Epoxide Migrations with α,β-Epoxy Alcohols

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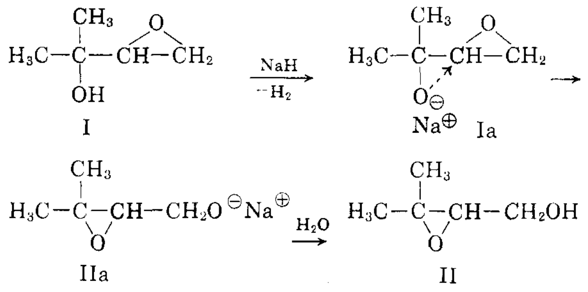
The phenomenon of "epoxide migration," noted heretofore only in the sugar series, has been shown to occur with simple α,β-epoxy alcohols. In general, this conversion of one epoxy alcohol into another was effected readily in 0.5 *N* aqueous sodium hydroxide at 25°. A tertiary alcohol underwent 92% conversion to primary. On the other hand, rearrangement of secondary to primary and tertiary to secondary alcohols appeared to be strongly influenced by steric factors.

As part of a study concerned with the reactivities of a variety of epoxy compounds, we were interested in determining if any rearrangement occurred when 2-methyl-3,4-epoxybutan-2-ol (I) was treated with an equivalent amount of sodium hydride in tetrahydrofuran:



A molar equivalent of hydrogen was evolved during the 1.5-hour reaction period at 10°. The clear solution of sodium alcoholate (Ia) was then acidified to give I in 70% recovery. Gas chromatographic (GLC) analysis indicated the possible presence of a maximum of 2% of II, thus indicating little or no rearrangement.[1]

Although our original question had been answered satisfactorily by this essentially negative result, the fact that epoxide migration in aqueous solution had recently[2] been reported in the sugar series led us to attempt the isomerization of I under similar conditions. Epoxy alcohol I was dissolved in 0.5 *N* aqueous sodium hydroxide and allowed to stand at room temperature for one hour. GLC analysis of the product mixture (82% yield) indicated a 92:8 distribution of II to I. Pure II was readily isolated by distillation and used for confirmation of the equilibration distribution.

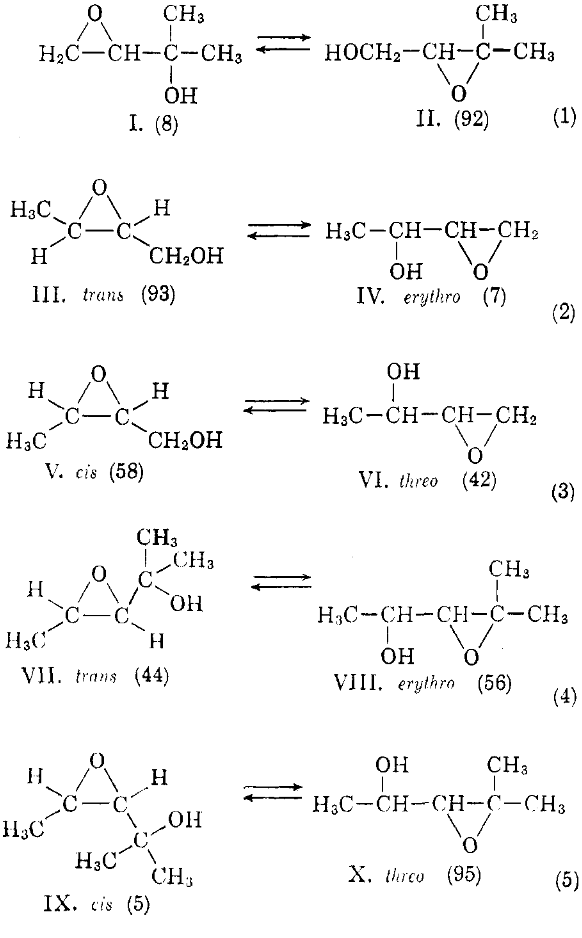
This facile isomerization in aqueous solution is believed to be a consequence of the generation of a "free" anion, Ia. In tetrahydrofuran it is probable that the alkoxide anion of Ia is bound to sodium as a tight ion-pair in such a manner as to preclude intramolecular nucleophilic attack on the oxirane ring.

The procedure used for isomerization of I was employed to determine equilibrium values for a series of model α,β-epoxy alcohols in 0.5 *N* aqueous sodium hydroxide.

Table I summarizes the results of isomerizations carried out in the present study. The percentage of each isomer present at equilibrium is indicated in brackets; reproducibility of results was ±1–2%.

TABLE I

EQUILIBRATION OF α,β-EPOXY ALCOHOLS IN 0.5 *N* SODIUM HYDROXIDE



Epoxy alcohols I, III, V, VII, and IX were prepared from the corresponding unsaturated alcohols by epoxidation using peroxyacetic acid. Epoxy alcohols II, VI, VIII, and X were isolated from equilibration mixtures.

In every case except one, equilibrium was approached from the direction of each pure isomer.

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[1] It was later established that II is not isomerized to I by sodium hydride in tetrahydrofuran.

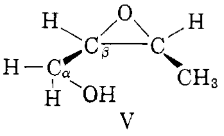
[2] S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 3691 (1957); see also F. H. Newth, *Quart. Rev.*, **13**, 30 (1959) for a discussion of sugar epoxides.

Since so little *erythro*-3,4-epoxybutan-2-ol (IV) was formed, it was not feasible to obtain a pure sample of that material. Fractional distillation, however, afforded an approximately 1:1 mixture of III and IV which was used for equilibration.

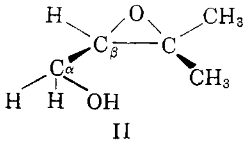
Discussion

Inspection of Table I shows that, in general, the epoxy alcohol with the less highly substituted carbinol carbon was favored over its more highly substituted isomer. It should also be noted, of course, that the favored isomer was the one having the more highly substituted (and presumably more stable) epoxide group.[3] In the absence of steric effects (examples 2 and 5), the ratio of isomers[4] was > 10:1 and appeared to correlate with relative acidic strengths of the carbinols.[5]

In example 3 the relatively large amount of secondary alcohol, VI (42%), was somewhat unexpected. A study of molecular models revealed, however, that in compound V the rotation about C_α—C_β is somewhat hindered by the hydrogens of the methyl group. Since no such hindrance is present in VI, more of the latter might be expected to be present at equilibrium than would have been predicted on the basis of relative acidic strengths of the carbinols.[6] Similarly, one can argue that the amount of II present at equilibrium (92%) is probably *less* than what one might have expected in the absence of a steric effect. In the case of II, rotation about C_α—C_β is again hindered by methyl group hydrogens:

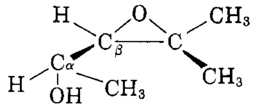


V



II

The relatively large amount of tertiary alcohol VII may also be rationalized on the basis of steric considerations. Models show that the hydrogens attached to one of the *gem*-dimethyls of VIII are so situated as to impede rotation about C_α—C_β:



VIII

No such effect is present in VII, where the *trans* configuration prevents any interaction between the *gem*-dimethyls and the terminal methyl group.

In the case of compounds IX and X it may be noted that models show them to be subject to about the *same* steric effects. It is not surprising then that the equilibrium distribution appears again to be governed by relative acidic strengths of the two carbinols.

Experimental

Materials.—*trans*-2-Buten-1-ol (E.K.Co., practical) was purified by fractional distillation, b.p. 121–122°. 2-Methyl-3-buten-2-ol (Air Reduction Co.) was redistilled, b.p. 98–99°. 2-Butyn-1-ol (Farchan) was redistilled, b.p. 87–88° (100 mm.).

***cis*-2-Buten-1-ol.**—The catalyst for the hydrogenation of 2-butyn-1-ol was prepared by a modification of the literature procedure.[7] A suspension of 50 g. of 5% palladium on calcium carbonate (Baker) in 500 ml. of water was treated with a solution of 5 g. of lead acetate in 100 ml. of water. After 1 hr. on the steam bath with frequent swirling, the catalyst was filtered, washed well with water, and vacuum-dried to constant weight.

A mixture of 1.0 g. of catalyst, 250 ml. of *n*-hexane, and 28.0 g. (0.400 mole) of 2-butyn-1-ol was charged to a 465-ml. capacity glass hydrogenation bottle and pressured to 40 pounds with hydrogen. After about 1 hr. of shaking, 34.3 lb. (0.404 mole) of hydrogen had been absorbed and the reaction was halted. During the hydrogenation, a strong air jet was directed against the vessel in order to hold the temperature at 25–27°.

After removal of the catalyst by filtration, the filtrate was distilled at 200 mm. using a 10-tray Oldershaw column. The concentrate, on distillation through a 0.7 × 50 cm. glass spiral-packed column, afforded 26.6 g. of *cis*-2-buten-1-ol, b.p. 63–64° (10 mm.); $n^{25}D$ 1.4319 (lit.,[8]) b.p. 122–123.7; $n^{25}D$ 1.4323.

***cis*-2-Methyl-3-penten-2-ol.**—1-Bromopropene (Matheson, Coleman and Bell) was redistilled slowly through a 40-tray Oldershaw column to remove a low-boiling impurity, b.p. 53–58°. Continued distillation on a 10-tray column gave a mixture of *cis*- and *trans*-1-bromopropenes, b.p. 58–61°.[9]

To a stirred suspension of 21 g. (3.0 g.-atoms) of lithium wire in 1500 ml. of ether was added at reflux over 1.5 hr. 182 g. (1.5 moles) of 1-bromopropene dissolved in 200 ml. of ether. After stirring overnight at room temperature, the mixture was cooled to 10° and treated with 87 g. (1.5 moles) of dry acetone (dried over potassium carbonate, then Drierite; finally vacuum flashed into a dry trap at room temperature). The addition was made at < 10° over about 1 hr. After stirring 0.5 hr. longer in the cold and 1 hr. at room temperature, the mixture was treated at < 10° with a saturated aqueous solution containing 180 g. of ammonium chloride. The ether was separated and the aqueous layer extracted with ether. The combined ether extracts were dried over potassium carbonate and Claisen-distilled to give 79 g. of crude product, b.p. 40–67° (60 mm.). Slow

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[3] See R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959), for a recent discussion of epoxide ring openings.

[4] Structure assignments were made by assuming an inversion of configuration; this would appear to be valid since epoxide ring opening resulting from nucleophilic attack always occurs with inversion; See ref. 3

[5] The acidic strengths of simple aliphatic alcohols decrease in the order primary > secondary > tertiary. See J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952), for a discussion of relative acidities of carbinols.

[6] This is a simplified picture. The hydroxyl group of V, for example, would most certainly be hydrogen-bonded to a water molecule; this could lead to a rotational hindrance far greater than that which is apparent from a study of models.

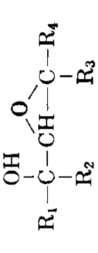
[7] H. Lindlar, U.S. Patent 2,681,938.

[8] L. D. Huestis and L. J. Andrews, *J. Am. Chem. Soc.*, **83**, 1963 (1961).

[9] D. Y. Curtin and J. W. Crump, *ibid.*, **80**, 1922 (1958) report an equilibrium mixture containing 68% *cis*–32% *trans*.

TABLE II

α,β-EPOXY ALCOHOLS



$R_1-C(OH)(R_2)-CH\overset{O}{-}C(R_3)-R_4$

Cpd. No.	R_1	R_2	R_3	R_4	Configuration	Method of preparation	Yield, %	B.p., °C.	$n^{25}D$	Calcd. C	Calcd. H	Calcd. Oxirane oxygen	Found C	Found H	Found Oxirane[a] oxygen
I	CH_3	CH_3	H	H	...	A	70	69–70 (50 mm.)[b]	1.4250	58.8	9.9	15.7	58.3	9.8	15.5
II	H	H	CH_3	CH_3	...	B	82	71–72 (10 mm.)	1.4276	58.8	9.9	15.7	58.9	9.9	14.4[e]
III	H	H	H	CH_3	*trans*	A	78	58–59 (10 mm.)[c]	1.4250	...	...	18.1	...	...	16.8
IV	CH_3	H	H	H	*erythro*	B	[d]	...	...	...	...	...	...	...	...
V	H	H	H	CH_3	*cis*	A	43	69–70 (10 mm.)	1.4308	54.5	9.1	18.1	54.2	9.1	17.6
VI	CH_3	H	H	H	*threo*	B	80	52–55 (10 mm.)	1.4282	...	...	18.1	...	...	17.8
VII	CH_3	CH_3	H	CH_3	*trans*	A	78	57–58 (20 mm.)	1.4200	62.0	10.4	13.8	62.1	10.4	13.1
VIII	CH_3	H	CH_3	CH_3	*erythro*	B	85	81–82 (20 mm.)	1.4249	62.0	10.4	13.8	62.1	10.4	11.2[e]
IX	CH_3	CH_3	H	CH_3	*cis*	A	69	54–55 (20 mm.)	1.4229	62.0	10.4	13.8	61.5	10.4	12.8
X	CH_3	H	CH_3	CH_3	*threo*	B	88	75–76 (20 mm.)	1.4238	62.0	10.4	13.8	62.0	10.4	10.9[e]

A = Epoxidation of unsaturated alcohol. B = Isomerization of α,β-epoxy alcohol; yields are for mixture of isomers recovered from isomerization medium. [a] By hydrobromic acid in acetic acid; see A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956). [b] O. N. Semikhatova-Aref'eva, *Chem. Abstr.*, **52**, 16273 (1958) reports b.p. 185–187°. [c] E. C. Jahn and H. Hibbert, *Can. J. Res.*, **8**, 199 (1933) report b.p. 93–97° (44 mm.). [d] No pure isomer obtained. [e] This relatively low value is undoubtedly a consequence of the tertiary epoxide function; more highly substituted epoxides generally show low oxirane oxygen values by this method; unpublished results, Shell Development Co.

redistillation through a Nester and Faust spinning band column (1 × 100 cm.) gave 28 g. of *cis*-2-methyl-3-penten-2-ol, b.p. 67–69° (100 mm.); $n^{25}D$ 1.4315 (lit.,[10] b.p. 60–61°/72 mm.; $n^{25}D$ 1.4352). The product showed a characteristic *cis* double bond absorption at 14.2 μ. Weak absorption at 10.3 μ indicated the possible presence of a small amount of the higher boiling *trans* isomer; this was ignored, since further purification was achieved by distillation of the epoxy alcohol (see below).

trans-**2-Methyl-3-penten-2-ol.**—To a stirred suspension of 25 g. (3.6 g.-atoms) of lithium wire in 1200 ml. of ether was added at reflux over 1 hr. a solution of 262 g. (1.85 moles) of methyl iodide in 200 ml. of ether. After 0.5 hr. longer at reflux, there was added 96 g. (0.84 mole) of ethyl crotonate (redistilled, b.p. 137–138°). The addition was made over 0.5 hr. at reflux.

After an additional 0.5 hr. at reflux, the mixture was cooled to room temperature and held there as 300 ml. of water was added dropwise with stirring. Stirring was continued overnight before the ether solution was separated. The aqueous layer was extracted with ether and the combined ether was washed with half-saturated ammonium sulfate. After drying and concentration on a 10-tray Oldershaw to an internal temperature of 80° the residue was analyzed by GLC (DC-710 on Fluoropak 80 at 100° and 60 cc./min.). Since an 85:15 mixture of product–ethyl crotonate was indicated, the residue was saponified. It was dissolved in 100 ml. of warm methanol and treated portionwise with a solution of 8 g. (0.2 mole) of sodium hydroxide in 25 ml. of water. After boiling for 1 hr. on the steam bath to drive off most of the methanol, the concentrate was diluted with water and extracted with chloroform. After washing and drying, the chloroform was removed using a 10-tray Oldershaw column. Distillation through the spiral column gave 49 g. (58% yield) of *trans*-2-methyl-3-penten-2-ol, b.p. 71–72° (100 mm.); $n^{25}D$ 1.4269 (lit.,[11] b.p. 121.6–122°; $n^{25}D$ 1.4295). GLC analysis indicated the absence of any ethyl crotonate.

Epoxidation of *trans*-**2-Methyl-3-penten-2-ol.**—The following procedure was typical for all epoxidations except that of 2-methyl-3-buten-2-ol (see below).

To a stirred solution of 44 g. (0.44 mole) of *trans*-2-methyl-3-penten-2-ol in 300 ml. of chloroform was added portionwise 90 g. (0.50 mole) of 42% peracetic acid. The latter had been previously treated with sodium acetate to neutralize the sulfuric acid present. During the addition, the reaction mixture was held at <10° by ice-bath cooling. After 2-hr. at <10° and 3 hr. at room temperature, the mixture was washed with saturated sodium carbonate solution until carbon dioxide evolution ceased. The aqueous layer was back-extracted with chloroform and the combined chloroform solutions were washed with half-saturated ammonium sulfate. After drying over magnesium sulfate, the chloroform was removed on the steam bath until the internal temperature reached 80–85°. Distillation through a 0.7 × 50 cm. glass spiral-packed column gave 39.9 g. (78%) of *trans*-2-methyl-3,4-epoxypentan-2-ol (VII), b.p. 57–58° (20 mm.); $n^{25}D$ 1.4200. See Table II for analysis.

Epoxidation of 2-Methyl-3-buten-2-ol.—A solution of 86 g. (1.0 mole) of 2-methyl-3-buten-2-ol in 400 ml. of methylene chloride was treated with 200 g. of 42% peracetic acid (sulfuric acid previously neutralized with 5 g. of anhydrous sodium acetate). After standing for 24 hr. in a tap water bath, the mixture was stirred with 300 ml. of water in a large beaker as 200 g. of sodium carbonate was added portionwise. When carbon dioxide evolution had stopped, excess solid was removed by filtration through a sintered glass funnel. The organic layer was washed with half-saturated ammonium sulfate and dried over

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[10] A. N. Nesmeyanov, A. E. Borisov, and N. V. Novikova, *Doklady Akad. Nauk S.S.S.R.*, **119**, 712 (1958); *Chem. Abs.* **52**, 17161 (1958).

[11] N. van Keersbilck, *Bull. soc. chim. Belges*, **38**, 207 (1929); *Chem. Zentr.*, **100**, II, 2036 (1929).

magnesium sulfate. A pinch of 10% palladium-on-carbon catalyst was also added to ensure the decomposition of any peroxidic material.

Claisen-distillation gave 70 g. of crude product, b.p. 47–53° (20 mm.). Redistillation through the spiral-packed column afforded 61.2 g. (70% yield) of 2-methyl-3,4-epoxybutan-2-ol (I), b.p. 69–70° (50 mm). See Table II for analyses.

Isomerization of *trans*-2-Methyl-3,4-epoxypentan-2-ol (VII).—The following procedure was a general one for the isomerization of epoxy alcohols.

A 32.8-g. sample (0.28 mole) of *trans*-2-methyl-3,4-epoxypentan-2-ol (VII) was treated with 150 ml. of 0.5 *N* sodium hydroxide previously cooled to about 5°. The solution was allowed to warm to room temperature and remain there for 1 hr. After saturation with 100 g. of ammonium sulfate, the solution was extracted with three 50-ml. portions of chloroform. The combined chloroform was washed with 25 ml. of half-saturated ammonium sulfate, dried over magnesium sulfate, and concentrated on the steam bath to an internal temperature of 80–85°. Gas chromatographic (GLC) analysis of the concentrate was made by means of a 2.5-m. column packed with DC-710 on Fluoropak 80. The temperature was 100° and a flow rate of 60 cc./min. of helium was used. Emergence times of 9 and 15 min., respectively, were observed for the starting material (45%) and its isomer, *erythro*-4-methyl-3,4-epoxypentan-2-ol (VIII, 55%).

The crude mixture of products was distilled through the glass spiral-packed column at 20 mm. pressure to give the following fractions: (A) 12.2 g., b.p. 57–64°; (B) 2.0 g., b.p. 64–80°; (C) 13.6 g., b.p. 80–81°; n^{25}_{D} 1.4249. GLC analysis of (C) indicated it to be essentially free of impurities. Analysis was in agreement with *erythro*-4-methyl-3,4-epoxypentan-2-ol (VIII) as the structure (see Table II).

A 4.8-g. sample of (C) was isomerized as above in 25 ml. of base. GLC analysis of the chloroform concentrate indicated a 43:57 mixture of *trans* to *erythro* compounds.

Sodium Hydride Isomerization of 2-Methyl-3,4-epoxybutan-2-ol.—To a stirred suspension of 4.7 g. (0.10 mole) of 50.9% sodium hydride in 200 ml. of purified tetrahydrofuran held at 5–10° was added 10.2 g. (0.10 mole) of 2-methyl-3,4-epoxybutan-2-ol (I). A 1940-ml. volume of gas was collected over 20 min. The resulting clear solution was allowed to stir at 10° for 1.5 hr.

After washing with 50 ml. of saturated ammonium sulfate, the organic layer was dried over magnesium sulfate and concentrated on the steam bath to an internal temperature of 85°. GLC analysis indicated a 98:2 ratio of starting material to 3-methyl-2,3-epoxybutan-1-ol (II). In another experiment, a 70% recovery of epoxy alcohol was secured by distillation.

Sodium hydride isomerization of 3-methyl-2,3-epoxybutan-1-ol (II) was attempted using the above procedure. GLC analysis of the crude product indicated that little or no isomerization had occurred.

Acknowledgment.—The author wishes to express his thanks to Dr. F. H. Newth for helpful discussions.

The Synthesis of 17β-Amino-17α-(2′-carboxyethyl)androstane Lactams[1]

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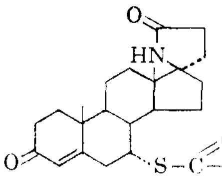
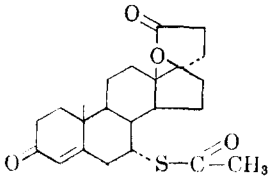
The synthesis of 17-nitroandrostanes is described from the corresponding oximes. The addition of methyl acrylate to these nitro derivatives, followed by reduction, leads to spirolactams.

As part of our program on steroidal aldosterone antagonists, we decided to prepare 17-spirolactams such as I because of their close similarity to spirolactone antagonists such as II.[2] It seemed to us that the unique feature of the spirolactones as a class was the spiro structure at C-17. If so, then changes in this element might be fruitful in altering intrinsic activity in response to the type of cellular bonding which is involved. We were not alone in the selection of this objective since Burtner and Nysted[3] of the Searle group have also synthesized several C-17 spirolactams.



I



II

Of various ways of preparing this function, we were attracted by the procedure which is based on a Michael addition α- to a nitro group. We were guided in this selection by recent publications of Hill[4] which draw attention to and develop this method.

We probed three procedures for the synthesis of 17-nitro steroids and decided to base our work on Iffland's oxidation of oximes.[5] We are not in a position to rule out the ultimate applicability of two other methods, the peracid oxidation of 17-

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[1] First presented by one of us (A.A.P.) at the Gordon Research Conference on Steroids and Other Natural Products, New Hampton, New Hampshire, August, 1961.

[2] For the chemistry and some of the biology of the spirolactones see J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959); J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959); E. . Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960) and N. W. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, Z. W. Nysted, and P. B. Sollman, *ibid.*, **26**, 3097 (1961).

[3] R. R. Burtner and L. N. Nysted, U.S. Patent 3,001,986 (September 26, 1961).

[4] R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957); R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

[5] D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassiou, and S. M. White, *J. Am. Chem. Soc.*, **75**, 4044 (1953); D. C. Iffland and G. X. Criner, *ibid.*, **75**, 4047 (1953); and D. C. Iffland and T.-F. Yen, *ibid.*, **76**, 4083 (1954).