 1-Hydroxy-2-chloro-3-butene and 1,2-Epoxy-3-butene

BY F. F. BLICKE AND JOHN H. BIEL[1,2]

RECEIVED MAY 16, 1957

1-Chloro-2-hydroxy-3-butene, 1-hydroxy-2-chloro-3-butene and 1,2-epoxy-3-butene reacted with aqueous solutions of secondary amines to form 1-dialkylamino-2-hydroxy-3-butenes. When 1-hydroxy-2-chloro-3-butene was allowed to react with anhydrous diethylamine, the principal reaction product was 1-hydroxy-4-diethylamino-2-butene, the formation of which was probably due to an allylic rearrangement. The basic olefinic alcohols were hydrogenated to the corresponding known basic alkanols. Various derivatives of the alcohols were prepared.

During a study of the preparation of certain basic alcohols, we allowed 1-chloro-2-hydroxy-3-butene (I) to react with 94% aqueous diethylamine and obtained 1-diethylamino-2-hydroxy-3-butene (III) in good yield. Compound III also was formed in about the same yield by interaction of 1-hydroxy-2-chloro-3-butene (IV) with 60% aqueous diethylamine. We believe that the formation of the basic butene III from IV, and possibly also from I, was *due to* the intermediate formation of 1,2-epoxy-3-butene (II).[3] In separate experiments it was found that the epoxybutene reacted with 94 and 60% aqueous diethylamine, respectively, to yield III. Incidentally, it was discovered that the speed of these reactions was greatly accelerated by the presence of a small amount of benzenesulfonic acid.

Hydrogenation of the basic butene III yielded 1-diethylamino-2-butanol (V), a product which has been prepared by other procedures.[4,5]

1-Chloro-2-hydroxy-3-butene (I) reacted with aqueous dimethylamine and with aqueous piperidine, in the same manner as with diethylamine, to form 1-dimethylamino- and 1-piperidino-2-hydroxy-3-butene, respectively. The 1-dimethylamino-2-hydroxy-3-butene was hydrogenated to form 1-dimethylamino-2-butanol which was converted by thionyl chloride into 1-dimethylamino-2-chlorobutane.

When 1-hydroxy-2-chloro-3-butene (IV) was allowed to react with anhydrous diethylamine, the principal reaction product was 1-hydroxy-4-diethylamino-2-butene (VI) but a small amount of III was also formed.

The hydrobromides of III and VI were obtained only in the form of oils, but the dibromide hydrobromides (X and X′) were isolated in crystalline form.

Initially, we considered the product obtained from IV and anhydrous diethylamine to be a compound represented by structure VI′. This substance (VI′), upon hydrogenation, would yield 2-diethylaminobutanol (VII′) while a compound which possessed structure VI would be converted into 4-diethylamino-butanol (VII). Both alcohols VII[6–9] and VII′[5,10] have been obtained by other procedures. The basic alcohol which we obtained possessed properties which correspond to those described for VII.

(1) This paper represents part of a dissertation submitted by J. H. Biel in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1947.

(2) Frederick Stearns and Co. Fellow.

(3) F. C. Whitmore, H. S. Mosher, D. P. Spalding, R. B. Taylor, G. W. Moersch and W. H. Yanko (THIS JOURNAL, **68**, 531 (1946)) reported that 1-hydroxy-2,3-dibromopropane and piperidine reacted to form 1-hydroxy-2,3-dipiperidino-1,3-dipiperidino-2-hydroxypropane, and suggested that the latter substance probably was produced through the intermediate formation of 1,2-epoxy-3-bromopropane.

(4) J. Houben and K. Führer, *Ber.*, **47**, 75 (1915).

(5) W. T. Olson and F. M. Whitacre, THIS JOURNAL, **65**, 1019 (1943).

(6) O. J. Magidson and I. T. Strukov, *Arch. Pharm.*, **271**, 569 (1933).

(7) W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, THIS JOURNAL, **59**, 2248 (1937).

(8) British Patent 565,745; *C. A.*, **40**, 5534 (1946).

(9) A. W. D. Avison, *J. Appl. Chem.*, **1**, 469 (1951); *C. A.*, **46**, 11109 (1952).

(10) E. Rajner, E. Cerknovnikow and P. Stern, *Arch. Pharm.*, **281**, 78 (1943).