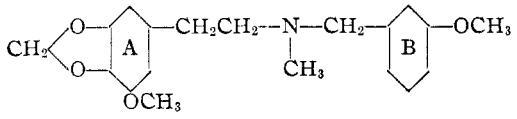
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Synthesis of N-(3-Methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine

BY ALEXANDER R. SURREY

The synthesis of N-(3-methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine (I) was undertaken in order to determine whether it was identical with α-fagarine,



I

the antifibrillatory agent isolated from the plant *Fagara coco*.[1,2] In 1945, Deulofeu and coworkers[3,4] proposed a structure for α-fagarine in which the positions of the methoxy and methylenedioxy groups in ring A of I were not fixed. Inasmuch as the proposed structure can be considered an opened 2-benzyltetrahydroisoquinoline, it seemed reasonable to suspect that the groups in ring A would occupy the positions as shown in I.

The synthesis of the tertiary amino compound I has now been accomplished and its structure confirmed by degradation studies. A comparison of the physical properties of I with that of α-fagarine (Table I) indicates that the two compounds are not identical.

TABLE I

	I, M. p., °C.[5]	α-Fagarine, M. p., °C.
Base	Oil	169–170[4]
HCl	170.4–171.2	192–193[4]
MeI	176.6–177.1	205 dec.[4]

Attempts to obtain a solid base from the purified hydrochloride of I were unsuccessful. A comparison of the ultraviolet absorption spectra (Fig. 1[6]) confirms the non-identity of I with α-fagarine. Preliminary investigations indicate that compound I has little if any antifibrillatory activity.[7]

The starting material required for the preparation of I was myristicin aldehyde (II) which can be synthesized by reported procedures[8] from myristicin *via* isomyristicin. Part of the myristicin used in the preparation of II was isolated from nutmeg oil.[9] The remainder was synthesized by a series of reactions[10] shown in Chart I. Pyrogallol 1-monomethyl ether[11] was treated with one mole of allyl bromide and the crude product was heated at 200° to effect rearrangement of the allyl group and then vacuum distilled. The crude distillate, with the exception of a small forerun, was allowed to react with methylene iodide. After separation from

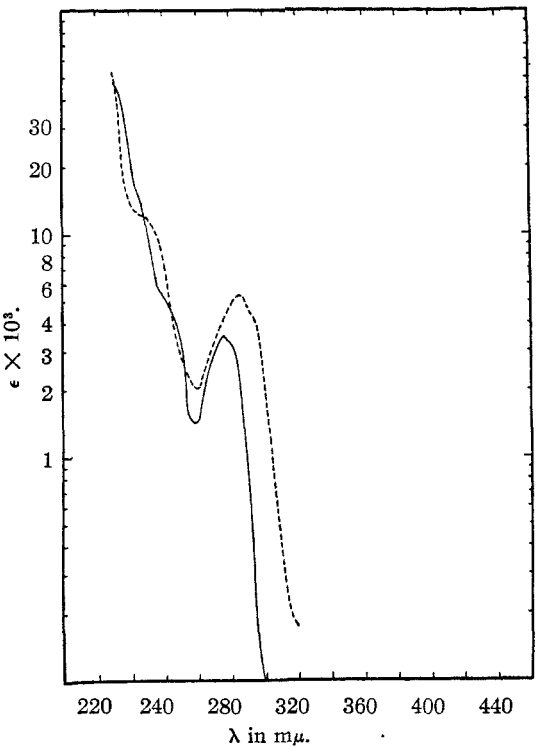


Fig. 1.—Ultraviolet absorption spectra: alcoholic solutions of compound I hydrochloride —; of α-fagarine hydrochloride - - -.

(1) Stuckert, *C. A.*, **29**, 2298 (1935).

(2) Deulofeu, Labriola and De Langhe, THIS JOURNAL, **64**, 2326 (1942).

(3) Deulofeu, Labriola, Orias, Maisset de Espanés and Tequini, *Science*, **102**, 69 (1945).

(4) Deulofeu, Labriola and Berinzaghi, *J. Org. Chem.*, **12**, 217 (1947).

(5) Corrected melting points.

(6) The author is indebted to Dr. F. C. Nachod for the ultraviolet absorption determinations.

(7) The pharmacological testing was carried out by Dr. J. R. Di Palma, Long Island Medical School, N. Y.

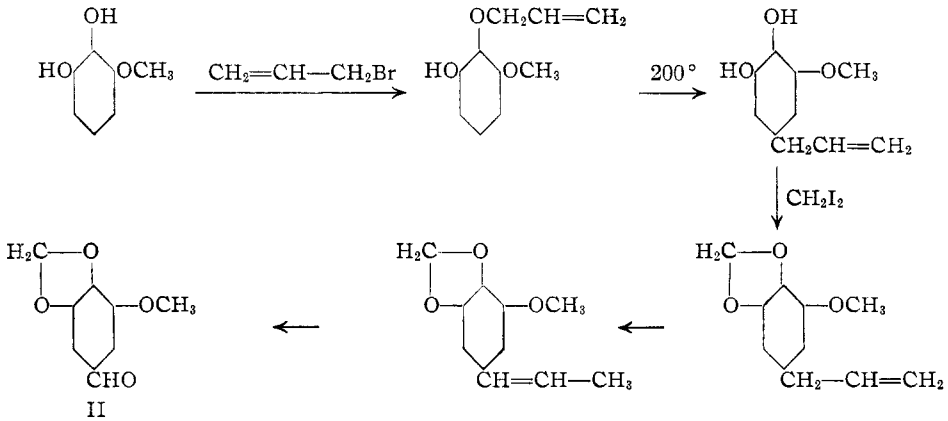
(8) Salway, *J. Chem. Soc.*, 1204 (1909).

(9) The author is indebted to Drs. J. S. Buck and G. Fohlin and Mrs. Mary Now Haskell for the isolation of myristicin from nutmeg oil and for the preparation of myristicin aldehyde therefrom.

(10) Trikojus and White, *Nature*, **144**, 1016 (1939), reported in a brief note the preparation of myristicin by a similar series of reactions. However, no experimental data and few physical constants were described. The authors did report the isolation of two isomeric allyl ethers by fractional distillation after treatment of pyrogallol 1-monomethyl ether with allyl bromide, both of which yielded myristicin after rearrangement and methylenation. Attempts in this laboratory to separate the two possible isomers by fractional distillation were unsuccessful. In all instances evidence of rearrangement was noted. Even at temperatures around 100° the inside temperature exceeded the bath temperatures. If the bath was heated quickly to about 130° the inside temperature rose rapidly to over 200°. For this reason, in subsequent runs, no attempts were made to effect any real purifications up to the preparation of myristicin aldehyde.

(11) "Organic Syntheses," **26**, 90 (1946).

CHART I



II

any free phenolic compounds, the product was distilled to give a 30% yield of crude myristicin, a sample of which, on treatment with bromine, yielded dibromomyristicin dibromide.[12] The myristicin was treated with alcoholic potassium hydroxide solution and the resulting isomyristicin was oxidized to give myristicin aldehyde (II) which was purified by recrystallization.

The reaction of malonic acid with II gave the desired cinnamic acid derivative[13] which was reduced catalytically with Raney nickel to the hydrocinnamic compound.[13] A Hofmann reaction on the corresponding amide[14] gave 3-methoxy-4,5-methylenedioxyphenethylamine (III) which was characterized by its hydrochloride.

The reaction of III with 3-methoxybenzaldehyde followed by catalytic reduction yielded N-3-methoxybenzyl-3-methoxy-4,5-methylenedioxyphenethylamine (IV). Methylation of IV with formaldehyde and formic acid[15] gave the desired tertiary amine I.

By a similar series of reactions, N-(3-methoxybenzyl)-N-methyl-3,4-methylenedioxyphenethylamine (V) was prepared starting with piperonal. The methiodides of both tertiary amines I and V were degraded by refluxing with sodium hydroxide solution to yield in both instances, N,N-dimethyl-3-methoxybenzylamine.[16] This type of cleavage would preclude the presence of a tetrahydroisoquinoline compound which might possibly have been formed in the preparation of I and V from the known phenethylamine derivatives.

The hydrochloride of V was reduced catalytically in 80% acetic acid solution in the presence of a palladium catalyst. The N-methylhomopiperonylamine which was isolated was characterized by its hydrochloride, hydrobromide and picrate derivatives.[17] The methiodide of V was also degraded by catalytic reduction to give N,N-dimethylhomopiperonylamine.

(12) Thoms, *Ber.*, **36**, 3446 (1903).

(13) Salway[8] treated II with ethyl acetate and reduced the cinnamic acid derivative with sodium amalgam.

(14) Salway, *J. Chem. Soc.*, 1208 (1910).

(15) Clark, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(16) Stedman, *J. Chem. Soc.*, 1902 (1927).

(17) Decker and Becker, *Ann.*, **395**, 328 (1913).

Experimental[18]

2(?)-Allyloxy-3-methoxyphenol.—A mixture of 115 g. of pyrogallol-1-monomethyl ether, 103 g. of allyl bromide, 143 g. of anhydrous potassium carbonate and 435 ml. of dry acetone was refluxed with stirring for fifteen hours. After distilling the acetone, the residue was treated with water, acidified with dilute sulfuric acid and extracted with ether. The combined ether was extracted with dilute sodium hydroxide, the alkaline extracts reacidified and reextracted with ether. Removal of the ether gave 113 g. (80%) of crude product.

6(?)-Allylpyrogallol-1-monomethyl Ether.—The crude allyl ether was heated slowly over a period of three hours to 200° and kept at this temperature for an additional hour. After the rearrangement was complete the product was distilled at a pressure of 0.3 mm. with a short Vigreux column to give the following fractions: (a) 7.5 g. at 190–196°, $n^{25}D$ 1.5610; (b) 29 g. at 196–206°, $n^{25}D$ 1.5588; (c) 17 g. at 206°, $n^{25}D$ 1.5580; (d) 31.5 g. at 206–210°, $n^{25}D$ 1.5580. Fractions (b), (c) and (d) were combined; yield 68%.

Anal. Calcd. for $C_{10}H_{12}O_3$; OCH_3, 17.23. Found: OCH_3, 16.96.

Myristicin.—A mixture of 76 g. of 6(?)-allylpyrogallol-1-monomethyl ether, 120 g. of methylene iodide and 150 g. of anhydrous potassium carbonate in 300 ml. of dry acetone was refluxed with stirring for fifteen hours. After distilling the acetone, dilute sulfuric acid was added to the residue and the latter extracted with ether. The combined ether extracts were washed with several portions of 2% sodium hydroxide (750 ml. total), then with water, and dried. The product was distilled *in vacuo* (a) 26.2 g. 87–91° at 0.4 mm. ($n^{25}D$ 1.5403), (b) 13.5 g. 91° at 0.3–0.45 mm. ($n^{25}D$ 1.5395). The yield was 49% (lit.,[19] $n^{20}D$ 1.5403).

A sample of product on treatment with bromine in acetic acid gave the dibromomyristicin dibromide. After two recrystallizations from ethanol it melted at 128–129° (lit.[12] 130°).

Anal. Calcd. for $C_{11}H_{10}Br_4O_3$: OCH_3, 6.09. Found: OCH_3, 6.01.

Myristicin Aldehyde.—The crude myristicin was rearranged to isomyristicin with alcoholic potassium hydroxide according to Salway.[8] The product which distilled at 105–110° at 0.8 mm., $n^{25}D$ 1.5708 (lit.,[19] $n^{45.5}D$

(18) All melting and boiling points were uncorrected unless otherwise indicated. The corrected melting point determinations were carried out by immersing the capillary approximately 20° below the melting point and raising the temperature 3° per minute.

(19) Power and Salway, *J. Chem. Soc.*, 2037 (1907).

1.5655), yield 50%, was oxidized with potassium permanganate[6] to give a 13.5% yield of myristicin aldehyde, m. p. 128–130°.

3-Methoxy-4,5-methylenedioxycinnamic Acid.—A mixture of 16.5 g. of myristicin aldehyde, 20.5 g. of malonic acid, 1 ml. of piperidine and 60 ml. of dry pyridine was heated on a steam-bath for three hours. After allowing to cool, the reaction mixture was poured into a mixture of 60 ml. concentrated hydrochloric acid and 105 g. of ice. The solid which separated was filtered off and washed with 20 ml. of 3 *N* hydrochloric acid and then 30 ml. of water. The solid was stirred with 60 ml. of acetone, heated to reflux, cooled and refiltered; yield 15 g., m. p. 222–226° dec.[20] The material was used directly for the next step.

The acetone filtrate was evaporated to dryness and the residue stirred with dilute sodium bicarbonate solution and filtered. The insoluble material was washed with water and dried, 2.2 g., m. p. 124–126°. This unreacted myristicin aldehyde was retreated with malonic acid to give a total of 16.4 g. of product.

β-(3-Methoxy-4,5-methylenedioxyphenyl)-propionic Acid.—The cinnamic acid derivative (16.4 g.) was dissolved in a slight excess of 0.5 *N* sodium hydroxide solution and reduced catalytically with Raney nickel. The catalyst was filtered off, and the filtrate was acidified with dilute hydrochloric acid. The solid which crystallized out was filtered and washed with water and dried; yield 14.3 g., m. p. 95–100°.

β-(3-Methoxy-4,5-methylenedioxyphenyl)-propionamide.—The above acid was refluxed with 11 ml. of thionyl chloride and 50 ml. of chloroform on the steam-bath for two hours. The chloroform was distilled *in vacuo* and the residue dissolved in a small amount of dioxane and was poured with stirring into cold concentrated ammonium hydroxide. The solid was filtered off, washed with water and dried; yield 13.5 g., m. p. 122–126°. A sample was recrystallized from a large volume of benzene to give colorless needles, m. p. 128–129° (lit.[14] 129–130°).

Anal. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28. Found: N, 6.48.

3-Methoxy-4,5-methylenedioxyphenethylamine Hydrochloride.—The finely powdered amide (12.5 g.) was added with stirring to an aqueous solution containing 1.1 moles of chlorine and 6 moles of sodium hydroxide. The mixture was heated to 70° over a period of thirty minutes and kept at this temperature for an additional thirty minutes. Eighty milliliters of 50% potassium hydroxide was added and the temperature was kept at 80° for one hour. After cooling, the reaction mixture was extracted with ether (total of 370 ml.) and the combined extracts dried over solid potassium hydroxide.

Ten milliliters of ether was treated with alcoholic hydrogen chloride to yield 0.3 g. of hydrochloride, m. p. 161–162° with softening at 150°. It was recrystallized twice from a mixture of ethyl alcohol, ethyl acetate, and ether, m. p. 167.2–168.1°, cor. (lit.[14] 165°).

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: Cl, 15.34. Found: Cl, 15.11.

N-(3-Methoxybenzyl)-3-methoxy-4,5-methylenedioxyphenethylamine Hydrochloride.—The ether from 180 ml. of the above solution was distilled to give 4.4 g. of crude residue. To it was added 3.3 g. of *m*-methoxybenzaldehyde and the mixture was allowed to stand at room temperature for twenty-four hours. The resulting mixture was dissolved in 100 ml. of alcohol and reduced in the presence of palladium–charcoal. After removing the catalyst, the alcoholic solution was evaporated to about one-third its volume and alcoholic hydrogen chloride was added, followed by ether. The crude hydrochloride (5.5 g.) was recrystallized from isopropanol to yield 4.1 g., m. p. 137–139°. Recrystallization twice more from isopropanol gave a product melting at 144.2–145°, cor.

Anal. Calcd. for $C_{18}H_{22}ClNO_4$: C, 61.45; H, 6.31; Cl, 10.08. Found: C, 61.24; H, 5.96; Cl, 10.02.

(20) Salway (ref. 14) reported sintering at 200° and melting with decomposition at 228°.

N-(3-Methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine Hydrochloride.—The above hydrochloride (1.76 g.) was suspended in water, treated with an excess of sodium hydroxide, and warmed until no more solid remained. The oil was extracted with ether, the latter washed with water and distilled. To the residual oil was added with cooling 0.57 g. of 100% formic acid followed by 0.45 ml. of 35–40% formaldehyde solution and the mixture heated on a steam-bath. Heating was continued for several hours after the evolution of gas ceased. The reaction mixture was treated with water, rendered strongly alkaline with sodium hydroxide solution and extracted with ether. The combined extracts were washed with water, dried, and treated with ethereal hydrogen chloride. The ether was decanted from the gummy mass and the latter rinsed with dry ether and dissolved in warm isopropanol. Ether was added to turbidity and the solution on standing deposited a crystalline product, 1.36 g., m. p. 149–151°. Recrystallization from isopropanol gave 0.63 g., m. p. 170.4–171.2°, cor.

Anal. Calcd. for $C_{19}H_{23}NO_4 \cdot HCl$: C, 62.37; H, 6.61; Cl, 9.69. Found: C, 62.20; H, 6.42; Cl, 9.60.

The isopropanol filtrates were combined and dry ether added. On long standing a small amount (0.05 g.) of a solid melting at 181–186° was obtained. Recrystallization from isopropanol and ether raised the melting point to 186–188° (a mixed melting point with the analytical sample above was depressed).

Anal. Found: C, 62.50; H, 6.15; N, 3.83.

The **methiodide** was prepared by refluxing the base with methyl iodide in dry acetone, m. p. 176.6–177.1°, cor.

Anal. Calcd. for $C_{20}H_{26}INO_4$: C, 50.97; H, 5.56. Found: C, 50.87; H, 5.48.

N-(3-Methoxybenzyl)-homopiperonylamine Hydrochloride.—A mixture of 5.5 g. of homopiperonylamine and 4.6 g. 3-methoxybenzaldehyde was allowed to stand at room temperature overnight, dissolved in ethanol and reduced catalytically in the presence of palladium-charcoal catalyst. The hydrochloride of the product (7 g.) after recrystallization from isopropanol melted at 160–161.4°, cor.

Anal. Calcd. for $C_{17}H_{20}ClNO_3$; C, 63.45; H, 6.20; N, 4.35. Found: C, 63.65; H, 6.28; N, 4.11.

N-3-Methoxybenzyl)-N-methyl-homopiperonylamine Hydrochloride.—Seven grams of the above amine hydrochloride was converted to base and methylated with formaldehyde and formic acid to give 4.5 g. of product melting at 161.6–163.5°, cor., after recrystallization from isopropanol.

Anal. Calcd. for $C_{18}H_{22}ClNO_3$: C, 64.37; H, 6.30; N, 4.17. Found: C, 64.62; H, 6.43; N, 4.08.

The methiodide was recrystallized from ethanol and then triturated with acetone, m. p. 174.5–176.5°, cor.

Anal. Calcd. for $C_{19}H_{24}INO_3$: C, 51.71; H, 5.48; I, 28.76. Found: C, 51.57; H, 5.69; I, 28.84.

Catalytic Reduction of N-(3-Methoxybenzyl)-N-methyl-homopiperonylamine Hydrochloride.—The amine hydrochloride (3.35 g.) was reduced with palladium–charcoal in 100 ml. of 80% acetic acid at 50–55°. After filtering off the catalyst the filtrate was evaporated to dryness, and the solid residue was recrystallized from isopropanol to give 2 g. of N-methylhomopiperonylamine hydrochloride melting at 176–179° (lit.[16] 178–180°).

The picrate of the above base melted at 165–166° (lit.[16] 166–167°, cor.). The hydroiodide melted at 138–139° (lit.[16] 135–136°, cor.).

Degradation of N-(3-Methoxybenzyl)-N-methyl-homopiperonylamine Methiodide.—A. One gram of the methiodide in 40 ml. of water was catalytically reduced with 0.1 g. of Adams catalyst in the presence of 0.6 g. of sodium acetate. After ten hours of shaking under pressure of approximately 2 atmospheres of hydrogen, the reduction was stopped and the reaction mixture extracted with ether. The combined ether extracts were dried and treated with alcoholic hydrogen chloride. The solid,

N,N-dimethylhomopiperonylamine hydrochloride, which separated was recrystallized twice from an alcohol–ether mixture, m. p. 203–204°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.52; H, 7.02; N, 6.10. Found: C, 57.88; H, 7.31; N, 5.96.

B. A solution of 1 g. of the methiodide in 80 ml. of water was refluxed for one hour with 15 g. of sodium hydroxide. The cooled reaction mixture was extracted with ether and the ether extracted with *N* hydrochloric acid. The acid extracts were made alkaline with dilute sodium hydroxide and extracted with ether. After drying, the ether was treated with alcoholic hydrogen chloride and the crystalline solid which separated was recrystallized from an alcohol–acetone–ether mixture. The N,N-dimethyl-3-methoxybenzylamine hydrochloride melted at 173–174° (lit.[17] m. p. 173°).

Degradation of N-(3-Methoxybenzyl)-N-methyl-3,4-methylenedioxy-5-methoxyphenethylamine Methiodide.—A solution of 0.7 g. of the methiodide in 56 ml. of water was refluxed one hour with 12.6 g. of sodium hydroxide. The product, N,N-dimethyl-3-methoxybenzylamine hydrochloride, melted at 176–177°, cor., and was identical with the product obtained from the corresponding homopiperonylamine methiodide described above.

Summary

The preparation of myristicin aldehyde by a series of reactions starting with pyrogallol 1-monomethyl ether is reported.

N-(3-Methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine has been synthesized and found to be different from α-fagarine.

The synthesis of N-(3-methoxybenzyl)-N-methyl-3,4-methylenedioxyphenethylamine is also reported.

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[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

The Isomerization of Cyclohexane and Methylcyclopentane in the Presence of Aluminum Halides. I. The Nature of the Catalyst

BY D. P. STEVENSON AND O. BEECK

Introduction

In the recent past a number of papers dealing with the aluminum halide catalyzed isomerization of hydrocarbons, particularly the alkanes, have appeared.[1] Leighton and Heldman[1a] and Powell and Reid[1b] interpreted the results of their investigations of the isomerization of the butanes as providing substantiation for the theory that the catalytic isomerizing activity of the aluminum halides resides in the hypothetical, strong acids, $HAlX_4$.[2] The more recent work of Pines and Wackher[1c,1d] has shown that substances other than hydrogen halide must be present in order that the aluminum halides may have isomerizing activity for the butanes and pentanes.

A general investigation of the nature of aluminum halide catalyzed reactions of hydrocarbons has been under way in these laboratories for several years. In this and the following paper some of the results obtained in a study of the isomerization of cyclohexane and methylcyclopentane are reported. This paper deals with the nature of the catalyst. It is shown that, as Pines and Wackher[1c,1d] found for alkane isomerization, hydrogen halide by itself is not a promoter of isomerizing activity of the aluminum halides for cyclohexane and methylcyclopentane, and thus that the simple hydro-aluminum halide complex, $HAlX_4$, is not the catalytically active species.[3] The second paper presents new data on the equilibrium composition of liquid mixtures of cyclohexane and methylcyclopentane and the side reactions which accompany the isomerization reaction.

The interconversion of cyclohexane and methylcyclopentane has been the subject of several previous investigations.[4] These authors agree that pure, anhydrous aluminum chloride is without catalytic activity toward the isomers, cyclohexane and methylcyclopentane. They have shown that in the presence of small quantities of water, aluminum chloride becomes a very active isomerization catalyst and that the reaction is reasonably free from side reactions.

The results of these investigations indicated that the rate of isomerization of cyclohexane and methylcyclopentane should be measurable in an easily accessible temperature range, 25–70°. The ready availability of the pure isomers combined with their physical properties, which results in ease of handling and analysis, suggested that this isomerization should be particularly suitable for studying the nature of the catalysis. Thus this reaction was selected for intensive investigation.

Experimental Methods

The isomerization of cyclohexane and methylcyclopentane was investigated in the presence of three catalysts. These catalysts were: (a) an atmospheric moisture dampened aluminum chloride, (b) anhydrous aluminum chloride and (c) anhydrous aluminum bromide. The "moist aluminum chloride," (a), was taken from a five-pound bottle of J. T. Baker C. P. anhydrous aluminum chloride powder which had been originally opened one year before

(1)(a) Leighton and Heldman, THIS JOURNAL, **65**, 2276 (1943); (b) Powell and Reid, *ibid.*, **67**, 1020 (1945); (c) Wackher and Pines, *ibid.*, **68**, 1642 (1946); (d) Pines and Wackher, *ibid.*, **68**, 2518 (1946).

(2)(a) Egloff, Wilson, Hulla and Van Ardsell, *Chem. Rev.*, **20**, 345 (1937); (b) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Pub. Corp., New York, N. Y., 1941, Chapter 4, pp. 57–76; (c) II, THIS JOURNAL, **70**, 2773 (1948).

(3) Some of the results described in the present paper were discussed by one of the authors (O. B.) at Gibson Island, June, 1944, AAAS Conference on Catalysis.

(4)(a) Nenitzescu and Cantunari, *Ber.*, **66**, 1097 (1933); (b) Glasebrook and Lovell, THIS JOURNAL, **61**, 1717 (1939); (c) Mizusima, Morino and Hugisiro, *Sci. Papers Inst., Phys. Chem. Res. (Tokyo)*, **38**, No. 1034, 401 (1941); (d) Pines, Abraham and Ipatieff, Atlantic City meeting, American Chemical Society, April, 1947, Div. of Phys. Inorg. Chem.