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

Synthesis of 1-Phenylpropane Derivatives. II

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2-Amino-3-ethoxypropiophenone hydrochloride afforded *erythro*-2-amino-3-ethoxy-1-phenyl-1-propanol as a single product on being reduced by sodium borohydride or by catalytic hydrogenation. By contrast, 2-acetamido-3-ethoxypropiophenone afforded a mixture of *threo*- and *erythro*-2-acetamido-3-ethoxy-1-phenyl-1-propanol as a result of the same treatments. Hydrolysis of *erythro*-2-acetamido-3-ethoxy-1-phenyl-1-propanol acetate with hydrogen bromide-acetic acid-acetic anhydride replaces acetoxy with hydroxyl group with inversion, while treatment of *erythro*-2-amino-3-ethoxy-1-phenyl-1-propanol with hydrobromic acid gives without inversion *erythro*-2-amino-1-phenylpropane-1,3-diol. The steric course of these and related reactions has been discussed.

In the previous paper[1] a stereospecific synthesis of DL-*threo*-2-amino-1-chloro-1-phenyl-3-propanol and DL-norephedrine starting with β-chloropropiophenone was described. The authors now wish to report further syntheses of a number of related 1,2,3-trisubstituted 1-phenylpropane derivatives from the same starting material. The syntheses which have been achieved are summarized in Figs. 1 and 2, and Tables I and II. Among the processes described therein, the stereochemistry of the reduction of aminopropiophenone derivatives seems to be of special interest. While 2-acetamidopropiophenones (V and X) were reduced to a mixture of *threo*- and *erythro*-2-acetamido-1-phenyl-1-propanol derivatives by catalytic hydrogenation as well as by means of sodium borohydride, the corresponding free 2-aminopropiophenones were reduced through a stereospecific path to *erythro*-2-amino-1-phenyl-1-propanol derivatives by both methods (Table I and Fig. 2).

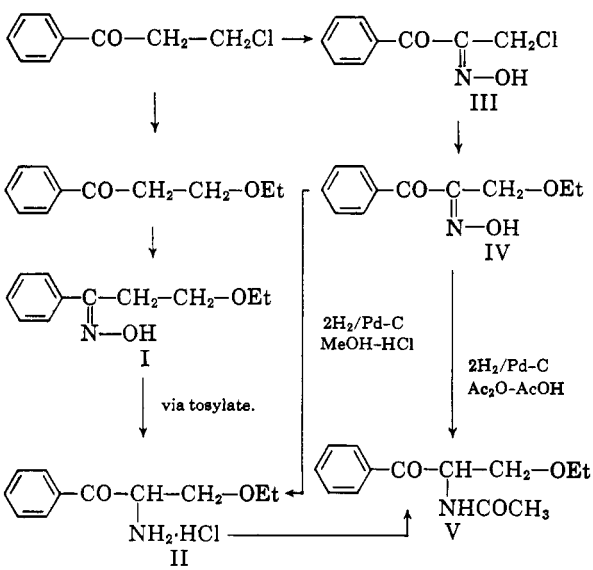


Fig. 1. Formation of Aminoketones

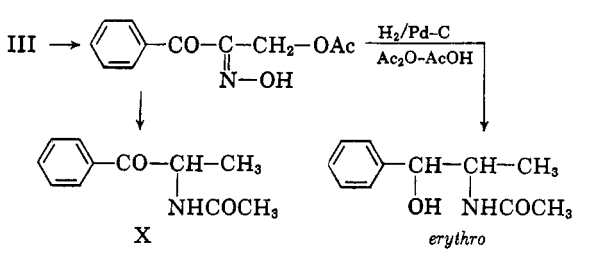


Fig. 2. Hydrogenolysis at C-3

TABLE 1

REDUCTION OF AMINO KETONES

Starting Material	Reagent	Product
IV	H_2/Pd-C/CH_3OH-HCl	*erythro*-VI (55%) *threo*-VI
IV	H_2/Pd-C/$(C_2H_3O)_2O$-$C_2H_3O_2$	*erythro*-VII *threo*-VII
II	H_2/Pd-C/CH_3OH	*erythro*-VI (88.5%)
II	$NaBH_4$	*erythro*-VI (94%)
V	$NaBH_4$	*erythro*-VII *threo*-VII

TABLE 2

INVERSION AND RETENTION AT C-1

Starting Material	Reagent	Product
erythro-VI	aq. HBr	*erythro*-IX
erythro-VIII	HBr-$C_2H_3O_2H$	*threo*-IX *erythro*-IX
erythro-VIII	HBr-$C_2H_3O_2H$-$(C_2H_3O)_2O$	*threo*-VII

At first, attempts were made to oximate β-ethoxypropiophenone, which in turn was obtained from β-chloropropiophenone in almost quantitative yield by a modification of Kohler's[2] method. Usual methods for oximation afforded 3-phenyl-isoxazoline[3] and the desired oxime I was not obtained.

(1) T. Matsumoto and K. Hata, *J. Am. Chem. Soc.*, **79**, 5506 (1957).

(2) E. P. Kohler and B. M. Coll, *Am. Chem. J.*, **42**, 375 (1909). Original method afforded a product containing considerable amount of acrylophenone. This compound yielded bis-(β-benzoylethyl)-hydroxylamine dioxime on being treated with hydroxylamine. Since the completion of this phase of the present study, a report describing formation of the oxime from acrylophenone and hydroxylamine has appeared; D. J. Casey and C. Marvel, *J. Org. Chem.*, **24**, 1022 (1959).

(3) This compound has been prepared from β-chloropropiophenone and hydroxylamine. Z. Y. Kyi and W. Wilson, *J. Chem. Soc.*, 790 (1953).

However, oximation by the recently described method of Higuchi,[4] which makes use of hydroxylammonium acetate in acetic acid, gave a satisfactory result, the oxime (m.p. 44–45°) being produced in 88.5% yield. Attempt to convert this oxime to its tosylate by means of tosyl chloride and pyridine resulted in the formation of β-ethoxypropionanilide, identified by comparison with an authentic sample, apparently through the Beckmann rearrangement of intermediary oxime tosylate.[5] On the basis of the well known steric course of tosylation and of the Beckmann rearrangement, structure I, in which hydroxyl and phenyl groups are placed in *anti* position, may be concluded. In contrast to the above attempt, where pyridine was used, tosylation with the aid of sodium hydroxide in acetone furnished the desired oxime tosylate as an oil. Since the product was unstable, it was directly treated without purification under Neber's[5] condition. Desired α-amino-β-ethoxypropiophenone hydrochloride (II), m.p. 141–141.5°, was obtained in pure form in 55% over-all yield based on oxime I. This Neber's rearrangement provides a further example in support of the mechanism postulated by Cram,[6] since the C-2 carbon atom attacking the nitrogen atom and the departing tosyl group are placed in *syn* position. α-Amino-β-ethoxypropiophenone hydrochloride (II) was prepared also by an alternative route; hydrogenation of α-oximino-β-ethoxypropiophenone with palladium-on-charcoal in saturated methanolic hydrogen chloride afforded II, after uptake of two moles of hydrogen, in 92.5% yield.[7] When the hydrogenation was continued until three equivalents of hydrogen had been absorbed, *erythro*-2-amino-3-ethoxy-1-phenyl-1-propanol[8] (VI), m.p. 55–57°, was obtained in 55% yield in pure state.[9] The presence of the *threo* isomer was suggested by rather low yield of the *erythro* compound, but could not be confirmed owing to difficulties in separation of the *threo* isomer. However, when the intermediary aminopropiophenone hydrochloride (II) was hydrogenated in methanol without addition of hydrogen chloride, only one isomer of VI, identical with that separated in the foregoing instance, was obtained in 88.5% yield. Since in general the catalytic hydrogenation of oximinoketones follows a stereospecific course to afford *erythro*-aminoalcohols,[10] product VI with m.p. 55–57° may possess *erythro* configuration. On the other hand, catalytic reduction of α-oximino-β-ethoxypropiophenone in acetic acid–acetic anhydride followed an irregular steric course to afford a mixture, from which on acetylation *threo*[8]- (m.p. 87–89°) and *erythro*[8]- (m.p. 100–101°) 2-acetamido-3-ethoxy-1-phenyl-1-propanol acetate (VIII) were obtained in about 1:1 ratio. When the reaction was interrupted after two moles of hydrogen had been taken up, α-acetamido-β-ethoxypropiophenone (V) was obtained as a sirupy product.[11] The configuration of *threo*- and *erythro*-diacetyl compounds (VIII) was deduced as follows. According to infrared studies on chloramphenicol and allied compounds by M. Suzuki and H. Shindo,[12] compounds with *erythro* configuration invariably possess in crystalline state an intermolecular hydrogen bond between amide groups stronger than that of corresponding *threo* series;[13] moreover, a relative strong absorption band always appears at 950–1000 cm.$^{-1}$ region in *threo* compounds and at 900–950 cm.$^{-1}$ region in *erythro* compounds. Infrared spectra (Fig. 3) of two diacetyl compounds (VIII) clearly indicate that the compound with m.p. 87–89° belongs to the *threo* series and one with m.p. 100–101° belongs to the *erythro* series (note the bands marked with arrows). This conclusion was further supported through the conversion of previously described

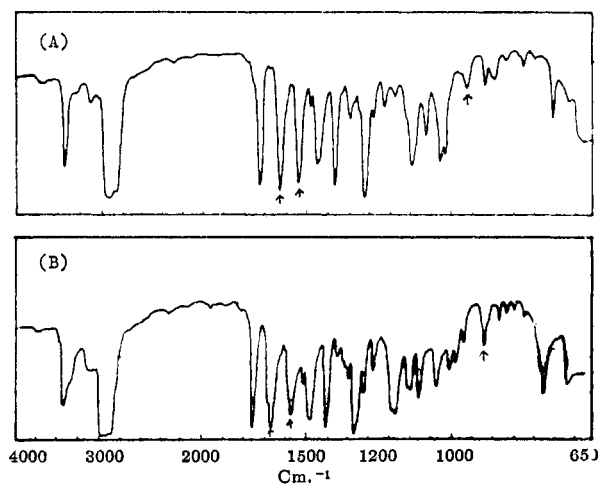


Fig. 3. Infrared spectra of VIII. (A) *erythro;* (B) *threo*

(4) T. Higuchi and C. H. Barnstein, *Anal. Chem.*, **28**, 1022 (1956).

(5) For similar instances, see P. W. Neber and G. Huh, *Ann.*, **515**, 283 (1935). These authors obtained propionanilide by treatment of propiophenone oxime with tosyl chloride in pyridine. However, acetophenone oxime tosylate has been obtained without rearrangement from acetophenone oxime under similar conditions. S. Tatsuoka and co-workers, *J. Pharm. Soc. Japan*, **71**, 781 (1951).

(6) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

(7) For examples of catalytic hydrogenation of oximinoketones to aminoketone hydrochlorides, see W. H. Hartung, *J. Am. Chem. Soc.*, **53**, 2248 (1931).

(8) Configurational assignment of *threo* and *erythro* isomers will be discussed later.

(9) In earlier experiments (ref. 1) *erythro*- and *threo*-VI could not be separated.

(10) Y. Chang and W. H. Hartung, *J. Am. Chem. Soc.*, **75**, 89 (1953).

(11) Although the product could not be induced to crystallize, it is believed to be practically pure V on the basis of infrared spectrum (see Experimental). Acetylation of α-amino-β-ethoxypropiophenone hydrochloride, obtained by the Neber rearrangement, also gave a product with identical infrared spectrum.

(12) M. Suzuki and H. Shindo, *J. Pharm. Soc. Japan*, **76**, 927 (1956).

(13) Difference between wave numbers of amide I and amide II bands is therefore small in *erythro* compounds.

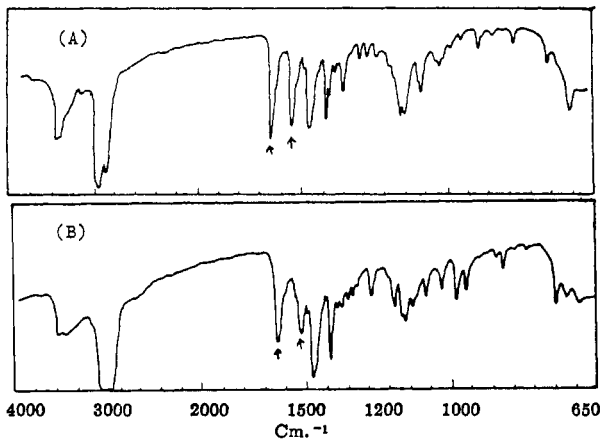


Fig. 4. Infrared spectra of VII. (A) *erythro;* (B) *threo*

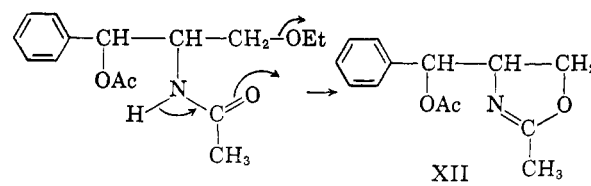
erythro-2-amino-3-ethoxy-1-phenyl-1-propanol to diacetyl compound with m.p. 100–101°.

Use of sodium borohydride in the reduction of hydrochloride of α-amino-β-ethoxypropiophenone (II) and of α-acetamido-β-ethoxypropiophenone (V) afforded results quite reminiscent of catalytic hydrogenation. While reduction of the former (II) in methanol gave *erythro*-2-amino-3-ethoxy-1-phenyl-1-propanol in 94% yield, treatment of acetyl compound (V) under the same conditions gave rise to a mixture, from which after acetylation and subsequent chromatography on alumina *threo*- and *erythro*-diacetyl compounds (VIII) were isolated in a ratio of about 1:1. For the explanation of the results obtained from borohydride treatment, it seems reasonable to assume participation of the lone pair on the nitrogen atom in the course of the reduction. Attack of the coordinated borine[14] hydrogen upon the carbonyl carbon atom from the least hindered site[15] will give rise to *erythro* isomer, in agreement with experimental results. The reason for the lack of stereospecificity in the reduction of V may then be ascribed to decrease in the complexing ability of nitrogen atom to boron atom, caused by the resonance effect of amide group.[16]

Further, the complexing of borohydride ion with oxygen atom attached to β-carbon atom rather than with nitrogen atom might then become operative[17] and lead to the formation of *threo* isomer, thus strengthening the decrease in stereospecificity of the reduction process. Supporting evidence for the participation of oxygen atom at C-3 is provided by the stereospecific borohydride reduction of α-acetamidopropiophenone, in which oxygen atom at C-3 is lacking, to an *erythro* compound *N*-acetylnorephedrine.[18]

The striking similarity between the steric courses of catalytic hydrogenation and of borohydride reduction strongly suggests the similarity of the reduction mechanism itself.[19]

We next examined the possibility whether treatment of *erythro*-VIII with hydrogen bromide saturated in a mixture of acetic acid and anhydride might lead to 2-acetamido-3-acetoxy-3-phenyl-1-propanol through an oxazoline intermediate XII.



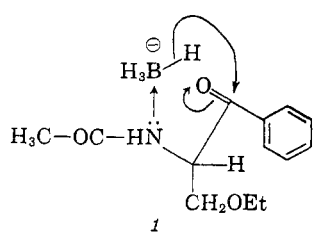
XII

However, the desired displacement of the ethoxy group did not take place and a product with m.p. 100–111° was obtained. As a result of elemental analysis and comparison of the infrared spectrum (Fig. 4) of the product with that of previously described *erythro*-VII, *threo*-2-acetamido-3-ethoxy-1-phenyl-1-propanol structure was assigned to this compound. As expected, the spectrum of the *erythro*

(14) Effective reducing agent may be amino-borine rather than borohydride ion since reaction of sodium borohydride with amine hydrochloride generally affords amine-borine [G. W. Schaeffer and E. R. Anderson, *J. Am. Chem. Soc.*, **71**, 2143 (1949); H. Nöth and H. Beyer, *Chem. Ber.*, **93**, 928 (1960)].

(15) This concept is known as Cram's rule; D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(16) In the reduction of V, the effective redu tant may be borohydride itself since the reaction is affected in neutral condition. Transition state may be pictured as (1)



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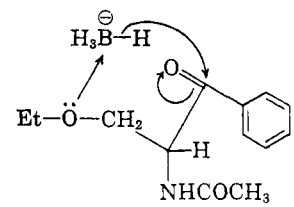
(17) Decrease in the complexing tendency alone does not satisfactorily account for the experimental results. Predominant formation of *erythro*-VII is expected even in the absence of complex formation according to Cram's concept ($CH_2OC_2H_5$ > $NHCOCH_3$ > H). Transition state in which C-3 oxygen atom participates may be expressed as (2)



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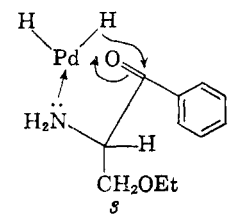
(18) T. Matsumoto and H. Shirahama, to be published.

(19) For example, following structure (3) may be pictured as the intermediate state for the catalytic hydrogenation of II.



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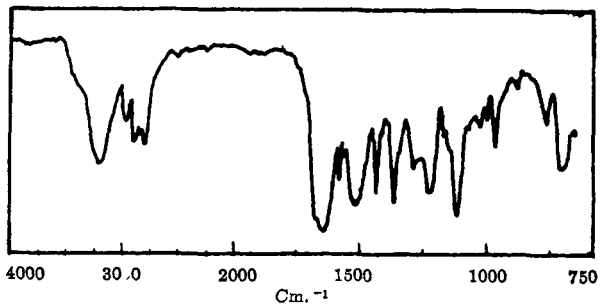

Fig. 5. Infrared spectra of V

isomer shows smaller wave number difference between amide I and II bands.

On the contrary, treatment of *erythro*-VIII with hydrogen bromide saturated in acetic acid (without addition of acetic anhydride) gave rise to a mixture from which *threo*- and *erythro*-2-amino-1-phenylpropane-1,3-diol were isolated in a ratio of 3:1. As in the foregoing case, the *threo* isomer is supposed to be formed through acyl migration. Upon hydrolysis of *erythro*-VI with constant boiling hydrobromic acid, *erythro*-2-amino-1-phenylpropane-1,3-diol was obtained as a sole product.[20]

Lastly, catalytic hydrogenation of β-acetoxy-α-oximino-propiophenone in acetic acid–acetic anhydride was attempted in hope to prepare 2-acetamido-3-acetoxy-1-phenyl-1-propanol. However, contrary to expectation, the acetyl group was hydrogenolyzed and *N*-acetylnorephedrine was isolated as a main product. Absence of isolable amount of *N*-acetylpseudonorephedrine suggests that the reaction proceeds through α-acetamidopropiophenone, on the ground discussed before. In fact, presence of the latter compound at an intermediary phase of the reduction was confirmed by isolation of the material.

EXPERIMENTAL[21]

β-Ethoxypropiophenone. This compound was prepared by a modification of the method of Kohler.[2] To a cold solution of 3 g. of β-chloropropiophenone[1,22] in 80 ml. of absolute ethanol was added dropwise a solution of 1.2 g. of potassium hydroxide in 90 ml. of the same solvent with stirring under ice cooling over a period of 1.5 hr. The resulting mixture was poured into 700 ml. of water and extracted with three 100-ml. portions of ether. The combined extracts were washed, dried, and evaporated to leave a slightly yellow oil, (3.2 g., 100%), which did not consume potassium permanganate in acetone solution and gave 2,4-dinitrophenylhydrazone, m.p. 160° (ethyl acetate), which proved to be identical with the authentic sample[1] by mixed m.p. determination.

(20) It is interesting to note that *erythro*-2-amino-1-phenylpropane-1,3-diol gave *threo* isomer upon treatment with 56% hydrobromic acid [J. Kollonitsch, A. Hajós, V. Gábor, and M. Kraut, *Acta Chim. Sci. Hung.*, **5**, 13 (1954)].

(21) All melting points are uncorrected. Infrared spectra were obtained by means of a Kōken Model 301 and a Hilger H 800 infrared spectrophotometers. Microanalyses were performed by Miss Noriko Fujino of this laboratory, to whom our sincere thanks are due.

(22) W. J. Hale and E. C. Britton, *J. Am. Chem. Soc.*, **41**, 841 (1919).

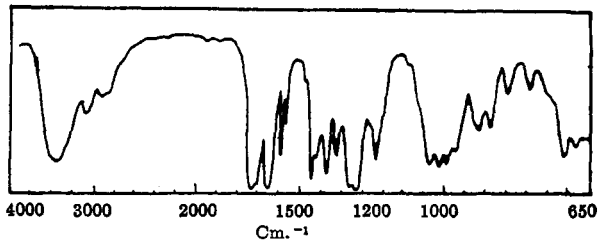

Fig. 6. Infrared spectra of β-acetoxy-α-oximinopropiophenone

Since the β-ethoxyketone had a tendency to decompose to acrylophenone upon distillation even under diminished pressure,[23] it was used in the next oximation without further purification.

β-Ethoxypropiophenone oxime (I). A solution of 3.2 g. of β-ethoxypropiophenone in 10 ml. of acetic acid was added to a solution of 2.4 g. of hydroxylammonium acetate[4] in 30 ml. of the same solvent, and the mixture was set aside for 2 days. The resulting solution was evaporated *in vacuo*, and the residue was extracted twice with benzene. After removal of undissolved substance by filtration, the combined benzene extracts were washed successively with water, 5% sodium bicarbonate, and again with water. Evaporation of the dried benzene solution left a sirup, which was overlayed with a small amount of petroleum ether (b.p. 50–70°). Scratching and allowing the mixture to stand for several hours usually led to the solidification of the crude oxime. Recrystallization from petroleum ether yielded 3.1 g. (88.5%) of pure I as white crystals, m.p. 44–45°, ν_{max}^{Nujol} 3360, 1190, 1020, 935, and 760 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.30; H, 7.78; N, 7.31.

α-Amino-β-ethoxypropiophenone hydrochloride (II). A. *By the Neber rearrangement of I.* To a cold solution of 3.02 g. of I in 30 ml. of 2*N* sodium hydroxide there was added at once a solution of 3.0 g. of *p*-toluenesulfonyl chloride in 20 ml. of acetone under ice cooling, and the resulting mixture was shaken at 0° for 30 min. The reaction mixture was poured into 200 ml. of ice water and extracted with four 50-ml. portions of ether. The combined ethereal extracts were washed with cold water and dried at 0°. The oily residue obtained after removal of the solvent *in vacuo* was taken up in 15 ml. of absolute ethanol and stored in a refrigerator. No further attempt to isolate the oxime tosylate in a crystalline state was made since attempted isolation resulted in decomposition of the product.

When pyridine was used in the above preparation in place of sodium hydroxide solution, the product of the Beckmann rearrangement was exclusively obtained. The product, β-ethoxypropionanilide (m.p. 45°), was proved by mixed m.p. determination and by comparison of infrared spectrum to be identical with that of a synthetic specimen prepared by condensation of β-ethoxypropionyl chloride and aniline.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.62; N, 7.16.

To a stirred solution of β-ethoxypropiophenone oxime tosylate in absolute ethanol prepared above, was added dropwise an alcoholic sodium ethoxide solution (from 0.36 g. of sodium in 10 ml. of absolute ethanol) over a period of 30 min. under ice cooling. The resulting mixture was allowed to warm to room temperature with stirring (2 hr.). The solids which had separated from the solution were removed by filtration. The filtrate was diluted with 60 ml. of ether and then extracted with three 20-ml. portions and finally with 10 ml. of 2*N* hydrochloric acid. The combined aqueous extracts were washed with benzene until the washing became colorless and evaporated to dryness at below 35° under reduced

(23) R. E. Leslie and H. R. Henze, *J. Am. Chem. Soc.*, **71**, 3480 (1949).

pressure. The partially solidified residue thus obtained was dried *in vacuo* over potassium hydroxide and then taken up in 15 ml. of absolute ethanol. The ethanolic solution was diluted with 35 ml. of dry ether and kept in a refrigerator. The white precipitates which had separated from the solution were collected by filtration and recrystallized from ethanol-ether to yield 1.55 g. of pure II as white needles, m.p. 141–141.5° dec.; λ_{max} 249 mμ (ε 13,400 in water).[24]

Anal. Calcd. for $C_{11}H_{16}O_2NCl$: C, 57.51; H, 6.58; N, 6.09. Found: C, 57.54; H, 6.69; N, 6.35.

From the initial mother liquor an additional II (0.4 g.) was obtained. The total yield (1.95 g.) of II from the oxime was about 55%.

B. *By catalytic hydrogenation of α-oximino-β-ethoxypropiophenone.* Hydrogenation of 0.98 g. of α-oximino-β-ethoxypropiophenone in 20 ml. of anhydrous methanol saturated with hydrogen chloride was carried out in the presence of 0.8 g. of 10% palladium-on-charcoal. The reaction was interrupted shortly after two equivalents (213 ml.) of hydrogen had been taken up. The solution was filtered from the catalyst and evaporated under reduced pressure to leave an oily residue, which was crystallized from ethanol-ether. Recrystallization from the same solvents yielded II, 1.01 g. (92.5%).

erythro-2-Amino-3-ethoxy-1-phenyl-1-propanol (VI). A. *By reduction of II with sodium borohydride.* To a cold solution of 0.2 g. of sodium borohydride in 5 ml. of methanol containing 5 drops of 20% sodium hydroxide was added dropwise a solution of 0.24 g. of II in 7 ml. of methanol over a period of 30 min. under occasional shaking and ice cooling. After being set aside overnight, the resulting mixture was diluted with 40 ml. of water and then extracted with four 20-ml. portions of ethyl acetate. The combined extracts were washed, dried, and evaporated to leave a glass, which was soon solidified. Recrystallization from petroleum ether yielded 0.19 g. (94%) of pure VI as white needles, m.p. 55–57°, ν_{max} 3360, 3320, 1600, 1575, 1110, 1085, 1050, 940, 905, 755, and 710 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.49; H, 8.66; N, 7.13.

B. *By catalytic hydrogenation of II.* A solution of 0.39 g. of II in 10 ml. of absolute methanol was hydrogenated in the presence of 0.4 g. 10% palladium-on-charcoal, one equivalent (38 ml.) of hydrogen being absorbed after 30 min. shaking. After the catalyst and the solvent were removed, the residue was taken up in 5 ml. of water. The solution was made alkaline and then extracted with ethyl acetate. Evaporation and recrystallization from petroleum ether yielded 0.26 g. (88.5%) of VI.

C. *By catalytic hydrogenation of α-oximino-β-ethoxypropiophenone.* Hydrogenation of α-oximino-β-ethoxypropiophenone was carried out in a manner previously reported.[1] The reaction product formed initially was a colorless glass, which was crystallized from petroleum ether (b.p. 50–70°). Recrystallization from the same solvent yielded 0.16 g. (55%) of pure VI.

erythro-2-Acetamido-3-ethoxy-1-phenyl-1-propanol (VII). A solution of 0.1 g. of VI in 1 ml. of benzene was treated with 0.1 ml. of acetic anhydride, and the solution was allowed to stand for 30 min. Evaporation *in vacuo* and recrystallization from ethyl acetate yielded VII as white crystals, m.p. 111–113°, ν_{max} 3340, 3300, 1645, 1545, 1300, 1130, 1105, 1065, 1020, 930, 845, 760, and 705 cm.$^{-1}$

Anal. Calcd. for $C_{13}H_{19}O_3N$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.91; H, 8.12; N, 5.77.

erythro-2-Acetamido-3-ethoxy-1-phenyl-1-propanol acetate (VIII). To a solution of 0.2 g. of VI in 5 ml. of pyridine was added 1 ml. of acetic anhydride, and the mixture was set aside overnight. Evaporation *in vacuo* and recrystallization of the residue from petroleum ether yielded 0.26 g. of VIII as white needles, m.p. 100–101°, ν_{max} 3325, 1735, 1640, 1550, 1240, 1200, 1170, 1105, 1070, 1035, 970, 905, 760, and 690 cm.$^{-1}$

The same compound was obtained from VII in good yield by acetylation.

erythro-2-Benzamido-3-ethoxy-1-phenyl-1-propanol benzoate. A solution of 0.18 g. of VII in 5 ml. of pyridine was treated with 0.4 ml. of benzoyl chloride as usual to yield 0.36 g. (98%) of *N,O*-dibenzoyl derivative as white crystals, m.p. 191.5–192°, ν_{max} 3420, 1710, 1640, 1530, 1330, 1280, 1260, 1115, 1070, 1025, 980, 920, 865, 805, 765, and 715 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{25}O_4N$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.13; H, 6.06; N, 3.72.

α-Acetamido-β-ethoxypropiophenone (V). A. To a cold mixture of 0.53 g. of II in 10 ml. of water and 1 ml. of acetic anhydride there was added dropwise 4.6 ml. of 1*N* sodium hydroxide under shaking. After the addition was completed, the mixture was shaken at room temperature for 30 min. and then was extracted with two 100-ml. portions of ethyl acetate. The oily residue which was obtained after evaporation *in vacuo* was extracted twice with boiling petroleum ether. The solvent was removed *in vacuo* to yield 0.32 g. of sirup which could not be induced to crystallize, ν_{max} 1674 (aroyl ketone), 1645 (amide I), 1516 (amide II), and 1111 cm.$^{-1}$ (ether).

B. A solution of 0.77 g. of α-oximino-β-ethoxypropiophenone in a mixture of 5 ml. of acetic anhydride and 5 ml. of acetic acid was hydrogenated in the presence of 0.4 g. of 10% palladium-on-charcoal. The reaction was interrupted shortly after 2 equivalents (179 ml.) of hydrogen had been taken up (45 min.), and the catalyst was filtered from the solution. The oily residue which was obtained after evaporation of the solvent *in vacuo* was treated with petroleum ether as described in A. The infrared spectrum of this product was completely superposable on that of the product obtained by procedure A.

Reduction of V *with sodium borohydride.* To a cold solution of 0.3 g. of sodium borohydride in 5 ml. of methanol in which a small piece of sodium had been dissolved was added dropwise a solution of 0.31 g. of V in 5 ml. of methanol over a period of 15 min. under occasional shaking and ice cooling. After being set aside overnight the solution was evaporated *in vacuo* to leave a white residue, which was taken up in 10 ml. of water, and the solution was made acidic with 2*N* hydrochloric acid and then extracted with three 10-ml. portions of ethyl acetate. The combined extracts were washed, dried, and evaporated to leave a colorless glass, which was taken up in 5 ml. of pyridine and then treated with 5 ml. of acetic anhydride. After being set aside overnight the solution was evaporated *in vacuo* to leave 0.37 g. (95%) of a colorless glass. The infrared spectrum of this product exhibited broad amide absorption bands [1680–1650 cm.$^{-1}$ (amide I) and 1560–1540 cm.$^{-1}$ (amide II)] and a broad ester band (1750–1730 cm.$^{-1}$) and suggested the presence of *threo* and *erythro* diastereomers.

The crude product obtained above was taken up in 1 ml. of benzene and chromatographed on 10 g. of alumina, being eluted successively with forty 10-ml. portions of benzene (fraction 1 to 40) and ten 10-ml. portions of ethyl acetate (fraction 41 to 50). Evaporation of fractions 6 to 14 left colorless crystals, which were recrystallized from petroleum ether to yield 0.04 g. of white needles, m.p. 87–89°, ν_{max} 3300, 1735, 1645, 1550, 1240, 1200, 1175, 1130, 1120, 1085, 1065, 1035, 990, 975, 960, 905, 760, and 700 cm.$^{-1}$; the spectrum was apparently different from that of *erythro*-VIII in the fingerprint region. When mixed with *erythro*-VIII the m.p. was observed to be 64–84°.

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.46; H, 7.58; N, 4.98.

Since elemental and infrared analyses were consistent only with VIII, this product must be a *threo* compound. From

(24) J. R. Parikh and J. E. Oneto, *J. Am. Pharm. Assoc.*, **45**, 219 (1956), reported λ_{max} 250 mμ (ε 12,624 in water) for α-amino-β-methoxypropiophenone hydrochloride. We are indebted to Dr. J. R. Parikh who called our attention to their report, in which attempts along lines similar to those reported in part I of our series were described.

fractions 15 to 40 additional 0.08 g. of *threo*-VIII was obtained.

Evaporation of fractions 44 to 47 left white solids, which were recrystallized from petroleum ether to yield 0.06 g. of *erythro*-VIII as white needles, m.p. and mixed m.p. 100–101°.

Evaporation of fractions 41 to 43 left 0.12 g. of colorless oil whose infrared spectrum revealed it to be a mixture of *threo*- and *erythro*-VIII. Rechromatography of this mixture on 3 g. of alumina in the similar manner described above afforded 0.04 g. of *threo*-VIII and 0.07 g. of *erythro*-VIII. The total yield of pure *threo*-VIII was 0.16 g. and that of pure *erythro*-VIII was 0.13 g.

In another run, 0.4 g. of V was treated with 0.5 g. of sodium borohydride in methanol to yield 0.12 g. of white crystals of VII, m.p. 109–110°. Concentration of the mother liquor afforded additional crystals whose infrared spectrum indicated the presence of two diastereomers. Acetylation of this mixture and subsequent chromatography afforded *threo*- and *erythro*-VIII.

Catalytic hydrogenation of α-oximino-β-ethoxypropiophenone. A solution of 0.53 g. of α-oximino-β-ethoxypropiophenone in a mixture of 10 ml. of acetic acid and 5 ml. of acetic anhydride was hydrogenated in the presence of 0.5 g. of 10% palladium-on-charcoal for 1.5 hr. until 3 equivalents (181 ml.) of hydrogen had been absorbed. The solution was filtered from the catalyst, treated with 5 ml. of pyridine, and then set aside overnight. Evaporation of the solution and chromatography of the residue (0.77 g.) on 15 g. of alumina in the manner previously described yielded 0.22 g. of *threo*- and 0.2 g. of *erythro*-VIII.

erythro-2-Amino-1-phenylpropane-1,3-diol and threo-2-amino-1-phenylpropane-1,3-diol (IX). A. A mixture of 0.34 g. of *erythro*-VIII in 10 ml. of saturated solution of dry hydrogen bromide in acetic acid was refluxed on a water bath for 4 hr. After being cooled, the solution was evaporated to dryness under reduced pressure to leave a brown residue, which was taken up in 10 ml. of water and heated for 1 hr. After being cooled and washed with ethyl acetate, the solution was made alkaline and then extracted with four 20-ml. portions of ethyl acetate. The combined extracts were washed, dried, and evaporated to leave a colorless residue, which was taken up in 1.5 ml. of ethanol containing 0.13 g. of benzoic acid. The solution was diluted with dry ether and then cooled in a refrigerator. White precipitates, 0.03 g., m.p. 193–203°, which had separated from the solution were recrystallized from absolute ethanol yielding white crystals, benzoic acid salt of *erythro*-IX, m.p. 206–207° (lit.[20] m.p. 207–208°).

Anal. Calcd. for $C_{16}H_{19}O_4N$: N, 4.84. Found: N, 5.04.

The residue obtained after evaporation of the mother liquor was extracted three times with boiling petroleum ether to remove unchanged benzoic acid and then crystallized from absolute ethanol yielding 0.1 g. of benzoic acid salt of *threo*-IX as white crystals, m.p. 157–160°. Recrystallization from the same solvent raised the m.p. to 161–163° (lit.[20] m.p. 159–161°).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.78; H, 6.63; N, 4.62.

B. *Hydrolysis with acetic anhydride–acetic acid–hydrogen bromide.* A solution of 0.41 g. of *erythro*-VIII in a mixture of 10 ml. of acetic anhydride and 5 ml. of saturated solution of hydrogen bromide in acetic acid was heated on a water bath for 5 hr. and then evaporated under reduced pressure. The residue was taken up in 10 ml. of water, washed with ethyl acetate, made alkaline, and then extracted with three 5-ml. portions of ethyl acetate. The combined extracts were washed, dried, and evaporated to leave 0.15 g. of colorless oil, which was crystallized upon treatment with petroleum ether. Recrystallization from ethyl acetate yielded white crystals of *threo*-VII, m.p. 110–111°, mixed m.p. with *erythro*-VI 88–98°; ν_{max} 3360, 3300, 1640, 1525, 1195, 1140, 1125, 1120, 1095, 1025, 990, 965, 880, and 750 cm.$^{-1}$

Evaporation of the washing (ethyl acetate) left 0.18 g. of colorless oil whose infrared spectrum was also superposable on that of *threo*-VII, but no further purification was attempted. Acetylation of *threo*-VII in the usual manner afforded *threo*-VIII.

C. A solution of 0.38 g. of *erythro*-VI in 10 ml. of 48% hydrobromic acid was refluxed for 2 hr. and then evaporated to one-half volume under reduced pressure. The resulting solution was diluted with 20 ml. of water and heated on a water bath for 1 hr. After being cooled and washed with ethyl acetate, the aqueous solution was treated as described in the method A yielding 0.03 g. of white solids. Recrystallization from absolute ethanol yielded benzoic acid salt of *erythro*-IX, m.p. 163–164°.

From the mother liquor additional 0.11 g. of the same compound was obtained.

β-Acetoxy-α-oximinopropiophenone. A mixture of β-chloro-α-oximinopropiophenone (1.2 g.) and anhydrous potassium acetate (2 g.) in 50 ml. of acetic acid was heated on a water bath for 5 hr. After completion of the reaction, acetic acid was removed under reduced pressure and the residue was extracted with 30 ml. of ethyl acetate. The extracts were then washed successively with aqueous sodium carbonate and water, and dried. Removal of the solvent left 0.77 g. of a yellow, chlorine-free oil, which was purified through extraction with hot petroleum ether. Although the product (0.623 g.) thus obtained could not be caused to crystallize, it seemed pure enough for practical purposes on the basis of infrared spectrum (Fig. 6).

Hydrogenation of β-acetoxy-α-oximinopropiophenone. The above product (0.623 g.) was taken in a mixture of acetic acid (10 ml.) and acetic anhydride (10 ml.) and hydrogenated in the presence of palladium-on-charcoal. During a period of 8 hr., 3.65 equivalents of hydrogen was taken up. Removal of the catalyst and of the solvent left 0.56 g. of a paste. This material was taken up in a mixture of benzene (5 ml.) and ethyl acetate (1 ml.) and passed through a column of alumina (10 g.). Elution with benzene (175 ml.) afforded 0.011 g. of unidentified product. Ethyl acetate (150 ml.) then eluted 0.3 g. of crude *N*-acetylnorephedrine, which on being recrystallized from ethyl acetate gave a pure sample with m.p. 131–134°. Continuation of elution with ethyl alcohol (210 ml.) afforded 0.035 g. of unidentified material.

In one run, 1.27 g. of acetoxyoximinoketone was hydrogenated in a similar way until 3.3 equivalents of hydrogen had been absorbed. Chromatography of the product on alumina column using benzene (100 ml.) as an eluant gave 0.18 g. of α-acetamidopropiophenone.

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