tive. The crude product was washed with petroleum ether and with water, and recrystallized from ethanol to yield 910 mg. of pure Δ^5-3-ethylenedioxypregnene-21-ol-11,20-dione acetate (VII), m.p. 193.5–194°, $[\alpha]^{25}D$ +52° (*c* 1.33 in chloroform); infrared spectrum: maxima at 5.71, 5.77 and 5.86 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.97. Found: C, 70.02; H, 7.65.

3-Dioxolane of Cortisone Acetate (VIII).—A mixture of 1.0 g. of cortisone acetate and 2.0 ml. of the dioxolane of mesityl oxide in 7.5 ml. of dry tetrahydrofuran was treated with 0.06 ml. of concentrated sulfuric acid and stirred at room temperature for two hours, then allowed to stand at 0° overnight. The acid catalyst was neutralized with pyridine, and sufficient petroleum ether added to complete precipitation of the ethylenedioxy derivative. The solution was filtered and washed with methanol and with water. The crude crystalline compound was recrystallized from pyridine, and traces of cortisone acetate removed by refluxing with methanol. Approximately 844 mg. of VIII which decomposed at 265–272° was obtained. Ultraviolet absorption analysis showed only a shoulder in the 2400 Å. region. A sample recrystallized for analysis from chloroform–petroleum ether decomposed variously over a five-degree range between 264° and 274°; $[\alpha]^{25}D$ +51.5° (*c* 0.815 in pyridine).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.25; H, 7.68. Found: C, 67.50; H, 7.49.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

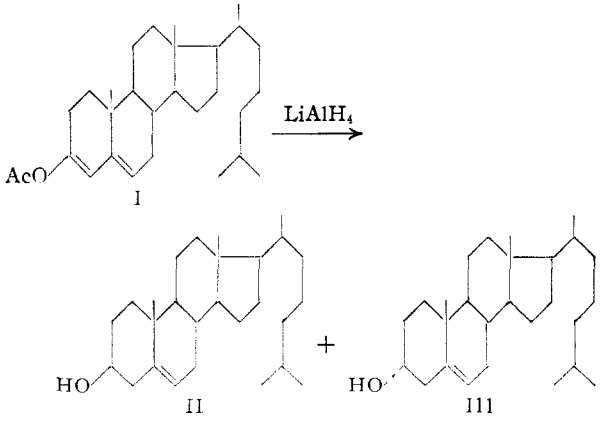
The Mechanism of the Reduction of Steroidal Enol Acetates by Lithium Aluminum Hydride[1]

BY WILLIAM G. DAUBEN AND JEROME F. EASTHAM

RECEIVED OCTOBER 24, 1952

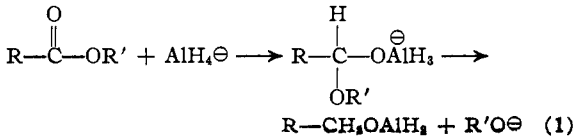
When steroidal enol acetates are reduced with lithium aluminum hydride, the products are epimeric saturated alcohols and starting ketone. It has been shown that the ketone cannot be the immediate precursor of the alcohols. The recovered ketone is a direct product of the reaction and is not formed by hydrolysis of unreacted enol acetate. The mechanism of the reduction is viewed as beginning with a nucleophilic attack of the aluminum hydride upon the carbonyl carbon atom. If the second attack by hydride is on the same carbon atom, as in a normal ester reduction, the products are ethoxide ion and the enolate ion of the ketone. This latter ion resists reduction under the conditions of the reaction and upon hydrolysis yields the starting ketone. Alternately, if the second attack by hydride is on the carbinol carbon atom of the double bond with concomitant formation of an organometallic bond, the complex, upon hydrolysis, yields saturated alcohols. Substantiation of these latter phases was obtained employing the deuterium tracer technique. Such a mechanism can account for the radically different product composition obtained upon reduction of the enol acetate as compared to the free ketone.

It has previously been reported[2] that when the enol acetate of cholestenone (I, 3-acetoxy-$\Delta^{3,5}$-cholestadiene) is reduced by lithium aluminum hydride, cholesterol (II) and epicholesterol (III) are the main products. This unique reaction has



been further investigated[3] to establish the fact that the second carbon–carbon double bond is not essential by a study of the reduction of the enol acetates of cholestanone and coprostanone. Again apparent carbon–carbon double bond reduction occurred. It was of interest, however, that the ratio of isomeric alcohols formed varied quite widely from that obtained by the direct reduction of the parent ketone and that in both cases an appreciable quantity of the ketone was recovered from the reduction of the ester. In order to gain further insight into the mechanism of this reaction, it has been investigated in more detail.

The first point to be considered is the isolation of the parent ketone from the reduction. It has been found that the same result was obtained when either a fivefold or a thirtyfold excess of lithium aluminum hydride was utilized or when the reaction time was varied from 1 to 24 hours.[2] Such results make it seem unlikely that the carbonyl compound could arise from unreacted enol acetate which would hydrolyze to the parent ketone upon decomposition of the reaction mixture with sodium hydrogen tartrate. A more plausible explanation would appear to be that this material arises from a moiety which is produced in the reaction but which is resistant to reduction and which upon acidification yields the ketone. Such a moiety could be the enolate ion of the ketone and such a species could arise in the reaction. In the reduction of esters with lithium aluminum hydride, the electrophilic carbonyl carbon atom is viewed as being the center for the first bimolecular attack by the anion, $AlH_4^{\ominus}$, with subsequent transfer of a hydride ion. A second hydride attack displaces the original

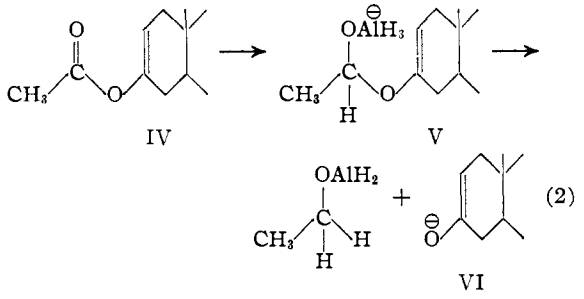


(1) This work was supported, in part, by a grant from the University of California Cancer Fund.

(2) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **73**, 3260 (1951).

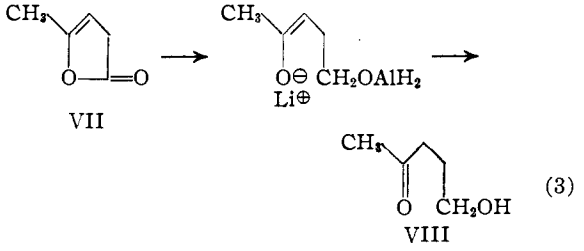
(3) W. G. Dauben, R. A. Micheli and J. F. Eastham, *ibid.*, **74**, 3862 (1952).

alkoxide group and gives rise to the anion of the newly formed alcohol (see eq. 1). If a similar pathway is considered as a possible one in the enol acetate reduction, then the route could be designated schematically as in equation (2). The



IV V VI (2)

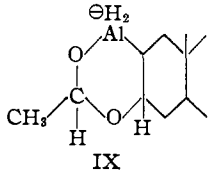
generated enolate ion of the ketone VI, perhaps in the form of the lithium salt, could resist further reduction. That such a species would resist reduction by lithium aluminum hydride was established by the following experiment. When cholestenone was allowed to react with excess hydride, rapid and complete reduction of the carbonyl group occurred. However, if prior to the reduction, the ketone was allowed to react with lithium diethyl amide to form some of the lithium salt of the enolate ion (such as above), as much as 30% of the starting ketone was recovered. Such a result would clearly indicate that the enolate ion is resistant to reduction with hydride. A direct analogy to this reaction can be found[4] in the reduction of α-angelica lactone (VII) to 3-acetylpropanol (VIII) (see eq. 3).



VII VIII (3)

The second point to consider is the mechanism of formation of the alcohols in the reduction. Birch[5] has postulated that in such a reaction of an enol acetate, the parent ketone is the moiety being reduced but this concept can be ruled out by a study of the ratio of isomeric alcohols obtained[2,3] (*vide supra*) and subsequent work reported below.

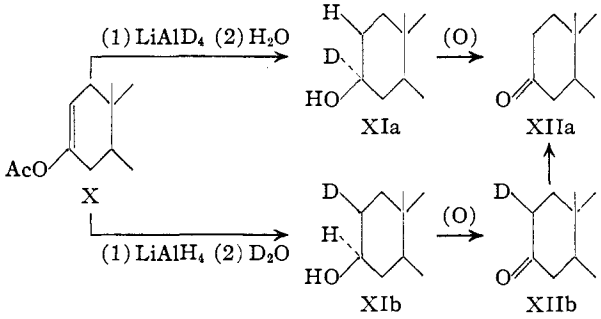
The direct reduction of the carbon–carbon double bond, a process not dissimilar to that established by Hochstein and Brown[6] in the reduction of cinnamyl alcohol, appears to be a more reasonable pathway. Such a mechanism could involve an intermediate of type IX.



IX

Such a complex could arise by addition of the hydride anion to the carbinol carbon atom of the double bond with concomitant formation of a carbon–aluminum bond by the adjacent carbon atom. Such a pathway has the merit in that the transition state varies markedly, in the stereochemical sense, from that involved in a ketone reduction and thus could allow for the different isomer ratio obtained. Nevertheless, no definite answer could be gained on these data alone and the exact nature of the reaction intermediate was determined in tracer experiments employing deuterium.

From the above considerations, it is apparent that if the reduction was conducted with lithium aluminum deuteride, an intermediate of type IX would yield a product containing deuterium on the carbinol carbon atom. When such an experiment was performed using cholestanone enol acetate (X), the cholestanol XIa isolated contained one atom of deuterium. Oxidation of this alcohol yielded cholestanone (XIIa) which contained only the natural atom per cent. excess of deuterium. These results show that the hydride anion attacked carbon atom three of the steroid as predicted by intermediate IX. Although the oxidation was conducted under conditions which should not affect the α-deuterium atom, this point was further confirmed by demonstration of the presence of an organometallic bond in the reduction complex. To do this, the reduction was repeated using lithium aluminum hydride and the reaction mixture was decomposed with heavy water. Again the cholestanol XIb contained only one atom of deuterium and upon oxidation, under the same conditions as above, cholestanone (XIIb) containing one atom of deuterium was obtained. Such a result demonstrated the presence of an organometallic bond and established that no deuterium



was lost upon oxidation of the alcohol. The deuterium containing cholestanone (XIIb) upon equilibration with water was converted into a ketone XIIa with only the natural excess of deuterium. Thus, in the reduction of an enol acetate with lithium aluminum hydride, an intermediate of type IX is present.[7]

In the foregoing discussion, the complex of the reduction has been written as an intramolecular compound for the sake of simplicity. To date, however, no proof has been obtained to substantiate such a simple complex and, indeed, a rough study of the stoichiometry of the reaction

(4) F. A. Hochstein, THIS JOURNAL, **71**, 305 (1949).

(5) A. J. Birch, *J. Chem. Soc.*, 2325 (1950).

(6) F. A. Hochstein and W. G. Brown, THIS JOURNAL, **70**, 3484 (1948).

(7) Previously published work[3] strongly suggests that the parent ketone is the intermediate in the reduction of an enol acetate with sodium borohydride.

leads one to the conclusion that such is not the case. If one assumes, as would seem most reasonable, that the end product of the reduction of the acetyl group of the ester is ethanol and that all four hydrogen atoms of the lithium aluminum hydride molecule can be utilized, then it might be expected that three-fourths of a mole of the hydride would be sufficient to reduce one mole of enol acetate (the fourth hydrogen in the reduction being supplied by the decomposition reagent). To test this assumption, a series of reductions were performed using one millimole of cholestenone enol acetate and various amounts of lithium aluminum hydride. In the seven experiments, the millimoles of hydride varied from 0.22 to 4.0, and in each case a clear, standardized solution was employed. A total time of 10 hours was allowed for each reduction to assure complete reaction and the mixture obtained was separated, by chromatography, into cholestenone, mixed alcohols (α and β) and amorphous material. This amorphous fraction came off the alumina following the alcohols, it gave a positive Liebermann–Burchard test but could not be obtained in crystalline form and was not further investigated. The weight of this fraction brought the material balance to over 90% in each case; its percentage contribution was greatest (*ca.* 15%) in the intermediate runs (0.4–1.0 mmole hydride) and it was essentially absent when four or more millimoles were utilized. The results are summarized in Table I.

TABLE I

REDUCTION OF 1 MMOLE OF CHOLESTENONE ENOL ACETATE USING VARYING AMOUNTS OF HYDRIDE

Hydride, mmoles	Mmole product -ol	-one	Sum
0.22	0.03	0.77	0.80
.43	.11	.66	.77
.70	.16	.59	.75
1.00	.21	.55	.76
2.00	.44	.41	.85
3.00	.54	.31	.85
4.00	.55	.32	.87

During the addition of the hydride, a dense precipitate appeared. The flocculent material formed with the addition of the first drop of hydride solution and seemed to reach a maximum quantity when about one-fourth mole of hydride had been added. Further addition of hydride caused the precipitate to dissolve slowly, complete dissolution occurring when three moles of hydride had been added. In order to obtain the maximum yield of Δ^5-cholestenols (55–60%) it was necessary to use sufficient hydride (3 mmoles) to effect solution of the precipitate but excess hydride beyond this point did not increase the yield of the alcohols. Neither stirring for a longer period (up to 36 hours) nor dilution with a large volume of ether could bring about dissolution of the precipitate. Even with the addition of the smallest amount of added hydride and with stirring of the reaction for many hours, excess hydride remained in the mixture (as measured by the evolution of gas upon addition of tartrate solution for decomposition).[8]

The results of the stoichiometry experiments are not conclusive but some general concepts of the reaction might be formulated. It would appear logical to assume that the first quarter of a mole of hydride could be almost completely consumed by reduction of the most labile point in the ester, the electrophilic carbon atom of the carbonyl group, to give a complex which is insoluble because of its very large weight (possibly four sterol groups per aluminum atom).[9] The dissolution of this complex could then occur by reaction with additional lithium aluminum hydride to yield further reduction products. It is not clear, however, as to the apparent utilization of only one hydrogen atom per molecule of lithium aluminum hydride. This could be either a fortuitous situation caused by the precipitation reaction or an actuality; no decision is possible at this time. There are examples, however, in which the stoichiometry of hydride reductions seems quite complex and some consideration has been given to possible differences between the hydrogens of the hydride molecule.[10,11]

Acknowledgment.—The deuterium analyses were carried out in the Division of Steroid Chemistry of the Sloan-Kettering Institute through the courtesy of Dr. T. F. Gallagher. The analyses were conducted following the procedure of Fukushima and Gallagher.[12] We are also indebted to Dr. Keith Freeman of the Donner Laboratory of this University for the infrared spectra results.

Experimental

$LiAlD_4$ Reduction of Cholestanone Enol Acetate.—The reduction was conducted as previously described[3] employing 0.90 g. of enol acetate in 25 ml. of ether and 0.30 g. of $LiAlD_4$ (96%) slurried in 25 ml. of ether. The reduction complex and excess deuteride was decomposed with 30 ml. of 10% sulfuric acid and processed; yield 161 mg. (20%) cholestanone, m.p. 129–130°, $[\alpha]^{25}D$ +41.3°; 130 mg. (16%) epicholestanol-3-*d*, m.p. 180–182°, $[\alpha]^{25}D$ +24° and 456 mg. (56%) cholestanol-3-*d*, m.p. 140–142°, recrystallized m.p. 141.5–142.5°, $[\alpha]^{25}D$ +22.7°. Infrared spectra of the deuterated sterols showed the characteristic C–D absorption at 2060 cm.$^{-1}$ and this band was absent in the ketone. Deuterium analysis of the alcohols showed 2.16 atom per cent. excess D, the theoretical value for replacement of one hydrogen is 2.08 atom per cent. excess D. The ketone showed only the natural atom per cent. excess D.

Oxidation of Cholestanol-3-*d* to Cholestanone.—A solution of 300 mg. of cholestanol-3-*d* in 6 ml. of dry benzene was placed in a 25-ml. erlenmeyer flask and cooled in an ice-bath until the benzene solidified. A solution containing 0.5 g. of crystalline sodium dichromate, 0.4 ml. of glacial acetic acid, 0.7 ml. of concentrated sulfuric acid and 2 ml. of water was cooled to 0°, added in one portion to the frozen benzene solution, the flask flushed with nitrogen and then stoppered. The reaction was allowed to warm slowly to 15° while the reaction mixture was stirred magnetically and the stirring continued for 10 hours. The benzene layer was

(8) In one experiment, after one-quarter of a mmole of hydride had been added, the supernatant was removed and processed in the usual manner. The product was not obtained crystalline but it amounted to less than 20% of the starting material and appeared to be impure enol acetate.

(9) Hochstein and Brown,[6] in their cinnamyl alcohol case, noted a white precipitate formed after addition of half of the hydride but it redissolved upon the addition of the remainder of the hydride and heating. The ether-soluble nature of this final intermediate led them to postulate an intermediate between two moles of alcohol and one mole of hydride.

(10) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

(11) R. E. Lutz, R. L. Wayland and H. G. France, *ibid.*, **72**, 5511 (1950).

(12) D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, in press.

then separated, washed with water and 10% sodium bicarbonate (both precooled in ice-bath), dried over sodium sulfate and the solvent removed. The final traces of benzene were removed by azeotropic distillation with ethanol and the product crystallized directly from this latter solvent; yield 245 mg. (82%), m.p. 128–129°, $[\alpha]^{25}D$ +41.5°. The cholestanone has an infrared spectrum identical with authentic material and displayed no bands at the C–D stretching frequency. Deuterium analysis showed only the natural atom per cent. excess D.

Decomposition of Reduction Complex with D_2O.—The reduction was conducted as described above using 0.9 g. of cholestanone enol acetate and 4.2 mmoles of lithium aluminum hydride. After the solution had been stirred for one hour, 0.5 g. (25 mmoles) of D_2O (99.98%) was added and the solution allowed to stand under a nitrogen atmosphere for 10 hours. Additional anhydrous ether was added, the mixture stirred for another two hours and then centrifuged. The ether was decanted and the residue was leached twice with additional anhydrous ether. Evaporation of the filtered decantate yielded 685 mg. of solid which was dissolved in hexane and chromatographed on alumina which had been neutralized and activated.[13] After elution of the cholestanone (251 mg.), with 15% ether in hexane, a volume of this same solvent containing a few per cent. methanol was passed through the column to elute the sterols (412 mg.).[14] A second chromatograph on less active alumina[15] yielded 100 mg. of epicholestanol-2-*d*, m.p. 180–182°, and 286 mg. of cholestanol-2-*d*, m.p. 140–142°, recrystallized, m.p. 141.5–142.5°, $[\alpha]^{25}D$ +23°. Both of these steroids show the characteristic C–D stretching frequency. Deuterium analysis of the cholestanols showed 2.20 atom per cent. excess D (theory 2.08 atom per cent. excess D).

A portion of the cholestanol-2-*d* was oxidized to cholestanone-2-*d* in the same manner as described for the oxidation of cholestanol-3-*d*. The product, m.p. 129.5–130.0°, retained the C–D absorption band at 2060 cm.$^{-1}$ and deuterium analysis shows a 2.28 atom per cent. excess D. A sample of this ketone was dissolved in hexane and passed onto a column of basic alumina.[16] After a quantity of hexane saturated with water had been passed through the column, the cholestanone was eluted with 15% ether in hexane. This ketone, as directly eluted, had a m.p. 126–128° and no longer showed any absorption in the C–D stretching frequency region. Deuterium analysis showed only the natural atom per cent. excess D.

Reduction of Cholestenone Enol Acetate with Varying Amounts of Lithium Aluminum Hydride.—The experiments were performed at 25° in a manner described previously for an inverse reduction.[2] The only significant difference was that saturated sodium potassium tartrate solution was employed to decompose the reduction complex in place of dilute mineral acid. Considerable attention was given to the maintenance of anhydrous conditions, to the employment of scrupulously dried equipment and to the standardization of the hydride solutions used. The stock hydride solution was prepared, stored and standardized both by titration and hydrogen evolution before each run. All equipment was dried at 100° in a vacuum oven immediately prior to use and the cholestenone enol acetate dried at room temperature for 10 hours at 10^{-5} mm. All experiments were performed with 0.500 g. of ester in 10 ml. of anhydrous ether. The reaction products were separated by chromatography in the usual manner on alumina. The results are listed in Table I.

Attempted Reduction of Cholestenone Enolate Ion.—To 50 ml. of dry butyl ether there was added, in turn, 0.45 ml. (4.4 mmoles) of freshly distilled diethylamine, 3.3 mmoles of phenyllithium in 4.6 ml. ethereal solution and after three hours, 0.80 g. (2.1 mmoles) of cholestenone. The mixture was stirred for four hours at room temperature in a nitrogen atmosphere and was then heated on a steam-bath and approximately 10 ml. of solvent was removed under reduced pressure.

A solution of 5 mmoles of lithium aluminum hydride in 3.5 ml. of ethyl ether was added to the butyl ether solution and the mixture stirred overnight at room temperature. After decomposition of the reaction complex, the mixture was processed in the standard fashion. There was obtained, 248 mg. (34%) of cholestenone, m.p. 76–78°; 325 mg. (45%) of mixed Δ^4-cholesten-3-ols, m.p. 125–138°; 127 mg. (17%) of Δ^4-cholesten-3β-ol, m.p. 131–133°.

(13) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(14) The alumina employed for this chromatograph was sufficiently active to prevent ready elution of hydroxylated material by the ordinary solvents, ether and hexane. While the sterols were absorbed on this very active alumina, the solution containing methanol was passed through the column in order to "wash off" any deuterium from the oxygen of the alcohol. Elution in this manner did not give a satisfactory separation of the sterols so it was necessary to perform a second chromatograph on less active alumina in order to separate the epimers.

(15) Merck, Aluminum Oxide Reagent, suitable for chromatographic adsorption.

(16) Fisher, Alumina Adsorption. This alumina had previously been shown to have sufficient basic strength to cause the hydrolysis of cholesteryl acetate during normal chromatographic procedures.

BERKELEY 4, CALIFORNIA

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

The Stereochemistry of the Furan–Maleic Acid Reaction[1]

BY JEROME A. BERSON AND RONALD SWIDLER

RECEIVED NOVEMBER 3, 1952

The reaction of furan with maleic acid in water is shown to be stereochemically heterogeneous. *endo*-Addition is kinetically favored but the *endo*-adduct gradually isomerizes to the more stable *exo*-adduct. A method is described for analysis of the diene reaction mixtures. The free energy change for isomerization of *endo* to *exo*-adduct is estimated to be not more than −1.2 kcal./mole. A discussion is given of the possible origins of energy differences in *endo*- and *exo*-isomers of 2,2,1-bicycloheptane derivatives.

The general occurrence of *endo*-stereospecificity in the products of diene additions investigated in a series of early studies was summarized in the well-known Alder rule.[2] Further investgations,[3–5] stimulated by the brief report[2] that the diene additions of fulvenes were stereochemically non-homogeneous, brought to light the dependence of the steric outcome of these additions upon the reaction conditions, the *endo*-adduct being formed more rapidly but giving way at longer reaction times or higher temperatures to the thermodynamically-favored *exo*-isomer. The reaction of furan with maleimide[6] now seems to conform to this energetic scheme, and even in the difficultly mobile cyclopentadiene–maleic anhydride *endo–exo* adduct equilibrium,[7] the same kinetic order and relative

(1) This work reported here will form a portion of the thesis to be submitted by Ronald Swidler in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) K. Adler and G. Stein, *Angew. Chem.*, **50**, 514 (1937).

(3) R. B. Woodward and H. Baer, THIS JOURNAL, **66**, 645 (1944).

(4) K. Alder, F. W. Chambers and W. Trimborn, *Ann.*, **566**, 27 (1950).

(5) K. Alder and R. Ruhmann, *ibid.*, **566**, 1 (1950).

(6) H. Kwart and I. Burchuk, THIS JOURNAL, **74**, 3094 (1952).

(7) D. Craig, *ibid.*, **73**, 4889 (1951).