[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Absolute Configuration at C-12 of α-Erythroidine[1]

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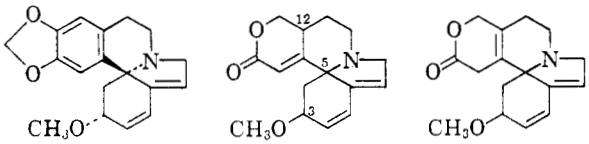
(+)-*o*-Ethylphenyl 3-tetrahydrofuryl ketone, a degradation product of α-erythroidine in which the asymmetric center corresponds to that at C-12 of the alkaloid, was synthesized from (+)-3-tetrahydrofuroic acid. The configuration of this acid was related to that of (+)-methylsuccinic acid by conversion of both to 3-methyltetrahydrofuran. These results establish the configuration at C-12 as that shown in XII.

One of the problems remaining in the chemistry of the erythrina alkaloids[2] concerns their stereochemistry and absolute configuration. The remarkable and clinically useful curariform activity which appears to be specifically associated with the spiroamine moiety[2] makes the determination of configuration a particularly significant problem. The relative orientation of the two asymmetric centers in erythraline (I), a representative of the aromatic group, was determined by x-ray analysis,[3] and it is presumed that the other members of this group have identical configurations because of the similarity in optical rotations; the absolute configuration is unspecified. The configurations at the corresponding positions of the lactonic alkaloids, α-erythroidine (II) and β-erythroidine (III), are unknown.



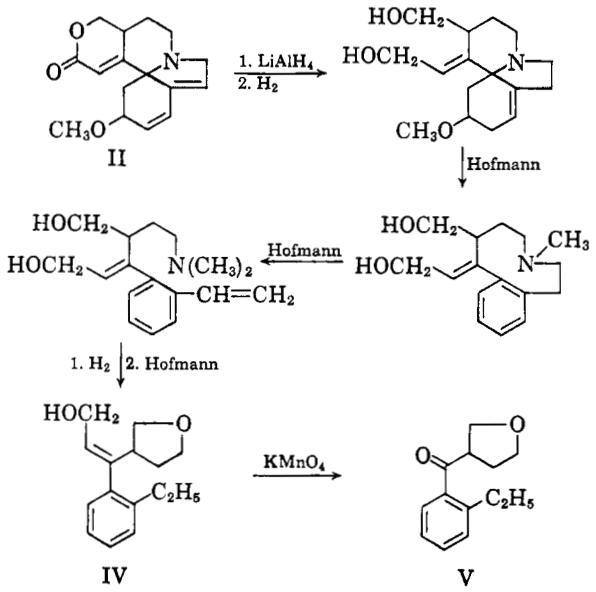
I II III

In addition to the two asymmetric centers at C-3 and C-5 common to all the alkaloids, α-erythroidine (II) possesses an additional center of asymmetry at C-12. The elucidation of the absolute configuration at this position is the subject of this paper.

An attack on this problem is feasible only because of the extensive structural investigations of Godfrey, Tarbell, and Boekelheide.[4] Employing the Hofmann exhaustive methylation procedure, these workers degraded the alkaloid, by the series of reactions shown in Chart I, to the optically active ketone V, in which the asymmetric center corresponds to C-12 of the alkaloid. The course of the degradation was verified by the subsequent synthesis of racemic IV and V.[5] Since none of the reactions in Chart I affected the asymmetric center concerned, the configuration at C-12 is directly related to that in V, and the problem is consequently reduced to the determination of absolute configuration of an uncomplicated tetrahydrofuran. This was accomplished in the following way.

CHART I

DEGRADATION OF α-ERYTHROIDINE[4]



II IV V

3-Tetrahydrofuroic acid (VI) was partially resolved by fractional crystallization of its quinine salt from acetone. The regenerated acid had $[\alpha]_D^{24}$ +4.59° (acetone).[6] Boekelheide and Morrison[5] had synthesized the *d,l*-ketone V from *d,l*-3-tetrahydrofuroic acid by treatment with *o*-ethylphenyllithium, but there would be serious danger of racemization in applying this procedure to the synthesis of an optically active product. Recourse was taken, therefore, to the organocadmium reagent; di(*o*-ethylphenyl)cadmium reacted with the acid chlo-

(1) Presented at the 140th Meeting of the American Chemical Society, Chicago, Ill., September 1961.

(2) For an excellent recent review of the erythrina alkaloids, see V. Boekelheide, in *The Alkaloids*, Vol. VII, edited by R. H. F. Manske, Academic Press, New York, 1960, p. 201.

(3) W. Nowacki and G. F. Bonsma, *Z. Krist.*, 110, 89 (1958).

(4) J. C. Godfrey, D. S. Tarbell, and V. Boekelheide, *J. Am. Chem. Soc.*, 77, 3342 (1955).

(5) V. Boekelheide and G. C. Morrison, *J. Am. Chem. Soc.*, 80, 3905 (1958).

(6) T. Kaneko, H. Katsura, H. Asano, and K. Wakabayashi, *Chem. & Ind.* (London), 1187 (1960), subsequently reported the obtention of acids with rotations of +10.3 and −14.1°.

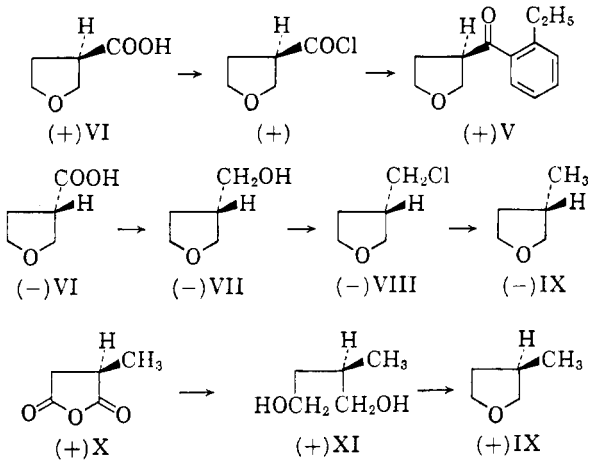
ride of the (+)-acid to form the dextrorotatory ketone V. The reaction of the organocadmium reagent was first tested with benzoyl chloride, and this preparation of *o*-ethylbenzophenone is described in the Experimental section.

In order to prove the absolute configuration of (+)-3-tetrahydrofuroic acid (VI), it was related to (+)-methylsuccinic acid by converting both to 3-methyltetrahydrofuran (IX). Lithium aluminum hydride reduction of (−)-VI gave (−)-3-hydroxymethyltetrahydrofuran (VII), which was converted to the (−)-chloride VIII with thionyl chloride. VIII was reduced by lithium aluminum hydride, though in poor yield, to (−)-IX.

Finally, lithium aluminum hydride reduction of (+)-methylsuccinic anhydride (X) gave (+)-2-methyl-1,4-butanediol (XI), which was cyclized by heating with *p*-toluenesulfonic acid to (+)-3-methyltetrahydrofuran (IX). These reactions are summarized in Chart II.

CHART II

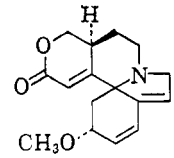
INTERRELATION OF *o*-ETHYLPHENYL 3-TETRAHYDROFURYL KETONE WITH (+)-METHYLSUCCINIC ACID



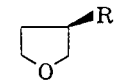
In a preliminary communication, Kaneko and co-workers[6] have reported recently an independent determination of the absolute configuration of the acid VI, and our results are in agreement with theirs.

The absolute configuration of (+)-methylsuccinic acid has been established unambiguously by Fredga's quasi-racemic compound method, as well as by two independent direct chemical interrelations with D-glyceraldehyde.[7] On this basis, configurations are assigned as shown in Chart II, and C-12 of α-erythroidine is correctly represented in formula XII.

Boekelheide and Benzinger have very recently determined the absolute configuration of the methoxyl group in the erythroidines,[8] and their



XII



XIII

conclusion is indicated also in formula XII. Thus, the only remaining center of unknown configuration is the spiro carbon, C-5.

The series of optically active β-substituted tetrahydrofurans of known configuration prepared during the course of this investigation provides an opportunity to test an empirical rule, formulated by Bose and Chatterjee,[9] relating optical rotation to absolute configuration of cyclic compounds. The rule predicts, in this case, that compounds of configuration XIII should be levorotatory, in agreement with the experimental results. That this rule should not be regarded as infallible for five-membered oxygen heterocycles, in spite of its considerable successes, may be seen by its failure to correlate correctly the sign of rotation and absolute configuration of 2-methyltetrahydrofuran,[10] α-hydroxy-γ-butyrolactone,[11] the 3-carboxyl of isocitric and alloisocitric acid lactones,[6] alkylsuccinic anhydrides,[7] and *O*-substituted derivatives of malic and tartaric anhydrides.[12]

EXPERIMENTAL

Melting points were taken in open glass capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer recording spectrophotometer, Model 21-C. Optical rotations were measured on a Rudolph photoelectric polarimeter, Model 200; concentrations of solutions for these measurements are given in g./ml.

(+)-*2-Methyl-1,4-butanediol* (XI). To a well stirred slurry of 1.87 g. of lithium aluminum hydride in 100 ml. of ether was slowly added an ethereal solution of 5.41 g. of (+)-methylsuccinic anhydride,[13] $[\alpha]_D^{23}$ +20.4° (ethanol). The mixture was stirred an additional hour and kept overnight, then treated with saturated sodium sulfate solution and solid magnesium sulfate. The granular precipitate was filtered and washed with methanol. Distillation of the filtrate afforded 1.13 g. of crude diol XI, b.p. 90–100° (5 mm.); redistillation gave 0.97 g. (20%), b.p. 126–127° (14 mm.), $[\alpha]_D^{24}$ +6.94° (*c*, 0.0658 in ethanol). Previous preparations recorded in the literature have given a diol of b.p. 123° (13 mm.), $[\alpha]_D^{22}$ +11.73° (neat), by hydrolysis of the diacetate prepared from (+)-2-methyl-1,4-dibromobutane,[14] and b.p. 94° (3 mm.), $[\alpha]_D$ +14° (methanol), from lithium aluminum hydride reduction of (+)-diethyl methylsuccinate.[6]

Resolution of 3-tetrahydrofuroic acid. In about 550 ml. of hot acetone were dissolved 57.5 g. of 3-tetrahydrofuroic acid[6] and 160 g. of quinine. The fine needles which sepa-

(7) J. A. Mills and W. Klyne, *Progress in Stereochemistry*, Vol. 1, W. Klyne, Ed., Academic Press, Inc., New York, 1954, pp. 188, 193, 202–203.

(8) Private communication from Professor V. Boekelheide.

(9) A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958).

(10) D. Gagnaire and A. Butt, *Bull. soc. chim. France*, 312 (1961).

(11) J. U. Nef, *Ann.*, **376**, 36 (1910).

(12) T. Purdie and P. S. Arup, *J. Chem. Soc.*, **97**, 1537 (1910).

(13) E. Berner and R. Leonardsen, *Ann.*, **538**, 1 (1939).

(14) J. v. Braun and F. Jostes, *Ber.*, **59**, 1444 (1926).

rated on cooling were recrystallized six more times from acetone, yielding finally 100 g. of the quinine salt, m.p. 134–135°, $[\alpha]_D^{24}$ −124.2° in ethanol. A solution of the salt in 500 ml. of 5% hydrochloric acid was continuously extracted with ether for 34 hr. The ether extracts were dried over magnesium sulfate and distilled to afford 23.0 g. of the dextrorotatory acid, b.p. 117.5–119° (6 mm.), $[\alpha]_D^{24}$ + 3.77° (*c*, 0.0623 in ethanol); +4.59° (*c*, 0.0746 in acetone).

(−)-*3-Hydroxymethyltetrahydrofuran* (VII). A solution of 12.46 g. of (−)-3-tetrahydrofuroic acid, $[\alpha]_D^{24}$ −2.73 (*c*, 0.0477 in ethanol), in 125 ml. of ether was added slowly to a well stirred slurry of 9.15 g. of lithium aluminum hydride in 200 ml. of ether. After the addition was complete (2.5 hr.), the mixture was stirred for 30 min. and allowed to stand overnight. The excess hydride was decomposed with a slight excess of saturated sodium sulfate solution and the alumina coagulated by the addition of magnesium sulfate. The precipitate was filtered and washed well with anhydrous ether (600 ml.). The filtrate and washings were combined and distilled, yielding 9.30 g. (85%) of colorless alcohol VII, b.p. 99.5–101° (17 mm.), $[\alpha]_D^{25}$ −4.1° (*c*, 0.0598 in ethanol).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.84; H, 9.93.

The enantiomorphic alcohol was prepared in a similar manner from the acid of $[\alpha]_D^{24}$ +2.70° (*c*, 0.0623 in ethanol). The (+)-alcohol distilled at 92–94° (15 mm.); $[\alpha]_D^{24}$ +4.1° (*c*, 0.0703 in ethanol). Its infrared spectrum in carbon tetrachloride was identical with that of the (−)-isomer.

The 3,5-dinitrobenzoate of the (+)-alcohol VII melted at 83–84°; $[\alpha]_D^{24}$ + 5.5° (*c*, 0.00842 in chloroform).

Anal. Calcd. for $C_{12}H_{12}O_7N_2$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.90; H, 3.86; N, 9.41.

(−)-*3-Chloromethyltetrahydrofuran* (VIII). In a three-necked flask cooled in ice were placed 9.1 g. of (−)-3-hydroxymethyltetrahydrofuran (VII) and 8.1 ml. of anhydrous pyridine. From a dropping funnel 14.3 g. of twice-distilled thionyl chloride was added dropwise with stirring. Stirring was continued for 30 min. after all the thionyl chloride was added, and the solution then heated at 60° for 4 hr. The reaction mixture was taken up in 125 ml. of ether, concentrated, and washed with three 2-ml. portions of water. The residual liquid was dried over magnesium sulfate and distilled at reduced pressure. The chloride was collected at 55–56° (16 mm.) and weighed 7.74 g. (72%), $[\alpha]_D^{24}$ −4.77° (*c*, 0.0762 in ethanol).

Anal. Calcd. for C_5H_9OCl: C, 49.80; H, 7.52; Cl, 29.41. Found: C, 49.60; H, 7.61; Cl, 29.65.

3-Methyltetrahydrofuran (IX). *Levorotatory isomer.* A mixture of 7.65 g. of (−)-3-chloromethyltetrahydrofuran and 2.44 g. of lithium aluminum hydride in 200 ml. of ether was refluxed for 92 hr. The excess hydride was decomposed with saturated sodium sulfate solution, magnesium sulfate added, and the solid filtered and washed with 50 ml. of ether. Careful removal of the ether from the combined filtrate and washings through a 55-cm. Vigreux column and fractionation of the residue gave two fractions: (a) 1.46 g. of (−)-3-methyltetrahydrofuran (IX), b.p. 87–88° (lit.[15] b.p. 86–87°), $[\alpha]_D^{23}$ −4.2° (*c*, 0.0777 in ethanol), and (b) 4.03 g. of colorless liquid, b.p. 161–162°, 55° (16 mm.), identified as starting chloride VIII by its infrared spectrum. Fraction (a) was redistilled from sodium for analysis.

Anal. Calcd. for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 70.00; H, 11.79.

Dextrorotatory isomer. In a semimicro distilling flask attached directly to a receiver cooled in ice were placed 0.96 g. of (+)-2-methyl-1,4-butanediol and 10 mg. of recrystallized *p*-toluenesulfonic acid. Heating the flask in an oil bath gradually over 30 min. to 200° caused the slow distillation of 0.73 g. of liquid. Redistillation from sodium gave 0.42 g. of colorless ether IX, b.p. 86–87°, $[\alpha]_D^{23}$ +22.1° (*c*, 0.0409 in ethanol). The infrared spectrum was identical with that of the (−)-compound.

1-Bromo-2-ethylbenzene. To a solution of 185 g. of technical *o*-ethylaniline in 880 ml. of 40% hydrobromic acid, cooled in a salt-ice bath, was added 116 g. of sodium nitrite in small portions over a period of 90 min., keeping the temperature below 10°. After 5 g. of copper powder was added, the mixture was allowed to warm to room temperature and then heated on the steam bath for 30 min. The reaction mixture was steam distilled, the distillate treated with 15 g. of sodium hydroxide, and the layers separated. The orange organic layer was washed with 50 ml. of concd. sulfuric acid, twice with water, and dried over calcium chloride. Three successive distillations through a short Vigreux column gave 77.4 g. of 1-bromo-2-ethylbenzene, b.p. 82–83° (14 mm.); lit.[16] b.p. 85–90° (15 mm.).

Anal. Calcd. for C_8H_9Br: C, 51.92; H, 4.90. Found: C, 52.15; H, 4.88.

(+)-*o-Ethylphenyl 3-tetrahydrofuryl ketone* (V). In a dry 250-ml. three-necked flask fitted with condenser, dropping funnel, and stirrer with Teflon blade were placed 1.20 g. (0.05 g.-atom) of magnesium turnings and a small crystal of iodine. A solution of 9.25 g. (0.05 mole) of 1-bromo-2-ethylbenzene in 125 ml. of ether was added slowly over 50 min.; the reaction began immediately. The mixture was refluxed for 90 min., then treated with 4.81 g. (0.026 mole) of anhydrous cadmium chloride in small portions. Stirring and refluxing were continued for 1 hr., after which the Gilman test for the Grignard reagent was negative. The ether was removed by distillation and replaced with benzene.

(+)-3-Tetrahydrofuroyl chloride was prepared in 65% yield by keeping a mixture of the acid, $[\alpha]_D^{24}$ +3.77° (ethanol) with 1.7 times its weight of thionyl chloride, and petroleum ether (b.p. 30–60°) at room temperature for 20 hr., then distilling at reduced pressure. The acid chloride, b.p. 64° (9 mm.), was hydrolyzed to the original acid, b.p. 122–124° (6 mm.), $[\alpha]_D^{23}$ +3.63°.

To the benzene solution of the organocadmium compound, cooled in ice, was slowly added a benzene solution of 5.30 g. (0.039 mole) of (+)-3-tetrahydrofuroyl chloride, with continuous stirring. The mixture was stirred at room temperature for 1 hr., kept overnight, stirred and refluxed another hour, and poured into 250 ml. of ice and water. The layers were separated and the aqueous layer extracted with benzene. The combined benzene solutions were filtered, washed successively with 5% sodium bicarbonate and water, and dried over sodium sulfate. Distillation gave 4.04 g. (49%) of the ketone (V), b.p. 96–99° (0.07 mm.), $[\alpha]_D^{22}$ +1.64° (*c*, 0.106 in ethanol). The degradation product from α-erythroidine is reported[4] to have b.p. 45° (0.001 mm.), $[\alpha]_D^{26}$ +7.2°, while the boiling point of the synthetic ketone[5] is 90° (0.05 mm.).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.93.

The infrared spectrum (film) of the ketone was identical with that of the racemic ketone synthesized by Boekelheide and Morrison.[5] Chromatography over acid-washed alumina in benzene–ether racemized the (+)-ketone.

o-Ethylbenzophenone. The cadmium reagent from 1-bromo-2-ethylbenzene was prepared as described above and treated with a benzene solution of 3.51 g. (0.025 mole) of benzoyl chloride. After stirring and refluxing for 90 min. and standing overnight at room temperature, the mixture was poured into ice and dilute sulfuric acid and worked up as described above. The crude product was chromatographed over alumina; 1:1 benzene–hexane eluted a fraction with infrared absorption at 5.98 μ. Distillation of this fraction gave

(15) C. Harries, *Ann.*, **383**, 170 (1911).

(16) M. Crawford and F. H. C. Steward, *J. Chem. Soc.*, 4443 (1952).

1.20 g. (23%) of colorless ketone, b.p. 165–166° (11 mm.); lit.[17] b.p. 166° (12 mm.).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.95; H, 6.86.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized from ethanol; m.p. 180.5–181.5°.

Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.60; H, 4.65; N, 14.35. Found: C, 64.41; H, 4.89; N, 14.60.

On standing, the mother liquor deposited a second, lighter colored, crop of crystals, m.p. 142–143°, apparently the geometrical isomer.

Anal. Found: C, 64.02; H, 4.72; N, 13.94.

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PRINCETON, N. J.

(17) A. F. Harms and W. T. Nauta, *Rec. trav. chim.*, **73**, 892 (1954).

[CONTRIBUTION FROM THE DIVISIÓN QUÍMICA ORGÁNICA, COMISIÓN NACIONAL DE ENERGÍA ATÓMICA, AND LABORATORIOS DE INVESTIGACIÓN, E. R. SQUIBB & SONS, ARGENTINA, S.A.]

Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. VII. Migration of Different Benzoyl Groups in the Ammonolysis of Penta-*O*-benzoyl-D-glucoses

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A study has been made of the yields of 1,1-bis(benzamido)-1-deoxy-D-glucitol (II) obtained from different poly-*O*-benzoyl-D-glucoses (Table I) by ammonolysis. 1,2,3,4,6-Penta-*O*-benzoyl-D-glucoses (Table II) and 2,3,4,6-tetra-*O*-benzoyl-D-glucoses (Table III), containing labeled benzoyloxy groups united to different carbon atoms, were submitted to the same reaction and it was found that benzoyloxy groups at C-3 and C-4 made the largest contributions to the migration that determines the formation of II, the benzoyloxy group at C-6 made a moderate one, and the benzoyloxy group at C-2, the smallest contribution of all (Table IV).

One of the steps in the Wohl degradation of monosaccharides is the formation of compounds named "aldose diamides" (I), that can be formally derived from the condensation of the aldehyde group of one mole of an aldose with two moles of an amide.

The "aldose diamides" can also be obtained by ammonolysis of acylated monoses having a free aldehyde group or a furanose or pyranose structure. This is a general reaction which has been applied with success to fully acetylated or benzoylated derivatives of D-glucose,[1] D-mannose,[2] D-galactose,[3] L-rhamnose,[4] and the pentoses.[5]

The formation of the diamide compound is determined by a migration of *O*-acyl groups to the amine groups that have been formed by fixation of ammonia at C-1. This migration, in all cases investigated, has been found to be intramolecular, as suggested by Isbell and Frush.[6] Experimental proof of the intramolecular mechanism was provided by Hockett, Deulofeu, and Deferrari,[7] who ammonolyzed tetra-*O*-acetyl-L-arabonic nitrile with methanolic ammonia containing N^{15} and added to solvent several moles of acetamide-N^{14}. The 1,1-bis(acetamido)-1-deoxy-L-erythritol formed contained practically the same atoms per cent of N^{15} as the original ammonia, showing that the molecules of acetamide in solution did not participate in the reaction. Identical results were obtained in similar experiments with the ammonolysis of hexa-*O*-acetyl-D-*glycero*-D-*gulo*-heptonic nitrile, when 1,1-bis(acetamido)-1-deoxy-D-glucitol was produced.[8]

$CH(NHCOR)_2$
|
$(CHOH)_n$ (I) (II): R = C_6H_5; n = 4; gluco
|
CH_2OH

The intramolecular mechanism has now been confirmed for the ammonolysis of penta-*O*-benzoyl-D-glucose. When treated with methanolic ammonia containing several moles of benzamide-*carbonyl* C^{14} in solution, a 1,1-bis(benzamido)-1-

(1) J. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1093 (1952).

(3) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1097 (1952).

(4) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **22**, 807 (1957).

(5) V. Deulofeu, J. O. Deferrari, and E. Recondo, *Anal. Asoc. Quím. Arg.*, **46**, 137 (1958); J. O. Deferrari, M. A. Ondetti, and V. Deulofeu, *J. Org. Chem.*, **24**, 183 (1959).

(6) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, **71**, 1579 (1949).

(7) R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Am. Chem. Soc.*, **82**, 1840 (1950).

(8) V. Deulofeu and J. O. Deferrari, *Anal. Asoc. Quím. Arg.*, **38**, 241 (1950).