(0.7–0.9 mm.). The yield was 12 g. (81%). The colorless diamine solidified on standing and was recrystallized from benzene–petroleum ether, m.p. 69–72.5°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19. Found: C, 57.38; H, 6.95.

The 2,6-diacetyl derivative crystallized from ethyl acetate as silky white needles melting at 194.5–196.5°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39. Found: C, 57.42; H, 6.12.

The diacetate of 2,6-diaminohydroquinone dimethyl ether was also prepared by acetylating 2-acetamido-6-amino-1,4-dimethoxybenzene (VI). Comparison of the two diacetates showed that they were identical.

2,8-Dimethyl-4,6-dihydroxy-5,10-dimethoxypyrido[3,2g]-quinoline (XV).—The condensation of 9.5 g. (0.056 mole) of 2,6-diamino-1,4-dimethoxybenzene with 20 g. (0.015 mole) of ethyl acetoacetate was carried out as described in the preparation of ethyl β-(2,5-dimethoxy-3-acetamidoanilino)-crotonate. After recrystallization from isoöctane, 16 g. (73%) of colorless crystals of **diethyl 2,5-dimethoxy-1,3-phenylenediaminodicrotonate** melting at 81.5–83.5° was obtained.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: N, 7.14. Found: N, 7.34, 7.35.

A bilateral Conrad–Limpach synthesis using diphenyl ether and the dicrotonate yielded 61% of a rather insoluble material which could be converted to an orange **dihydrochloride** in hot hydrochloric acid. The salt was recrystallized from acidified water and melted at 290° (dec.).

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_4$: C, 51.48; H, 4.86; N, 7.51. Found: C, 52.81; H, 4.98; N, 7.40.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, DAVIS]

The Stereochemistry of the Four α-Amino-β,γ-dihydroxybutyric Acids

BY EDWARD E. HAMEL[1] AND EDGAR PAGE PAINTER

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The four α-amino-β,γ-dihydroxybutyric acids are described. The configuration of each (relative to D-glyceraldehyde) was assigned by preparation and reactions of the oxazolines of the lactones.

Starting with DL-glyceraldehyde, Fischer and Feldmann[2] first prepared α-amino-β,γ-dihydroxybutyric acid by the Strecker synthesis. Soon after Fischer and Baer[3a] reported a convenient synthesis of acetone D-glyceraldehyde (by glycol cleavage of 1,2,5,6-diacetone-D-mannitol), Fischer and Feldmann[3b] repeated the amino acid synthesis using the D-aldehyde. With D-glyceraldehyde the number of expected products is reduced from four to the diastereoisomers I and II. The product they isolated had $[\alpha]^{20}D$ −13.74°. Niemann and Nichols[4] repeated the synthesis several years later and isolated two products, one having $[\alpha]D$ −13.7° and the other $[\alpha]D$ +16.0°. Interest in the compound stemmed from the claim of Klenk and Diebold[5] that they obtained α-amino-β,γ-dihydroxybutyric acid having $[\alpha]D$ −33.4° by oxidative cleavage of sphingosine. The results of Niemann and Nichols showed clearly that the compound from sphingosine was not one of the α-amino-β,γ-dihydroxybutyric acids.

Niemann and Nichols assigned the *threo* configuration to the levorotatory amino acid and the *erythro* configuration to the dextrorotatory amino acid. Their evidence was based on enzymatic reactions which are specific for the group of amino acids assigned the L-configuration and for the group assigned the D-configuration, rotation changes upon the addition of H^+,[6] and formation of N-benzoyl lactone from one amino acid and N-benzoyl acid from the other. The results on benzoylation were those they predicted from scale models of the *n*-benzoyl derivatives of the two diastereoisomers.[7]

Recent evidence on the steric course of oxazoline formation suggested a different approach to the configuration from that used by Niemann and Nichols. Reactions leading to oxazolines should establish with reasonable certainty the configuration[8] of the two amino acids prepared from D-glyceralde-

(1) E. I. du Pont de Nemours, Niagara Falls, N. Y.

(2) H. O. L. Fischer and L. Feldmann, *Ber.*, **65**, 1211 (1932).

(3) (a) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **17**, 622 (1934); (b) H. O. L. Fischer and L. Feldmann, *ibid.*, **19**, 532 (1936).

(4) C. Niemann and P. L. Nichols, *J. Biol. Chem.*, **143**, 191 (1942).

(5) E. Klenk and W. Diebold, *Z. physiol. Chem.*, **198**, 25 (1931).

(6) (a) G. W. Clough, *J. Chem. Soc.*, **107**, 1509 (1915); **113**, 526 (1918); (b) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931).

(7) The product obtained when the *erythro* acid (II) as benzoylated and the solution acidified is the N-benzoyl-free acid as Niemann and Nichols reported. Upon recrystallization of the benzoyl acid, crystals which proved to be the N-benozyl lactone slowly formed in the filtrate. The same N-benzoyl lactone is formed when the *erythro* lactone (III) is benzoylated in sodium carbonate solution. While the reactions described in this paper confirm the assignment of configuration of the two acids I and II by Niemann and Nichols, we do not consider our results on the preparation of the N-benzoyl derivatives evidence for assignment of configuration.

(8) One of our initial objectives was to convert one of the diastereoisomers to a naturally occurring amino acid by a method which did not involve a displacement at the optical center carrying the amino group. Thus, if the configuration of the optical carrying the amino group is known relative to the β-hydroxy optical center, a direct means of relating configuration of amino acids and carbohydrates is available. Shortly after these studies were undertaken two significant papers[9] relating configuration appeared. Wolfrom, *et al.*,[9a] reduced C_1 of D-glucosamine to methyl and, after glycol cleavage of the acetylamine, oxidized C_3 to carboxyl to give N-acetylalanine which had the same rotation as the N-acetyl derivative of the naturally occurring amino acid. The configuration of C_2 relative to C_5 in glucosamine had previously been established.[10] Shoemaker, *et al.*,[9b] confirmed by crystal structure analysis, the *threo* structure of L-threonine previously assigned by Meyer and Rose.[11] The β optical center of natural threonine has the same configuration as D-glyceraldehyde.[11]

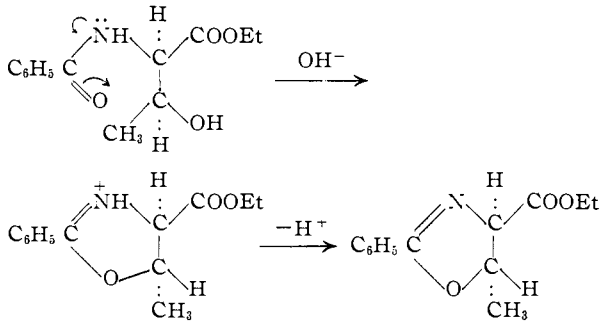
These observations permit us to assign the configuration of the α-amino-β,γ-dihydroxybutyric acids relative to both carbohydrates and amino acids. Compound I has the same configuration at each optical center as natural threonine. In naming the amino acids and their derivatives the β-carbon will be referred to D-glyceraldehyde. Thus I is the D-*threo* acid (the same as Niemann and Nichols[4]) and IV is the L-*erythro* acid. This should not be confused with the above designation for threonine where the subscript s refers to serine.

(9) (a) M. L. Wolfrom, R. U. Lemieux and S. M. Olin, THIS JOURNAL, **71**, 2870 (1949); (b) D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, *ibid.*, **72**, 2328 (1950).

(10) (a) W. N. Haworth, W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 271 (1939); (b) W. O. Cutler and S. Peat, *ibid.*, 782 (1939).

(11) C. E. Meyer and W. C. Rose, *J. Biol. Chem.*, **115**, 721 (1936).

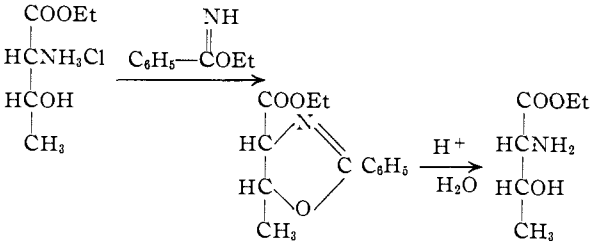
hyde. Reactions of oxazolines suggested a way to prepare the other two diastereoisomers. Attenburrow, Elliott and Penny[12] found one of the asymmetric centers in esters of N-benzoyl-*allo*-threonine inverted in the reaction sequence, benzamido ester → oxazoline → amino acid. Their proposed mechanism involved a backside attack on the carbon atom bearing the hydroxyl group by the oxygen of the benzamido group with subsequent displacement of the hydroxyl group and formation of an oxazolinium ion. Addition of bicarbonate gave the free base. The correctness of this mechanism has been verified by several investigators.[13] When



applied to cyclic systems containing *cis–trans* forms[13a,13b] it was found that *dl-trans*-2-benzamidocyclohexanol upon treatment with thionyl chloride yielded *dl-cis*-2-phenyl-4,5-cyclohexanoöxazoline hydrochloride. When *dl-cis*-2-benzamidocyclohexanol was treated in the same manner, instead of oxazoline formation, the hydroxyl group was displaced by chloride to give a compound which was identified as *dl-trans*-2-benzamidocyclohexyl chloride. Cyclopentane derivatives gave the same results in the series of reactions just described.

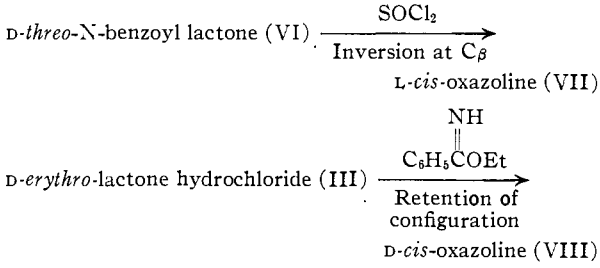
Thus, according to this mechanism, if the N-benzoyl lactones of the two α-amino-β,γ-dihydroxybutyric acids (I and II) reacted with thionyl chloride, the one possessing the *threo*, or *trans*, configuration should form an oxazoline, whereas the one having the *erythro*, or *cis*, configuration should either not react at all, or give a chloride by direct displacement of the hydroxyl group. The presence of the lactone ring is necessary, first, to prevent azlactone formation, which would occur with the free acid,[13d] and second, to prevent rotation about the α–β carbon–carbon bond. If free rotation were possible, oxazoline formation would take place regardless of the respective configurations of the two molecules.

A method for the preparation of oxazolines[13a,b,e] applicable to *cis*-1,2-amino alcohols has been described where the steric course of the reaction is retention of configuration. On treatment of *dl-allo*-threonine ethyl ester hydrochloride with ethyl iminobenzoate Elliott[13e] obtained an oxazoline identified as *cis*-2-phenyl-4-carbethoxy-5-methyl-Δ^2-oxazoline. Upon hydrolysis with dilute acid he obtained *allo*-threonine, showing that the steric result was retention of configuration



Sufficient proof of the correctness of this steric picture has appeared from experiments with cyclohexane and cyclopentane derivatives.

If the assignment of the D-*erythro* configuration to the lactone hydrochloride III (from II) is correct, reaction with ethyl iminobenzoate should yield an oxazoline which would be the enantiomorph of the oxazoline obtained from the D-*threo*-N-benzoyl lactone (VI) by reaction with thionyl chloride.



Evidence of Configuration from Formation and Reactions of Oxazolines

Benzoylation of the amino acid (I) assigned the *threo* configuration gave on acidification an N-benzoyl lactone (VI). When VI was allowed to react with thionyl chloride at 45° and the reaction product treated with pyridine an oxazoline (VII) was obtained. In view of the mechanism of oxazoline formation this observation gave strong support to the *threo* configuration.

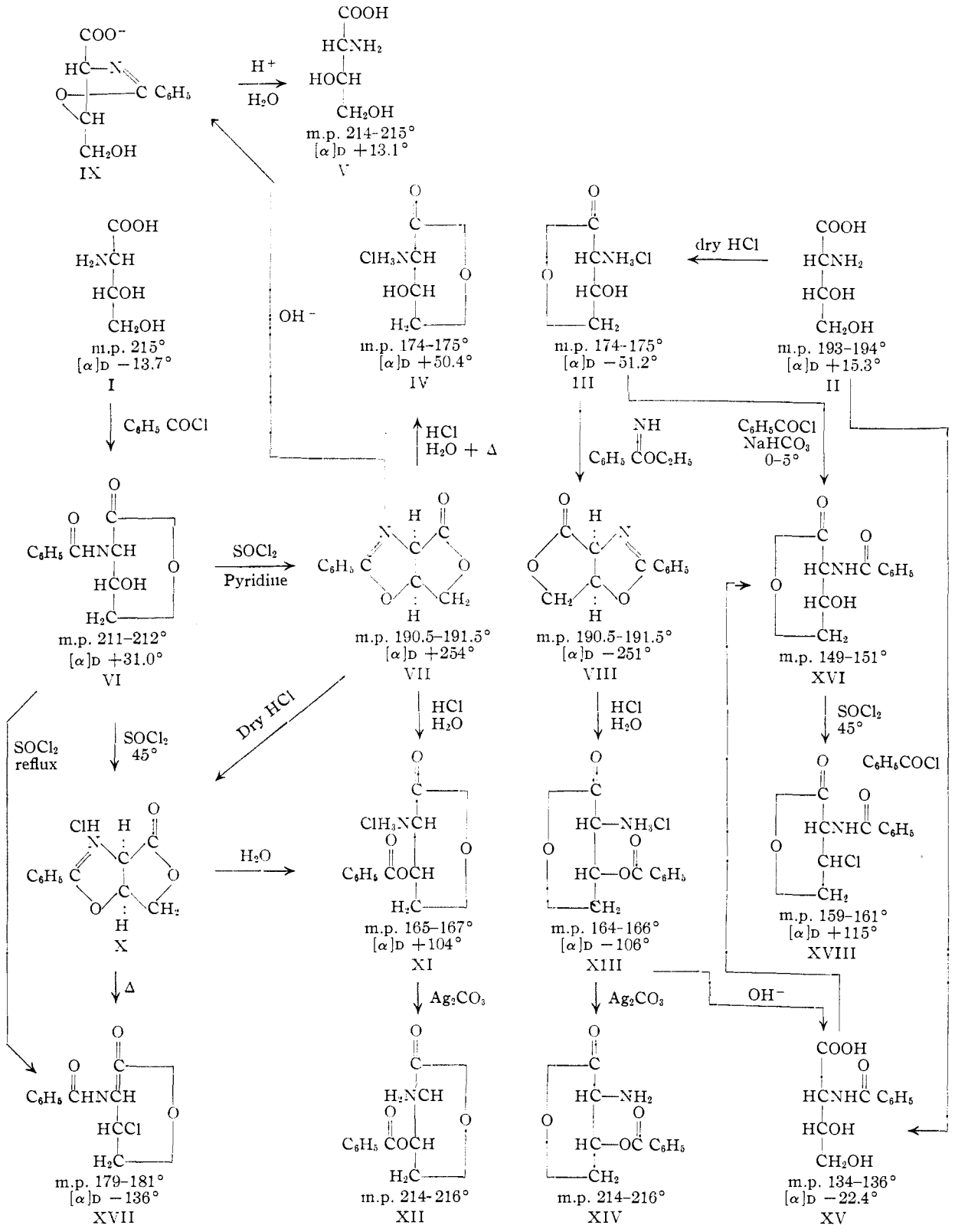
When D-*erythro*-α-amino-β,γ-dihydroxybutyric acid (II) was treated with dry hydrogen chloride in absolute ethanol, the compound isolated was the lactone hydrochloride (III). This compound reacted with ethyl iminobenzoate to give the oxazoline (VIII) which proved to be the enantiomorph of the oxazoline described above, a result which firmly established the structure of the original oxazoline. When the *threo*-amino acid (I) was treated with hydrogen chloride in the same manner as described above for the *erythro* compound, no crystalline lactone hydrochloride could be isolated. When the crude oil was heated with ethyl iminobenzoate in ethylene chloride in an attempt to prepare the *trans*-oxazoline, no apparent reaction could be detected.

Hydrolysis of VII by refluxing with dilute acid produced the L-*erythro*-lactone hydrochloride (IV) which proved, as predicted, to be the enantiomorph of III.

If the L-*cis*-oxazoline (VII) was allowed to stand in aqueous alcoholic barium hydroxide solution for several days then refluxed in acid, the amino acid

(12) J. Attenburrow, D. F. Elliott and G. F. Penny, *J. Chem. Soc.*, 310 (1948).

(13) (a) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950); (b) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); (c) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950); (d) K. Pfister, C. A. Robinson, A. C. Shabica and M. Tishler, *ibid.*, **71**, 1101 (1949); (e) D. F. Elliott, *J. Chem. Soc.*, **62**, (1950); 589 (1949); (f) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949); (g) G. E. McCasland and E. C. Horswill, THIS JOURNAL, **73**, 3744 (1951).

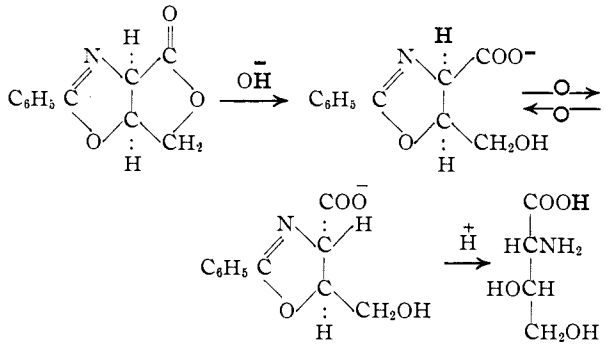


The specific rotations of compounds VI and XV are for the sodium salts of the free acids.

isolated was L-*threo*-α-amino-β,γ-dihydroxybutyric acid (V), the enantiomorph of I. The treatment with barium hydroxide caused mutarotation at the carbon atom alpha to the carbonyl oxygen of the oxazoline. Subsequent acid hydrolysis opened the oxazoline ring and hydrolyzed the resulting O-benzoyl ester.

While two amino acids, V and the enantiomorph of II, are the expected products in the route from VII to V, the equilibrium lies so far in favor of the

trans oxazoline, IX, that V is the only amino acid isolated. Elliott[13e] found the equilibrium far in favor of the *trans* compound with oxazolines of the threonines.



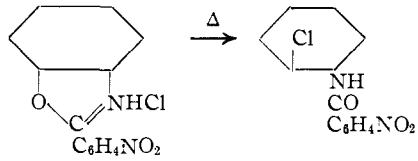
All four possible stereoisomers have thus been prepared and it is noteworthy that, with any one of the four isomers as a starting material, the other three may be prepared by the reaction scheme shown.

Treatment of the L-*cis*-oxazoline (VII) with dry hydrogen chloride in a cold, anhydrous solvent gave rise to the oxazoline hydrochloride (X), a compound which was rather difficult to handle due to its ease of hydrolysis and tendency to undergo rearrangement. Hydrolysis of the oxazoline hydrochloride gave rise to the O-benzoylamino hydrochloride (XI) which gave the free O-benzoylamine (XII), after neutralization with silver carbonate. The same series of reactions was carried out with the D-*cis*-oxazoline (VIII) and the results were these predicted from the assigned configurations. Thus VIII on mild hydrolysis gave XIII, the enantiomorph of XI, and XIII gave XIV, the enantiomorph of XII.

While the stereochemical configurations of the two amino acids in question have been demonstrated by the reactions to form the D- and L-*cis*-oxazolines, additional evidence for the assigned structures has been obtained by reactions leading to chlorides.

When the reaction between thionyl chloride and the *threo*-N-benzoyl lactone (VI) was carried out at the reflux temperature of thionyl chloride, the product isolated was not an oxazoline, but a neutral chloro compound, D-*threo*-α-benzamido-β-chloro-γ-butyrolactone (XVII), formed by rearrangement of the oxazoline hydrochloride. This compound could also be isolated by fusion of the oxazoline hydrochloride (X) and subsequent recrystallization. When the *erythro*-N-benzoyl lactone (XVI) reacted with thionyl chloride, the only product isolated was a neutral water-insoluble chloro compound which gave an analysis corresponding to that calculated for the β-chloro compound (XVIII). No oxazoline formation could be detected. This is in accordance with the assigned configuration of XVI and the well established steric course of oxazoline formation by reaction of N-acylamino alcohols with thionyl chloride. Since a backside attack by the carbonyl oxygen of the benzamido group on the carbon atom bearing the hydroxyl group is not possible, chloride formation occurs.

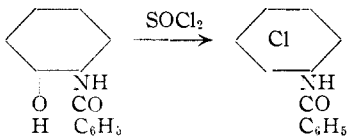
In physical appearance XVII and XVIII are identical and they are crystallized from the same solvent. The melting point and specific rotation (opposite in sign) of XVIII are, however, lower than those of XVII. This suggests the possibility that these two products may be primarily enantiomers, the difference in melting point and specific rotation being due to a mixture of two diastereoisomers in one of the products. The assignment of configuration of XVII is reasonably certain as the steric course of the reaction, oxazoline hydrochloride (X) → chloro compound (XVII), presents little difficulty. Since cleavage occurs at the carbon–oxygen bond of the oxazoline ring, and from what is known of displacement reactions, it seems very likely that an inversion takes place at the carbon atom which eventually bears the chlorine atom. The same reasoning holds for the conversion of VI to XVII in refluxing thionyl chloride, since the hydrochloride (X) is undoubtedly the intermediate. In accordance with this steric picture, McCasland and Smith[13b] have shown that when *dl*-2-*p*-nitrophenyl-4,5-cis-cyclohexanoöxazoline-2-hydrochloride was fused, *dl-trans*-2-*p*-nitrobenzoylaminocyclohexyl chloride was formed, an inversion having taken place at the carbon atom eventually bearing the chlorine atom.



The steric result of the reaction between XVI and thionyl chloride to give (XVIII) is, however, by no means as clear cut. There seems little possibility of intermediate oxazoline formation in this case so that inversion by this path is ruled out. The reaction between alcohols and thionyl chloride may go with retention or inversion of configuration depending on the conditions employed.[14] In an article which summarizes a large part of the previous investigations of these reactions, Gerrard[14c] states, "although it appears certain that the chloride, RCl, is formed by the decomposition of the chlorosulfinate when pyridine has been used in the system, it is by no means probable that the chlorosulfinate is an essential intermediate when thionyl chloride alone is used." Thus, in those cases where an inversion does apparently occur, the chlorosulfite is considered to be the intermediate, whereas in cases where retention occurs, the formation of an intermediate chlorosulfite is doubtful. Since both VI and XVI on treatment with thionyl chloride at room temperature dissolved and then yielded a copious precipitate which, on recrystallization from water or water–ethanol mixture gave back starting material it is probable that the chlorosulfite was the intermediate in the reactions VI → VII and XVI → XVIII. In the latter case this indicates that chloride formation probably proceeds with inversion. Furthermore, Johnson and Schubert[13a] have converted *dl-cis*-2-benzoylaminocyclohexanol into *dl-trans*-2-benzoylaminocyclohexyl

(14) (a) A. McKenzie and F. Borrow, *J. Chem. Soc.*, **99**, 1910 (1911); (b) J. Kenyon, A. G. Lipscomb and H. Phillips, *ibid.*, 415 (1930); (c) W. Gerrard, *ibid.*, 218 (1940).

chloride by treatment with thionyl chloride alone, showing that inversion can take place in the absence of pyridine. These authors made no attempt to determine whether or not the chlorosulfite was the intermediate. Fry,[13f] however, has shown that



chlorosulfites are intermediates when N-acylamino alcohols react with thionyl chloride to form oxazolines.

The evidence makes it seem likely that, in the formation of XVIII from XVI, the reaction goes primarily with inversion so that the major portion of the product is the *trans* compound (enantiomer of XVII).

Experimental

D-*threo*- and D-*erythro*-α-Amino-β,γ-dihydroxybutyric Acids (I and II).—After several unsuccessful attempts to prepare the amino acids from D-glyceraldehyde[15] or acetone-D-glyceraldehyde[16] by the hydantoin method, the procedure used was essentially the same as that described by Fischer and Feldmann.[3b] From 75 g. of 1,2,5,6-diacetone-D-mannitol,[17] 24.3 g. of crude D-*threo*-α-amino-β,γ-dihydroxybutyric acid, m.p. 190–200° dec. was obtained. Two recrystallizations from 60% aqueous methanol gave a product melting at 214–215° dec. and having $[\alpha]^{23}D$ −13.6° (*c* 1.60, in water); reported[4] for I, m.p. 215° and $[\alpha]^{24}D$ −13.7°.

Addition of methanol to the filtrate[4] from the *threo*-acid yielded 6.2 g. of D-*erythro*-α-amino-β,γ-dihydroxybutyric acid which separated as crystals. After three recrystallizations from 50% aqueous methanol and one recrystallization from water this product had m.p. 193–194° and $[\alpha]^{23}D$ +15.3° (*c* 7.02, in water); reported[4] for II, m.p. 192–194° and $[\alpha]^{24}D$ +16.0°.

D-*threo*-α-Benzamido-β-hydroxy-γ-butyrolactone (VI).—The procedure followed was similar to that described by Klosterman and Painter[18] for the benzoylation of α-amino-γ-hydroxybutyric acid. From 30 g. of crude *threo*-amino acid (I) the yield of almost pure N-benzoyl lactone, m.p. 209–211°, was 43 g. (87%). Recrystallization by dissolving in sodium hydroxide solution and acidifying to congo red paper gave a product which had m.p. 211–212° and $[\alpha]^{23}D$ +31.0° (*c* 3.00, in aqueous solution containing an equivalent amount of sodium hydroxide) for the anion of the free acid; reported[4] m.p. 210–211° and $[\alpha]^{24}D$ +31.3° measured in the same manner.

D-*erythro*-α-Benzamido-β,γ-dihydroxybutyric Acid (XV) and Isolation of D-*erythro*-α-Benzamido-β-hydroxy-γ-butyrolactone (XVI).—The D-*erythro*-amino acid (II) was benzoylated using the same procedure followed for the *threo*-acid, except that evaporation of the aqueous layer after ether extraction was not necessary. 2.2 g. of *erythro*-acid yielded 2.1 g. (54%) of crude N-benzoylamino acid. Recrystallization from hot water gave a product which had m.p. 134–136° and $[\alpha]^{23}D$ −22.4° (*c* 1.66, in aqueous solution containing an equivalent amount of sodium hydroxide). The previously reported values for XV are m.p. 135–136° and $[\alpha]^{24}D$ −23.3°[4] (also measured as a solution of the sodium salt).

Upon long standing at room temperature the filtrate from the above recrystallization deposited 0.55 g. of XVI as long, shining plates which were filtered off and dried; m.p. 144–146°. After two recrystallizations from 50% ethanol the product melted at 149–151°. The lactone did not dissolve in cold, saturated sodium bicarbonate solution or 3 *M* hydrochloric acid. *Anal.* Calcd. for $C_{11}H_{11}NO_4$: C, 59.80; H, 4.99; N, 6.33. Found: C, 59.87; H, 5.16; N, 6.23, 6.27.

D-*erythro*-α-Amino-β-hydroxy-γ-butyrolactone Hydrochloride (III).—When a suspension of 2.7 g. of D-*erythro*-amino acid (II) in 70 ml. of absolute ethanol was treated with a rapid stream of anhydrous hydrogen chloride for five minutes and the temperature allowed to rise, all of the amino acid went into solution. Upon cooling, white crystals separated. A stream of hydrogen chloride was passed in at 10° until saturation was evident and the mixture allowed to stand for one hour at this temperature. The crystals were then filtered, washed with a large volume of absolute ethyl ether, and dried in a vacuum desiccator over potassium hydroxide. The product weighed 2.0 g. (65%) and had m.p. 174–175° dec. and $[\alpha]^{23}D$ −51.2° (*c* 4.25, in water). *Anal.* Calcd. for $C_4H_8NO_3Cl$: C, 31.29; H, 5.21; N, 9.11; Cl, 23.22. Found: C, 31.12; H, 4.98; N, 9.20; Cl, 23.80.

D-*erythro*-α-Benzamido-β-hydroxy-γ-butyrolactone (XVI) from the *erythro*-Lactone Hydrochloride (III).—To a solution containing 3 g. of D-*erythro*-α-amino-β-hydroxy-γ-butyrolactone hydrochloride in 30 ml. of water plus 60 ml. of saturated sodium bicarbonate 2.25 ml. of benzoyl chloride was added over 20 minutes while the temperature was held below 5°. A white solid separated from the basic solution while the mixture was stirred an additional 1.5 hr. at 5°. The solid was filtered off, washed with a little water and recrystallized twice from 50% ethanol to yield 2.9 g. (67%) of long, shiny plates, m.p. 149–151°. The melting point was not depressed when this substance was mixed with the benzamido lactone isolated from the mother liquor from XV.

L-*cis*-2-Phenyl-5-hydroxymethyl-4-carboxyoxazoline Lactone (VII).—A suspension of 20 g. of the N-benzoyl *threo*-lactone (VI) in 100 ml. of ice-cold thionyl chloride was warmed gradually to 45° with stirring. The lactone went into solution and a heavy precipitate, presumably the chlorosulfite ester,[19] formed in a semi-solid mass. After an additional 80 ml. of thionyl chloride was added and the mixture again heated to 45° with stirring, the solid dissolved to give a clear, amber colored solution. If the temperature was allowed to rise above 45° the yield of oxazoline was reduced due to rearrangement to the β-chloro compound. The solution was protected from moisture by a drying tube and kept in a bath at 35–40° for seven hours. After the excess thionyl chloride was removed *in vacuo* at 30°, 100 ml. of cold (−5°) dry pyridine was added to the residue and the mixture warmed gradually to 30° until dissolved. The oxazoline precipitated when the dark red solution was added gradually to 850 ml. of a stirred solution of saturated sodium bicarbonate maintained at 5°. The light brown solid was washed with water, air dried and recrystallized by dissolving in hot chloroform and filtering with Norit. The yield of white, cubic crystals was 14.5 g. (79%), m.p. 190.5–1.5°, $[\alpha]^{23}D$ +254° (*c* 1.30, in methyl ethyl ketone). *Anal.* Calcd. for $C_{11}H_9NO_3$: C, 65.10; H, 4.43; N, 6.90. Found: C, 65.42; H, 4.20; N, 6.84.

L-*cis*-2-Phenyl-5-hydroxymethyl-4-carboxyoxazoline Lactone Hydrochloride (X).—This compound could be isolated from the thionyl chloride solution described above by adding an excess of absolute ether to the solution after the seven-hour heating period. The product obtained in this manner, however, was impure and purification was difficult due to its tendency to rearrange to the β-chloro compound (XVII) on heating and to hydrolyze to the O-benzoyl hydrochloride (XI) in the presence of small amounts of water.

The compound was more conveniently prepared by dissolving 0.5 g. of L-*cis*-oxazoline (VII) in 10 ml. of dry chloroform and passing in a slow stream of anhydrous hydrogen chloride for five minutes while cooling the solution in an ice-bath. The precipitate which formed was filtered after four hours at 0° and the white solid washed with a large volume of absolute ether and dried *in vacuo* over potassium hydroxide. The product weighed 0.4 g. (68%) and melted at 173–175° with a slight sinter at 153–155°. If the melting point tube was inserted at a temperature of 160° the solid melted completely, then solidified and remelted at 173–175°. This behavior is due to rearrangement of the hydrochloride to the β-chloro compound (XVII) at its melting point, 153–155°.

L-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone (XII).—A suspension of 2.0 g. of L-*cis*-oxazoline (VII) in 25 ml. of a

(15) E. Baer and H. O. L. Fischer, THIS JOURNAL **61**, 761 (1939).
(16) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 467 (1939).
(17) E. Baer, THIS JOURNAL, **67**, 338 (1945).
(18) H. J. Klosterman and E. P. Painter, *ibid.*, **69**, 1674 (1947).

(19) A little of this solid was filtered off, dried on a porous plate and recrystallized from water, yielding the original *threo*-lactone. The chlorosulfite would be expected to yield starting material, sulfur dioxide and hydrochloric acid by hydrolysis in water.

solution containing an equivalent amount of hydrochloric acid was shaken on a mechanical shaker for three hours. The solution was filtered and after the addition of a slight excess of silver carbonate and rapid filtration of the silver chloride, lustrous, white plates separated. After four hours at 0°, the product obtained weighed 1.9 g. (87%), and melted at 214–216°. Recrystallization from alcohol did not raise the melting point. This compound is insoluble in cold, saturated sodium bicarbonate solution but dissolves in 3 *M* hydrochloric acid. *Anal.* Calcd. for $C_{11}H_{11}NO_3$: C, 59.80; H, 4.99; N, 6.33. Found: C, 59.56; H, 5.20; N, 6.43.

L-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone Hydrochloride (XI). (A) **From L-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone (XII).**—Prepared by dissolving the aminobutyrolactone (XII) in an anhydrous solvent and passing in a slow stream of dry hydrogen chloride. The solid that separated was filtered after several hours at 0°, washed with a large volume of absolute ether and dried *in vacuo* over potassum hydroxide. This compound had m.p. 165–167° and $[\alpha]^{23}D$ +104° (*c* 4.60, in water). After 48 hours the specific rotation dropped to +48°, then remained constant. This was shown to be due to hydrolysis to benzoic acid and L-*erythro*-α-amino-β-hydroxy-γ-butyrolactone hydrochloride by the isolation of substantial amounts of benzoic acid and the rotation of isolated IV. *Anal.* Calcd. for $C_{11}H_{12}NO_4Cl$: N, 5.44; Cl, 13.78. Found: N, 5.10; Cl, 14.46.

(B) **From L-*cis*-2-Phenyl-5-hydroxymethyl-4-carboxyoxazoline Lactone (VII).**—A suspension of 0.3 g. of L-*cis*-oxazoline in 3.5 ml. of 3 *M* hydrochloric acid was shaken for five minutes. The solid went into solution gradually and shortly thereafter a gelatinous precipitate formed which was filtered off and washed with a little cold water. Drying of the product *in vacuo* over potassium hydroxide yielded 0.2 g. (53%) of white powdery solid melting at 164–166°. A mixed melting point with the hydrochloride prepared above was not depressed.

L-*erythro*-α-Amino-β-hydroxy-γ-butyrolactone Hydrochloride (IV).—A suspension of 3 g. of L-*cis*-oxazoline (VII) in 30 ml. of 3 *M* hydrochloric acid was dissolved by heating to boiling. After refluxing for one hour and forty-five minutes a little Norit was added and the hot solution filtered. After cooling, the filtrate was extracted with three 15-ml. portions of ether to remove benzoic acid and the aqueous layer evaporated to dryness *in vacuo* at 30–35°. The residue was taken up in 25 ml. of hot absolute ethanol and the solution filtered. Gradual addition of absolute ether (150 ml.) to the filtrate with scratching of the vessel wall produced fine, white needles which were filtered off and dried *in vacuo* over potassium hydroxide. The yield of product melting at 174–175° was 1.6 g. (70.5%), $[\alpha]^{23}D$ +50.4° (*c* 4.00, in water). *Anal.* Calcd. for $C_4H_8NO_4Cl$: N, 9.11; Cl, 23.22. Found: N, 9.33; Cl, 23.04.

D-*cis*-2-Phenyl-5-hydroxymethyl-4-carboxyoxazoline Lactone (VIII).—A solution of sodium carbonate was added to ethyl iminobenzoate hydrochloride[20] at 0–5° and the free base extracted with ether. After the solution was dried with Drierite, the ether was evaporated *in vacuo*, and the ethyl iminobenzoate distilled at reduced pressure. The fraction boiling at 101.5–102.5° was taken as reasonably pure ethyl iminobenzoate.

A mixture of 2.0 g. of the D-*erythro*-α-amino-β-hydroxy-γ-butyrolactone hydrochloride (III) in 6 ml. of water, and 2.94 g. of ethyl iminobenzoate in 30 ml. of ether was shaken vigorously on a mechanical shaker for 14 hours. The solid which had separated was filtered off and washed with water to remove ammonium chloride. The product was recrystallized from chloroform to yield white, cubic crystals melting at 190.5–191.5° and having $[\alpha]^{25}D$ −251° (*c* 1.74, in methyl ethyl ketone). *Anal.* Calcd. for $C_{11}H_9NO_3$: N, 6.90. Found: N, 6.72, 6.89.

D-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone (XIV).—This compound was prepared from the D-*cis*-oxazoline (VIII) in the manner previously described for the preparation of its enantiomer from the L-*cis*-oxazoline. It had m.p. 214–216° dec. *Anal.* Calcd. for $C_{11}H_{11}NO_3$: N, 6.33. Found: N, 6.54.

D-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone Hydrochloride (XIII).—This compound could be prepared from the amino lactone (XIV) or from the D-*cis*-oxazoline (VIII) in the same manner described previously for the L-compound. It melted at 164–166° and had $[\alpha]^{23}D$ −106° (*c* 4.00, in water). The specific rotation dropped to a final value of −49.5° after 48 hours. *Anal.* Calcd. for $C_{11}H_{12}NO_4Cl$: N, 5.44; Cl, 13.78. Found: N, 5.49; Cl, 13.91.

L-*threo*-α-Amino-β,γ-dihydrobutyric Acid (V).—To 25 ml. of a saturated solution of barium hydroxide, 25 ml. of methanol was added and the solution filtered to remove a little cloudiness. The flask was shaken until 2.0 g. of added L-*cis*-oxazoline (VII) dissolved. After the solution had stood at room temperature for four days, some cloudiness developed. Concentrated hydrochloric acid (11 ml.) was then added and the solution refluxed for one hour and fifteen minutes. The solvent was distilled off until the distilling temperature reached 100° and after cooling, the solution was thoroughly extracted with ether. The aqueous layer was made basic to litmus by adding a solution of barium hydroxide. Barium ion was removed by treatment with 6 *N* sulfuric acid, chloride ion by treatment with silver carbonate, and finally the slight excess of silver ion was removed quantitatively by addition of *N* hydrochloric acid. The resulting solution was evaporated to dryness *in vacuo* and the residue dissolved in a minimum volume of hot water. The solution was filtered and the hot filtrate treated with methanol until cloudiness developed. The white crystals that separated had m.p. 207–210° dec. Recrystallization by dissolving in hot water and adding methanol gave 0.5 g. (60%) of product that melted at 214–215° dec. and had $[\alpha]^{23}D$ +13.1° (*c* 4.80, in water). *Anal.* Calcd. for $C_4H_9NO_4$: N, 10.37. Found: N, 10.09.

D-*threo*-α-Benzamido-β-chloro-γ-butyrolactone (XVII). (A) **From D-*threo*-α-Benzamido-β-hydroxy-γ-butyrolactone (VI).**—Thionyl chloride (20 ml.) and 2.0 g. of the benzamido lactone (VI) were refluxed for 1.5 hours and the excess thionyl chloride removed by evaporation *in vacuo*. The residue was heated to 70° at 1 mm. for one hour to ensure complete rearrangement to the chloro compound and was then dissolved in hot absolute ethanol, decolorized with Norit, and filtered. Addition of three volumes of water to the filtrate and cooling gave 1.0 g. (46%) of white, fine needles. The melting point of this compound seemed to be dependent on the rate of heating. If the tube was inserted at 130° and the temperature raised slowly it melted 170–172°, whereas if the tube was inserted at 170° and the temperature raised rapidly it melted at 179–181°. Recrystallization by dissolving in hot ethanol and adding water had no effect on the melting point. The material had $[\alpha]^{24}D$ −136° (*c* 0.356, in absolute ethanol). *Anal.* Calcd. for $C_{11}H_{10}NO_3Cl$: C, 55.12; H, 4.21; N, 5.85; Cl, 14.83. Found: C, 54.90; H, 4.30; N, 5.99; Cl, 15.85.

(B) **From L-*cis*-2-Phenyl-5-hydroxymethyl-4-carboxyoxazoline Lactone Hydrochloride (X).**—Fusion of the oxazoline hydrochloride followed by recrystallization as described above gave a 53% yield of the β-chloro compound, m.p. 179–181° on rapid heating from 170°. A mixed melting point with the material prepared above was not depressed. The compound had $[\alpha]^{24}D$ −133° (*c* 0.300, in absolute ethanol).

Reaction of D-*erythro*-α-Benzamido-β-hydroxy-γ-butyrolactone (XVI) with Thionyl Chloride. Isolation of α-Benzamido-β-chloro-γ-butyrolactone (XVIII).—Ice-cold thionyl chloride (25 ml.) was added to 0.5 g. of the lactone (XVI) and after shaking a few minutes the solid dissolved. A precipitate soon formed[21] which dissolved when heated to 50°. After the solution had stood for eight hours at 45° the thionyl chloride was evaporated *in vacuo* and the light colored residue taken up in a minimum volume of hot absolute ethanol and filtered with a little Norit. Addition of three volumes of water to the filtrate and cooling gave 0.24 g. of white fine needles, m.p. 158–160°. Recrystallization by dissolving in hot ethanol and adding water gave a product melting at 159–161° and having $[\alpha]^{22}D$ +115° (*c* 0.150, in absolute ethanol). *Anal.* Calcd. for $C_{11}H_{10}NO_3Cl$: C, 55.12; H, 4.21; N, 5.85; Cl, 14.83. Found: C, 54.57; H, 4.53; N, 6.22; Cl, 14.41.

Attempted Preparation of D-*threo*-α-Amino-β-hydroxy-γ-butyrolactone Hydrochloride.—A suspension of 2 g. of the

(20) A. W. Dox, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 6.

(21) A sample of this material was removed, dried on a porous plate, and recrystallized from 50% ethanol. The crystals obtained proved to be identical with the starting material (XVI). When the solid was washed thoroughly with absolute ether and stored in a vacuum desiccator over potassium hydroxide it gave a positive test for chloride. It is very likely that this was the chlorosulfite.

D-*threo*-acid (I) in 50 ml. of absolute ethanol was treated with dry hydrogen chloride in the same manner as previously described for the D-*erythro*-acid, but, in this case, no crystalline product formed on cooling. Evaporation of the solvent gave an oil which failed to crystallize. When this residue was treated with ethyl iminobenzoate in the manner described by Johnson and Schubert[13a] there was no evidence of a *trans*-oxazoline being formed. A thick viscous oil was obtained which appeared to be starting material.

D-*erythro*-α-Benzamido-β-benzoxy-γ-butyrolactone.—A mixture of 2.0 g. of D-*erythro*-α-amino-β-hydroxy-γ-butyrolactone hydrochloride, 17 ml. of dioxane, 2.7 g. of anhydrous potassium carbonate and 0.7 ml. of water was stirred and cooled in an ice-bath while 1.5 ml. of benzoyl chloride was added over a 15-minute period. After the addition was complete the mixture was stirred for another hour and a half and was then poured into a mixture of cracked ice and water (70 g.). The precipitate which formed was filtered off and dried on a porous plate. Recrystallization from absolute ethanol gave 0.1 g. of white needles, m.p. 177–178°. *Anal.* Calcd. for $C_{18}H_{15}NO_5$: N, 4.31. Found: N, 4.58, 4.61.

Benzoyl Migration O → N_2 on Treatment of D-*erythro*-α-Amino-β-benzoxy-γ-butyrolactone Hydrochloride with Base.—A solution of 0.2 g. of the O-benzoyl hydrochloride (XIII) in 5 ml. of water was treated with a slight excess of dilute sodium hydroxide solution at room temperature. The solution was allowed to stand one-half hour and was then acidified to congo red paper with concentrated hydrochloric acid. After standing for several days the solid which had separated was filtered off and recrystallized from water to yield 0.14 g. (76%) of N-benzoyl acid XV, m.p. 133–136°. A mixed melting point with an authentic sample of N-benzoyl acid was not depressed.

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[CONTRIBUTION NO. 882 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Pyridylethylation of Active Nitrogen Compounds. II. Further Studies of the Reactions of 2-Vinylpyridine with Ketones

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Several ketones have been pyridylethylated with 2-vinylpyridine and the structures of a number of the products have been determined. Both metallic sodium and Triton B are effective catalysts for these reactions. For the first time, the pyridylethylation of a simple ester, ethyl isobutyrate, and of a nitrile, propionitrile, are reported.

Some time ago, we reported[2] that the Michael addition of a number of ketones to 2-vinylpyridine could be effected satisfactorily in the presence of sodium metal as the condensing agent. The present report is concerned with (a) a further elucidation of the course of reaction of methyl alkyl ketones with 2-vinylpyridine, (b) the preparation of di- and tripyridylethylated ketones and (c) the establishment of satisfactory conditions for the use of benzyltrimethylammonium hydroxide (Triton B) as a pyridylethylation catalyst.

After the publication of our first report[2] in which we gave proof that in the addition of 2-vinylpyridine to methyl isobutyl ketone and methyl ethyl ketone, reaction occurred at the α-methyl carbon atom of the former ketone and at the α-methylene carbon atom of the latter ketone, a patent by Clifford[3] was brought to our attention in which it was indicated that methyl ethyl ketone is pyridylethylated at the α-methyl carbon atom. Although no proof for this claim was given by Clifford, it appeared desirable to prove the structure of the compound by a method different from that which we had used previously. Our proof of structure is shown in the following scheme. The pyridylethylated ketone, I, was converted to its semicarbazone, which was then subjected to Kishner reduction[4] to give II, which was identical with the material obtained by the alkylation of α-picoline with 1-chloro-2-methylbutane using the Chichibabin reaction as modified by Brody and Bogert.[5]

$$\underset{\text{I}}{2\text{-}C_5H_4NCH_2CH_2CH(CH_3)COCH_3} \xrightarrow[\text{2. Kishner reduction}]{\text{1, semicarbazone}} \underset{\text{II}}{2\text{-}C_5H_4NCH_2CH_2CH(CH_3)CH_2CH_3}$$

$$2\text{-}C_5H_4NCH_3 + ClCH_2CH(CH_3)CH_2CH_3 \xrightarrow{NaNH_2} \text{II}$$

Depending on the molecular proportions of reactants (Table I), it was found that the degree of pyridylethylation of methyl ethyl ketone as well as other methyl alkyl ketones could be controlled. That the dipyridylethylated methyl ethyl ketone has both of the pyridylethyl groups on the methylene carbon atom, *i.e.*, that the compound formed was 3,3-bis-(2-(2-pyridyl)-ethyl)-2-butanone (III) was shown by the following series of reactions, involving the haloform oxidation of III to IV, which was then compared with an authentic sample. To our knowledge, the pyridylethylation of propionitrile represents the first reported use of a completely

$$\underset{\text{III}}{(2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)COCH_3} \xrightarrow{KOCl} \underset{\text{IV}}{(2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)CO_2H}$$

$$2\ 2\text{-}C_5H_4NCH{=}CH_2 + CH_3CH_2CN \xrightarrow{Na} \underset{\text{V}}{(2\text{-}C_5H_4NCH_2CH_2)_2C(CH_3)CN}$$

aliphatic nitrile containing no activating groups, as an addendum in a Michael reaction. Although the structure of the tripyridylethylated derivative of methyl ethyl ketone was not proved, it is probable that this compound was formed by the introduction of two pyridylethyl groups at the α-methylene car-

(1) This paper is based on part of a thesis presented by Myron H. Wilt to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(2) R. Levine and M. H. Wilt, THIS JOURNAL, **74**, 342 (1952).

(3) A. M. Clifford, U. S. Patent 2,579,419, Dec. 18, 1951.

(4) D. Todd, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, p. 396.

(5) F. Brody and M. T. Bogert, THIS JOURNAL, **65**, 1075 (1943).