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Cyclization of Some *O*-Substituted Derivatives of *N*-(3,4-Dimethoxy-β-phenylethyl)glycolamide; Synthesis of (±)-Calycotomine

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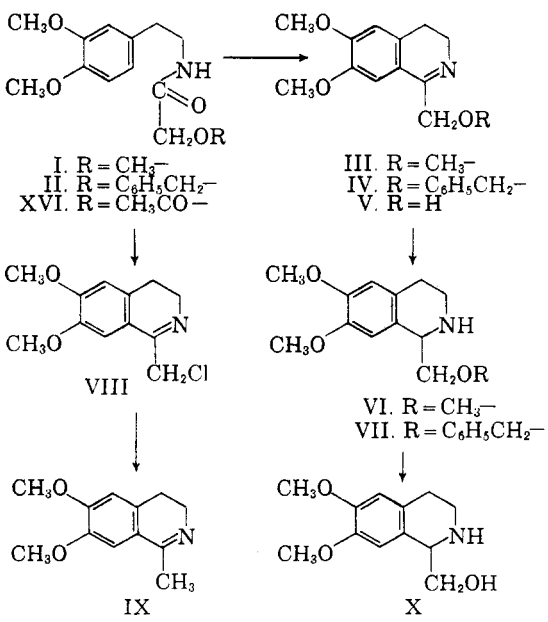
Received May 19, 1960

Attempts to cyclize *N*-(3,4-dimethoxy-β-phenylethyl)alkoxyacetamides with phosphorus oxychloride or phosphorus pentoxide resulted in extensive decomposition and tar formation rather than formation of the desired 1-alkoxymethyl-3,4-dihydroisoquinolines. Cyclization was effected by phosphorus pentachloride, but, in addition, cleavage occurred and a 1-chloromethyl-3,4-dihydroisoquinoline was formed. A possible mechanism for this reaction is discussed. A synthesis of (±)-calycotomine was achieved by cyclization of *N*-(3,4-dimethoxy-β-phenylethyl)acetoxyacetamide with phosphorus oxychloride followed by catalytic hydrogenation.

In the course of certain studies of the synthesis of isoquinoline compounds, we have had the occasion to examine various routes for preparing 1-hydroxymethylisoquinolines from readily available intermediates. At the beginning of this investigation, an examination of the literature concerning the Bischler-Napieralski ring closure[1] of *N*-acyl-β-phenethylamines failed to show any cyclizations which had given 1-hydroxymethyl-3,4-dihydroisoquinolines as end products.

The present study was undertaken to examine the possibility of cyclizing *N*-alkoxyacetylhomoveratrylamines (I and II) to the corresponding 1-alkoxymethyl-3,4-dihydroisoquinolines (III and IV) *via* the Bischler-Napieralski method; subsequent ring hydrogenation and ether cleavage of III and IV would accordingly be expected to yield (±)-1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-dimethoxyisoquinoline[2] (X).



The starting *O*-alkylglycolylamides I and II were obtained in good yield by treating an excess of homoveratrylamine respectively with methoxyacetyl chloride and benzyloxyacetyl chloride. As both amides are suitably activated for electrophilic ring closure by methoxy groups, it was expected that cyclization would occur readily in the presence of phosphorus pentoxide or phosphorus oxychloride.[1] However, neither I nor II was found to undergo cyclization to the corresponding 1-alkoxymethyl-3,4-dihydroisoquinoline III or IV when refluxed with either of these reagents in toluene or benzene. Polyphosphoric acid[3] was likewise ineffective in bringing about the cyclization of II to IV. In a further variation of conditions for the Bischler-Napieralski cyclization, II was subjected to the action of phosphorus pentachloride in chloroform solution at room temperature for about fifteen hours; the hydrogen chloride which was liberated during the first two hours of the reaction was taken as evidence of cyclization. The purified reaction product, obtained as a yellow hydrochloride salt, which was thought to be the dihydroisoquinoline V, was then hydrogenated in methanol solution over a 10% palladium-on-charcoal catalyst. The resulting hydrogenation product (free base) was found to give an incorrect analysis for X, and was subsequently identified as 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX), which had been described previously by Kaufmann and Radosevic.[4] The unhydrogenated cyclization product of II was shown to be identical with 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII) hydrochloride prepared by the cyclization of *N*-chloroacetylhomoveratrylamine as described by Child and Pyman.[5] The free base VIII on standing at room temperature undergoes

(1) R. Adams, *Org. Reactions*, *VI*, 74 (1951).

(2) Compound X is the naturally occurring alkaloid (±)-calycotomine, first isolated by E. P. White, *New Zealand J. Sci. Tech.*, **25B**, 152 (1944), from *Calycotome Spinosa*. Well after our study had been initiated, A. R. Battersby and T. D. Edwards, *J. Chem. Soc.*, 1909 (1959), described the first synthesis of X *via* cyclization of ethyl *N*-3,4-dimethoxyphenethyloxamate followed by reduction of the resulting 3,4-dihydroisoquinoline ester to X with lithium aluminum hydride.

(3) N. J. Leonard and J. H. Boyer, *J. Am. Chem. Soc.*, **72**, 2980 (1950).

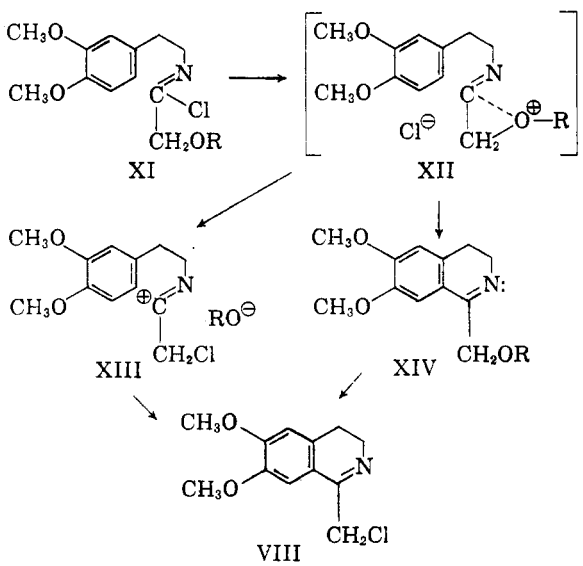
(4) A. Kaufmann and R. Radosevic, *Ber.*, **49**, 675 (1916).

(5) R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931).

an intermolecular reaction to form a dark, water-soluble quarternary salt which was not further characterized.

It was at first assumed that the ether cleavage which occurred during the cyclization of II to VIII was due to the tendency of reactive benzyl ethers to undergo scission with certain Lewis acids *via* a weak oxonium salt. However, when *N*-methoxyacetylhomoveratrylamine (I) was subjected to the action of phosphorus pentachloride under the same conditions used in the cyclization of II, the same reaction product, namely, 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII), was again obtained.

This evidence suggests two possible reaction mechanisms as being operative in the cyclization of *N*-alkyloxyacetylhomoveratrylamines with phosphorus pentachloride. The first step in the Bischler-Napieralski cyclization is the formation of an imino chloride, XI, resulting from the elimination of hydrogen chloride from the unstable grouping $ArCH_2CH_2NHCCl_2R$. An inductive shift then gives rise to the intermediate cyclic oxinium ion XII, in which the accompanying chloride anion shifts to the terminal carbon atom. The resulting shift takes place with the elimination of an alkoxyl anion, producing the carbonium ion XIII which, in turn, internally cyclizes to the final cyclic 1-chloromethyl compound VIII *via* an electrophilic



attack on the aromatic ring. A second mechanism would involve the direct cyclization of XI through the elimination of hydrogen chloride to form the 1-alkoxymethyl compound XIV. This, in turn, could undergo an S_N2-type nucleophilic displacement with Cl^- to form the same final 1-chloromethyl compound VIII. The fact that none of the 1-alkoxymethyl compound XIV was isolated would seem to favor occurrence of electrophilic cyclization prior to ether cleavage.

Several attempts were made to convert the 1-chloromethyl compound VIII to the corresponding 1-hydroxymethyl and 1-acetoxymethyl compounds. Refluxing VIII in methanol with silver hydroxide failed to give the desired compound V; instead, intractable tars were formed. Similarly, refluxing VIII with sodium acetate in the same solvent failed to give the corresponding 1-acetoxymethyl derivative.

In an alternative approach to obtaining X, *N*-acetoxyacetylhomoveratrylamine (XVI) was prepared by treating acetoxyacetyl chloride with homoveratrylamine. Refluxing XVI in dry toluene with phosphorus oxychloride resulted in a low yield of 1-hydroxymethyl-5,6-dimethoxy-3,4-dihydroisoquinoline (V). This result was somewhat surprising in that the acetyl group was eliminated during this reaction. Reduction of V in ethanol solution over 10% palladium-on-charcoal catalyst afforded (±)-1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-dimethoxyisoquinoline (X), identical in properties with (±)-calycotomine described by White[2] and Battersby.[2] The picrate salt of X prepared by us was higher in melting point than the (±)-calycotomine picrate described by White as a hydrated salt; our derivative, prepared under anhydrous conditions, gave a correct analysis for the picrate of X.

EXPERIMENTAL[6]

N-(3,4-Dimethoxy-β-phenylethyl)methoxyacetamide (I). A mixture of 45 g. of methoxyacetic acid and 59.5 g. of thionyl chloride was warmed at 40 to 60° on a water bath for 3.5 hr. while passing a slow stream of dry nitrogen through to remove sulfur dioxide and hydrogen chloride. The mixture was distilled under reduced pressure, and the fraction boiling at 46–49°/62 mm. was collected as methoxyacetyl chloride (reported[7] b.p. 51°/69 mm.); yield, 31.1 g. (57%). A solution of 22.7 g. of this acid chloride in 50 ml. of dry benzene was added gradually to a stirred solution of 75.7 g. of 3,4-dimethoxy-β-phenethylamine in 200 ml. of dry benzene. After stirring an additional 15 min., the precipitated amine hydrochloride was removed by filtration, benzene was stripped from the filtrate, and the residue was distilled under reduced pressure to recover pure *N*-(3,4-dimethoxy-β-phenylethyl)methoxyacetamide; b.p. 185–190°/0.5 mm.; yield, 47.9 g. (86%).

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.5. Found: C, 61.3; H, 7.4.

N-(3,4-Dimethoxy-β-phenylethyl)benzyloxyacetamide (II). To a stirred solution of 23 g. of clean sodium cut into small pieces in 475 g. of redistilled benzyl alcohol (stirring for 20 hr. and warming to 70° were required to effect complete solution) was added gradually 123 g. of freshly distilled ethyl chloroacetate with water bath cooling. The mixture was then stirred and heated at about 80° for 2 hr., cooled, treated with water, and the oil which separated was extracted from the aqueous layer with ether. The ether extract was dried (anhyd. magnesium sulfate), the solvent was removed, and the residue was distilled under reduced pressure to obtain a mixture of ethyl and benzyl esters of benzyloxyacetic acid, b.p. 50–165°/0.3 mm.; yield, 128 g. The mixed esters were saponified by refluxing for 1.5 hr. with a mixture of 150 ml. of methanol and 60 ml. of 45% potassium hydroxide. After

(6) Melting points are uncorrected.

(7) R. Leimu, *Ber.*, **70B**, 1049 (1937).

the methanol was removed by evaporation, the residue was diluted with water and then extracted with ether to remove unchanged benzyl alcohol; acidification of the aqueous phase released the crude benzyloxyacetic acid, which was taken up in ether and purified by distillation under reduced pressure; b.p. 135–140°/0.2 mm. (reported,[8] 136°/0.2 mm.); yield 63 g. (38%). The amide of this acid melted at 92–93° (reported,[8] m.p. 91°).

A mixture of 31.5 g. of benzyloxyacetic acid and 42 g. of thionyl chloride was refluxed for 35 min. and the acid chloride formed was purified by distillation under reduced pressure; b.p. 81–83°/0.6 mm.; yield, 34 g. (97%). To a stirred and cooled (ice bath) solution of 67 g. of 3,4-dimethoxy-β-phenethylamine in 600 ml. of dry ether was added portionwise 33.6 g. of benzyloxyacetyl chloride. After stirring a few minutes longer, the copious white precipitate which had formed was filtered by suction and washed with water to remove amine hydrochloride. When the solid had been washed free of chloride ion, it was dried in a vacuum oven at 50° to obtain 54.4 g. (91%) of crude II as a white solid, m.p. 61–63°. After recrystallization from benzene-ether-petroleum ether (b.p. 30–60°), a sample melted at 72–73°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; N, 4.26. Found: C, 69.1; H, 6.8; N, 4.18.

Attempted cyclization of I *and* II *with phosphorus oxychloride or phosphorus pentoxide.* A mixture of 26.5 g. of II, 160 ml. of dry toluene, and 120 g. of phosphorus oxychloride was refluxed for 6 hr., during which time hydrogen chloride was evolved. As no hydrochloride separated on cooling, the mixture was poured into ice water and the aqueous layer was separated and made alkaline with 20% aqueous sodium hydroxide. A brown oil separated and solidified to a dark resinous mass which was insoluble in most solvents and could not be induced to crystallize. Similar results were obtained with phosphorus pentoxide in boiling benzene by the method described by Battersby.[2] Treatments of the amide I with phosphorus oxychloride or phosphorus pentoxide in benzene or toluene also resulted in the formation of intractable tars from which none of the desired dihydroisoquinolines could be isolated.

Action of phosphorus pentachloride on I *and* II; *1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline* (VIII). To a cold solution of 15 g. of II in 125 ml. of chloroform was added in portions 22 g. of phosphorus pentachloride. The phosphorus pentachloride gradually dissolved, and a yellow solid deposited. After standing overnight at room temperature, a clear brown solution was obtained. Most of the chloroform was removed by evaporation, and the residue was dissolved in 50 ml. of water with cooling. After extraction with ether, the aqueous solution was treated with concd. ammonia solution until alkaline, extracted thrice with ether, and the ether solution was washed with water and dried (anhydrous magnesium sulfate). Treatment of the dried ether solution with dry hydrogen chloride precipitated a yellow gum, which was separated from the supernatant ether by decantation and dissolved in boiling alcohol. On cooling a yellow crystalline solid deposited; yield, 9.7 g. of a product, m.p. 200–202° dec. Recrystallization from alcohol gave 7.9 g. (64%) of yellow crystals, m.p. 209–210° dec. This product was identified as 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride, first reported by Child and Pyman[5] (reported m.p. 217° dec.).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_2$: C, 52.2; H, 5.4; Cl (ionic), 12.9. Found: C, 52.2; H, 5.4; Cl (ionic), 12.8.

Catalytic hydrogenation of 6.8 g. of VIII hydrochloride in 150 ml. of methanol over 1 g. of 10% palladium-charcoal at 3 atm. and room temperature gave 5.4 g. of a product m.p. 200–201° as the hydrochloride and m.p. 105–106° as the free base, which contained no halogen. This compound was identified as 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX) (reported[4] m.p. 108° for free base and 200° for hydrochloride).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.3; H, 7.3; N, 6.8. Found: C, 70.2; H, 7.4; N, 6.7.

An authentic specimen of VIII hydrochloride was prepared for comparison purposes by cyclization of *N*-(3,4-dimethoxy-β-phenylethyl)chloroacetamide, m.p. 95–96° (reported,[5] m.p. 96°), as described by Child and Pyman.[5] By refluxing a mixture of 12.9 g. of the amide in 40 ml. of dry toluene and 13 ml. of phosphorus oxychloride there was obtained 11.2 g. (81%) of VIII hydrochloride, m.p. 209–210° dec., which did not depress the melting point of the product obtained from II and phosphorus pentachloride.

Treatment of 10 g. of the amide I in 50 ml. of chloroform with 8 g. of phosphorus pentachloride at 5° for 3 days also resulted in the formation of VIII, which was isolated as the hydrochloride, m.p. 209–210° dec.

N-(3,4-Dimethoxy-β-phenylethyl)acetoxyacetamide. A mixture of 57 g. of glycolic acid and 114 g. of acetyl chloride was refluxed for 3 hr., when evolution of hydrogen chloride had ceased. The mixture was stripped under reduced pressure to remove excess acetyl chloride, and the residue (86 g.) was refluxed for 2 hr. with 119 g. of thionyl chloride. The reaction product was distilled under reduced pressure, and the fraction boiling at 58–61°/19 mm. was collected as acetoxyacetyl chloride; yield, 51 g. (50%); (reported[9] b.p. 51°/14 mm.).

To a stirred solution of 23.3 g. of acetoxyacetyl chloride in 25 ml. of dry benzene was added gradually a solution of 62.7 g. of 3,4-dimethoxy-β-phenethylamine in 300 ml. of dry benzene. After stirring a few minutes longer, the precipitated amine hydrochloride was removed by filtration and washed with additional benzene. The solvent was distilled from the filtrate, and the residue was distilled under reduced pressure; b.p. 212-214°/0.2 mm.; yield, 34.7 g. (73%) of a colorless oil.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.8. Found: C, 60.0; H, 6.9.

(±)-*Calycotomine* (X). A mixture of 21.2 g. of *N*-(3,4-dimethoxy-β-phenylethyl)acetoxyacetamide, 150 ml. of dry toluene, and 112 g. of phosphorus oxychloride was refluxed for 2 hr. Dilution of the cooled solution with petroleum ether (b.p. 30–60°) precipitated a black viscous oil from which the hydrocarbon layer was decanted after settling. The black oil was treated with ice and water, and the resulting solution extracted with ether and then made alkaline with sodium hydroxide solution. The dark oil which separated was extracted with four ether extractions; the ether solution was dried and treated with hydrogen chloride to precipitate a dark-brown gummy hydrochloride. This was dissolved in methanol and the solution treated with small portions of ethyl acetate and ether to give, after standing overnight, three crops of brown crystals. After two recrystallizations from methanol-ether, the product was obtained pure; m.p. 199–200° dec.; yield, 3.1 g. (16%). Analysis showed that the acetyl group had been removed by hydrolysis, and the product isolated was *1-hydroxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride.*

Anal. Calcd. for $C_{12}H_{16}ClNO_3$: C, 56.0; H, 6.2; Cl, 13.8; N, 5.4. Found: C, 56.4; H, 6.2; Cl, 13.6; N, 5.3.

A solution of 1 g. of this hydrochloride in 50 ml. of methanol was shaken with 3 atm. of hydrogen in the presence of platinum oxide catalyst for 30 min. The catalyst was removed by filtration, and the solvent evaporated to a volume of 10 ml. Cooling and treatment with ether induced crystallization, and 800 mg. (80%) of a colorless solid was obtained; m.p. 195–196°, after one more recrystallization from methanol-ether (reported[2] for (±)-calycotomine hydrochloride, m.p. 194–195°). Treatment of a water solution of the hydrochloride with dilute sodium hydroxide gave (±)-calycotomine, m.p. 134–135°, after recrystallization from benzene (reported[2] for (±)-calycotomine, 133–134°).

(8) W. Wenner and J. T. Plati, *J. Org. Chem.*, **11**, 751 (1946).

(9) R. Anschutz, *Ber.*, **36**, 467 (1903).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.6; N, 6.3. Found: C, 64.4; H, 7.5; N, 6.2.

The *picrate* melted at 203–204°.

Anal. Calcd. for $C_{20}H_{22}N_4O_{11}$: C, 47.8; H, 4.4. Found: C, 47.6; H, 4.5.

Acknowledgment. This research was supported by a Battelle Memorial Institute grant.

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The L-Glyceric Acid Monophosphates

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Received April 22, 1960

The syntheses of L-glyceric acid 2- and 3-phosphate from L-arabinose are described. The two new phosphate esters have been characterized by comparison with the previously synthesized D-isomers.

Studies of the effect of the unnatural isomers of substrates and substrate analogues on enzymatic reactions have given information about the configuration of the enzymes' catalytic sites.[1] With the intention of applying this kind of studies to the enzyme enolase, it was of interest to prepare the pure L-isomers of glyceric acid 2- and 3-phosphate. The D-isomers have been prepared previously from D-galactose,[2] but as L-galactose is not readily available as a starting material, a new synthetic route leading to the glyceric acid monophosphates was developed, starting with a more common L-sugar, L-arabinose.

The key intermediate, methyl 2-*O*-benzyl-L-glycerate, was obtained from L-arabinose by the following reaction sequence:

L-arabinose (I) → benzyl β-L-arabinopyranoside (II) → benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (III) → benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-β-L-arabinopyranoside (IV) → 2-*O*-benzyl-L-arabinose (V) → 2-*O*-benzyl-L-arabitol (VI) → 2-*O*-benzyl-L-glyceric acid (VII) → methyl 2-*O*-benzyl-L-glycerate (VIII).

VIII could be phosphorylated in the 3-position and unblocked in the usual manner[2-4] to give the 3-phosphate ester, or it could be benzoylated, debenzylated, phosphorylated, and unblocked again according to standard procedures[2-4] to give the 2-phosphate ester.

II, III, and IV were prepared in good yield, the first according to published methods,[5,6] and were obtained as readily characterizable crystalline products. The hydrolysis of IV to give V was not as easy to accomplish. The hydrolysis conditions must be chosen to give a minimum of hydrolysis of the benzyl ether, and yet be drastic enough to cleave the relatively stable benzyl glycoside. By refluxing for two to three hours with 1*N* hydrochloric acid moderately good yields of V could be obtained. During the first fifteen to twenty minutes of refluxing, the compound would slowly go into solution as the acetal was hydrolyzed. (If the reaction were cooled at this stage, a near quantitative yield of benzyl 2-*O*-benzyl-β-L-arabinoside would crystallize out of the aqueous solution.) After the removal of the acetal, the reducing power of the reaction mixture would slowly increase leveling off after two to three hours. At this time the acid was neutralized and the reaction mixture was taken to dryness. The product could be extracted into hot chloroform, leaving the inorganic salt and some free arabinose behind. A low and variable yield of crystals could be obtained from the chloroform solution upon concentration, and it was found that a drop of concentrated hydrochloric acid would increase the amount of crystalline material, indicating mutarotation and crystallization of one of the anomeric forms. This phenomenon was not investigated further. In practice the chloroform solution was taken to dryness, and if benzyl 2-*O*-benzylarabinoside and free arabinose were shown to be absent by paper chromatography, the sirup was used in the subsequent step without further purification. After reduction to VI and periodate cleavage to give 2-*O*-benzylglyceraldehyde, perpropionic acid oxidation[7] of the aldehyde to the acid was attempted; however, this led to cleavage of the benzyl ether. The iodine oxidation previously described[2] was therefore used giving variable yield.

The two monophosphate esters of L-glyceric acid were characterized by chromatography, titration, and optical rotation, in comparison with the known

(1) M. London, R. McHugh, and P. B. Hudson, *Arch. Biochem. Biophys.*, **73**, 72 (1958); L. I. Pizer and C. E. Ballou, *J. Biol. Chem.*, **234**, 1138 (1959).

(2) C. E. Ballou and H. O. L. Fischer, *J. Am. Chem. Soc.*, **76**, 3188 (1954).

(3) C. E. Ballou, *J. Am. Chem. Soc.*, **79**, 984 (1957).

(4) F. Wold and C. E. Ballou, *J. Am. Chem. Soc.*, **81**, 2368 (1959).

(5) E. Fischer and H. Beensch, *Ber.*, **27**, 2478 (1894).

(6) C. E. Ballou, S. Roseman, and K. P. Link, *J. Am. Chem. Soc.*, **73**, 1140 (1951).

(7) R. Barker, Doctorate thesis, University of California, Berkeley, 1958; J. d'Ans and W. Frey, *Ber.*, **45**, 1845 (1912).