The Chemistry of a Diazo Ketone and Its Derivatives Obtained from Cholanic Acid

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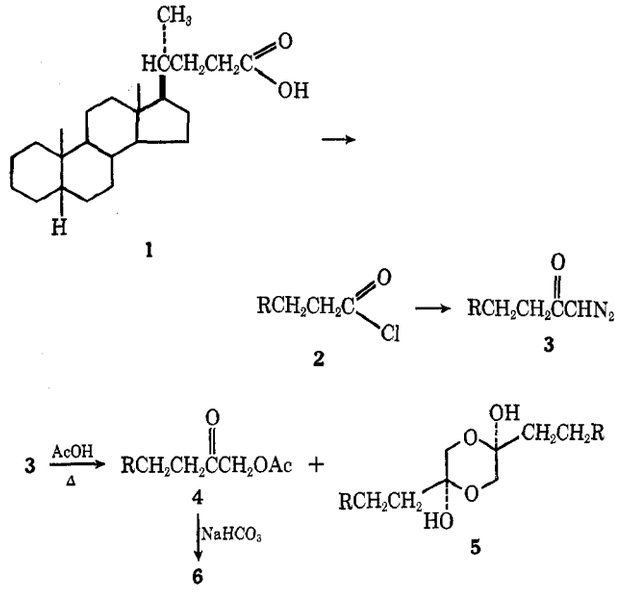
Received December 8, 1971

Treatment of the steroidal diazo ketone **3** with hot acetic acid afforded, besides the expected ketol acetate **4**, the as yet unknown steroidal dioxane derivative **5**. The latter compound is the dimeric form of ketol **6**. The dimeric structure was inferred from physical data and from the high optical purity observed in the α-hydroxy acids, the tautomerized and oxidized products of steroidal ketols. The characteristic chemical behavior of the dimeric compound **5** and the operative factors determining its properties are reported.

The chemistry of diazo ketones and diazo compounds has been recently reviewed.[1,2]

Diazo ketone **3** was obtained in high yield by the well-known procedure[3] starting with cholanic acid (**1**). In boiling acetic acid the diazo ketone **3** was converted into two products, the expected ketol acetate **4** and the hitherto unknown dioxane derivative **5**, which can be regarded as the dimer of ketol **6** (Scheme I).

SCHEME I



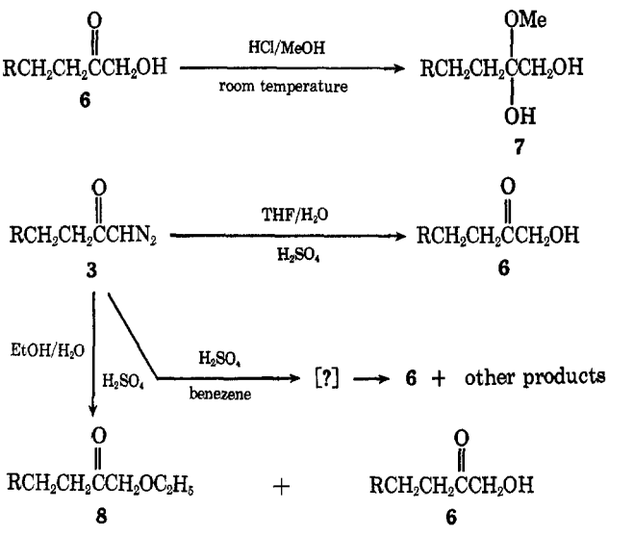
The yields of dimer **5** varied, for reasons as yet not clear, from a few per cent up to 12%, from run to run. A convenient procedure for the synthesis of dimeric compounds from ketols has been reported.[4,5]

Reaction of ketol **6** with gaseous HCl has led to the preparation and isolation of the hemimethylal **7**, which slowly decomposed into its components. The dimeric compound **5** was by no means present.

We further attempted unsuccessfully the synthesis of **5** by treating diazo ketone **3** with H_2SO_4 in various solvents. Ketol **6** and the corresponding ethyl ether **8** were obtained as the major products in aqueous THF and EtOH, respectively (Scheme II).

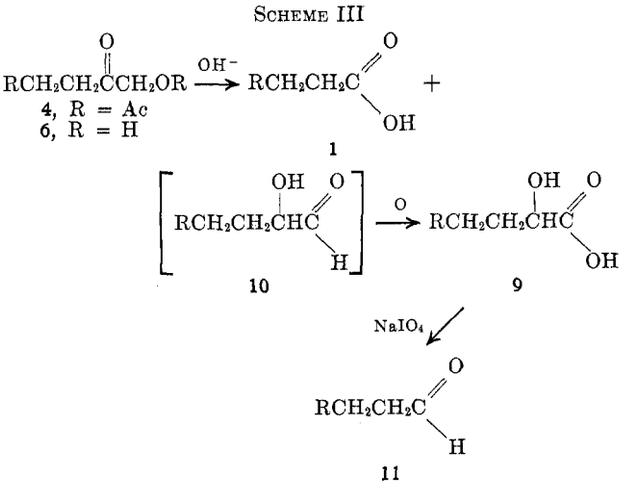
With dry benzene as solvent, a curious reaction took place. A colorless compound was obtained which melted at 130° and could not be stored without decomposition, yielding ketol **6** and other products (Scheme II). So far, its structure could not be solved from the physical data at hand (see Experimental Section) and its elucidation is under further study.

SCHEME II



The monomeric ketol **6** was obtained from ketol acetate **4** by mild alkaline hydrolysis, or preferably from diazo ketone **3** by the use of acid in aqueous THF (Schemes I and II). When subjected to the action of alkali in ethanolic solution, both ketol acetate **4** and ketol **6** underwent fragmentation and rearrangement leading to cholanic acid (**1**) and α-hydroxyhomocholanic acid (**9**) (Scheme III).

SCHEME III

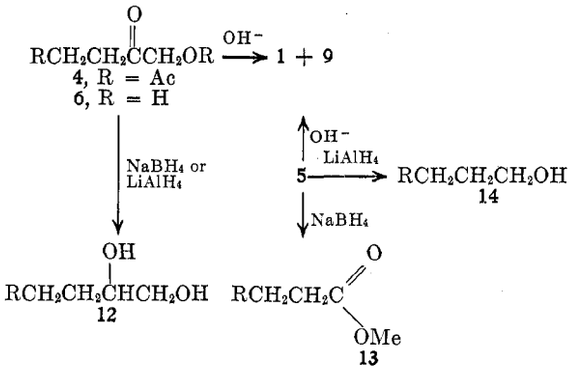


(1) L. L. Rodina and I. K. Korobitsyana, *Russ. Chem. Rev.*, **36**, 260 (1967).
(2) O. P. Studzinskii and I. K. Korobitsyana, *ibid.*, **39**, 834 (1970).
(3) F. Arndt, B. Eistert, and W. Partale, *Ber.*, **60**, 1364 (1927).
(4) E. Fischer, *ibid.*, **28**, 1161 (1895).
(5) L. Szotyori, L. Fey, and A. Kovendi, *Rev. Roum. Chim.*, **15**, 1615 (1970).

The intermediacy of the hydroxy aldehyde **10** could be followed by tlc, when the reaction was conducted under nitrogen atmosphere. By a known procedure[6] the hydroxy acid **9** was oxidized to the corresponding cholanic aldehyde **11**.

The sensitivity of **4** and **6** to strong base is clearly evident. Even the action of $NaBH_4$ and $LiAlH_4$ in the appropriate solvents did not give a straightforward reaction. Only when conditions were carefully observed did ketol acetate **4**, and to a lesser extent ketol **6**, afford the diol **12** (Scheme IV).

SCHEME IV



In contrast, the dimeric compound **5** failed to yield diol **12**; rather methyl cholanate (**13**) and cholanol (**14**) were the main products, on reaction with $NaBH_4$ and $LiAlH_4$, respectively.

Analysis shows that the composition of the dimeric compound **5** corresponds with the formula $(C_{25}H_{45}O_2)_n$. The parent molecular ion at *m/e* 748 provides evidence for its dimeric structure; it is twice as great as that of ketol **6**. The nmr data are in good accord with the structure and are unambiguous. Nevertheless, the strong absorption in the 1740 cm^{-1} region is a little puzzling.

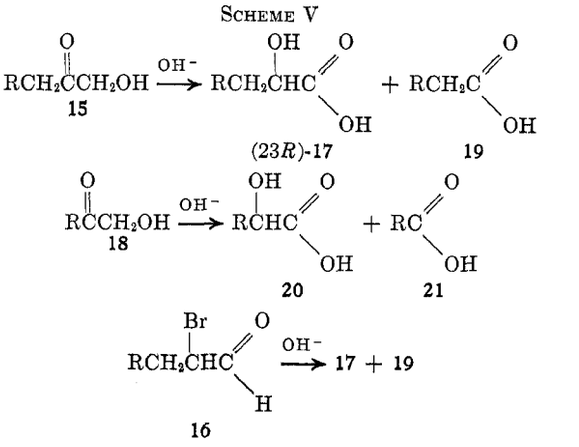
Supporting evidence which was of great use in clarifying the nature of the dimeric structure was gained in the observation that the conversion ketol → α-hydroxy acid was stereospecific. Thus the action of OH^- on ketol[7] **15** or even α-bromoaldehyde **16** provided an extremely facile synthesis of (23*R*)-hydroxycholanic acid (**17**) in 90–95% optical yield. Similar behavior was also observed in the lower homolog[8] **18** (Scheme V).

A comparison of our data with those reported by Griffiths and Gutsche[9] for dimers derived from mandelaldehyde is of some interest.

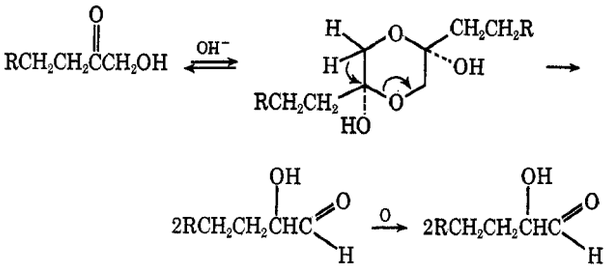
To account for the observed high optical yield in the above reaction, the intermediacy of dimeric structures in the oxidative isomerization ketol → α-hydroxy acid is postulated. Fortunately, such a dimeric compound **5** could be isolated and identified in the homocholanic series. We further assume that in the process of dimerization, which is involved in these reactions, the configuration of the pertinent carbon, bearing the steroidal alkyl and hydroxyl groups, is established. The bulky alkyl group is accommodated in the preferable equatorial orientation (Scheme VI).

(6) Y. Yanuka, R. Katz, and S. Sarel, *Tetrahedron Lett.*, 1725 (1968).
(7) Y. Yanuka, R. Katz, and S. Sarel, *ibid.*, **60**, 5229 (1970).
(8) Y. Yanuka, R. Katz, and S. Sarel, unpublished work.
(9) D. W. Griffiths and C. D. Gutsche, *J. Org. Chem.*, **36**, 2184 (1971).

SCHEME V



SCHEME VI

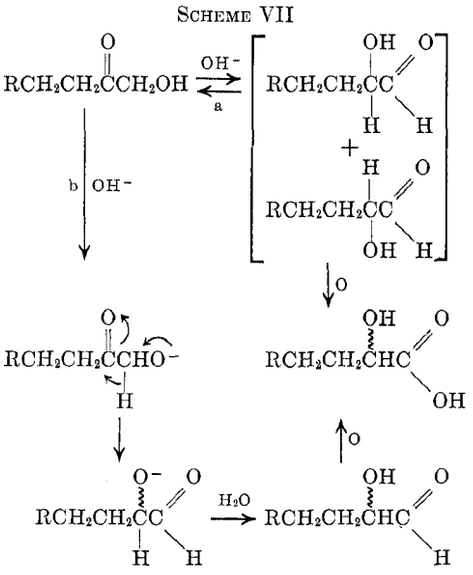


The tendency of such dimeric compounds to collapse is enhanced by virtue of the steric strain inherent in the steroidal dioxanelike derivatives. The C–O bond breaking and hydride shift are two processes in one concerted reaction.

Noteworthy is the observation that the yield of the hydroxy acid rises from 3% in the homocholanic series up to nearly 50% in the lower homologs, in line with the higher tension exercised by the molecule as the chain becomes shorter.

As no stereospecificity could be anticipated in the two following alternative mechanisms, paths a and b (Scheme VII), they are, in our opinion, unsuitable.

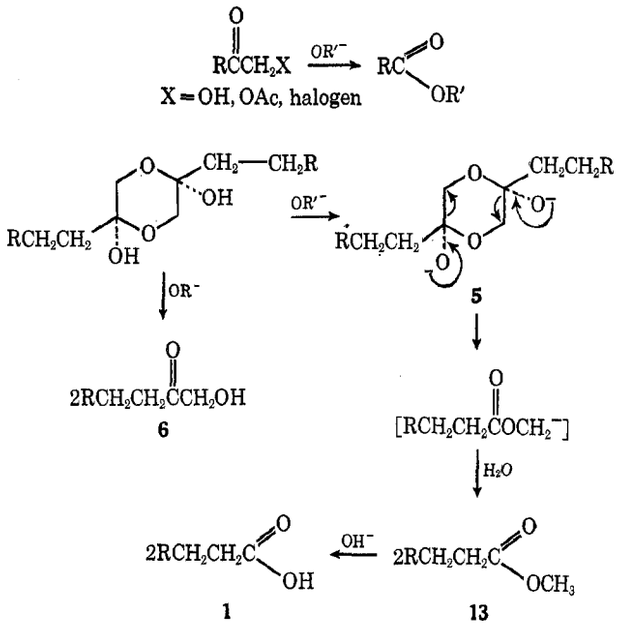
SCHEME VII



The fragmentation reaction may be visualized either as a result of a nucleophilic attack of a base on the

C=O carbon[10] or alternatively, taking place intramolecularly, again through the intermediacy of the dioxanelike structure (Scheme VIII).

SCHEME VIII



As the only product obtained in the reaction of $NaBH_4$ on the dimeric compound **5** was methyl cholanate (although two basic species are present in the solution, namely OR^- and BH_4^-), the intramolecular mechanism is more likely in cases where the dimeric compound interferes.

Experimental Section

Cholanoyl Chloride (2).—Cholanic acid (10 g) in dry benzene (150 ml) was treated with thionyl chloride (10 ml) and the resulting solution was stirred for 3 hr at 60°. The benzene and excess thionyl chloride were removed *in vacuo* and the solid residue was dissolved in dry benzene.

24-Oxo-25-diazohomocholane (3).—To the above solution was added during 15 min a slight excess of diazomethane in benzene. After an additional 15 min, the excess diazomethane was decomposed with the aid of acetic acid. The solvent was removed *in vacuo*. The product was chromatographed on silica gel (Hopkins and Williams). Elution with 20% benzene–cyclohexane gave 24-oxo-25-chlorohomocholane: mp 111°; ir ν_{CO} 1720 cm^{-1}; nmr (CCl_4) 234 cps (s, 2, CH_2); nmr ($CDCl_3$) 235 cps. Benzene eluted a readily crystallized diazo ketone (97%): mp 117°; $[\alpha]^{CHCl_3}D$ + 18.4°; ir ν 1215 (s), 1630 (s), 2105 cm^{-1} (s); nmr ($CDCl_3$) 312 cps (s, 1, CH); nmr (CCl_4) 309 cps.

24-Oxo-25-acetoxyhomocholane (4) and Dimeric Compound 5.—Diazo ketone **3** (15.0 g) was dissolved in acetic acid (50 ml) and refluxed for 24 hr. The acetic acid was removed by distillation at reduced pressure. The residue was chromatographed on silica gel. Elution with 40% benzene–cyclohexane gave **5** (2–12%), as a viscous oil: ir 1740 cm^{-1}; nmr ($CDCl_3$) 255 cps (s, 2, CH_2); nmr (CCl_4) 250 cps; mass spectrum *m/e* 748; $[\alpha]^{CHCl_3}D$ +18.6°.

Anal. Calcd: C, 80.2; H, 11.2. Found: C, 80.15; H, 11.09.

Elution with 50% benzene–cyclohexane gave pure ketol acetate **4** (90%): mp 83°; $[\alpha]^{CHCl_3}D$ +22.6°; ir ν_{CO} 1727 cm^{-1}; nmr ($CDCl_3$) 280 cps (s, 2, CH_2); nmr (CCl_4) 270 cps.

Anal. Calcd: C, 77.9; H, 10.6. Found: C, 77.55; H, 10.7.

(10) Plattens, H. Heusser, and Boyce, *Helv. Chim. Acta*, **31**, 603 (1948).

24-Oxo-25-hydroxyhomocholane (6). A. By Alkaline Hydrolysis of 4.—To a refluxing solution of the ketol acetate **4** (1.2 g) in *t*-BuOH (50 ml) a solution of 10% sodium bicarbonate in water (5 ml) was added, and the resulting solution was refluxed for 24 hr. The solvent was removed, and the residue was extracted with chloroform and washed with dilute HCl (1 *N*) and water. The chloroformic solution was dried over sodium sulfate and evaporated. The resulting ketol **6** (95%) was recrystallized from petroleum ether (bp 40–60°): mp 101°; $[\alpha]^{CHCl_3}D$ +29.5°; mass spectrum *m/e* 374; ir ν_{CO} 1720 cm^{-1}; nmr (CCl_4) 245 cps (s, 2, CH_2); nmr ($CDCl_3$) 255 cps.

Anal. Calcd: C, 80.2; H, 11.2. Found: C, 79.9; H, 11.6.

B. By Acid Treatment of Diazo Ketone 3.—To a stirred solution of **3** (0.5 g) in THF (30 ml), 0.2 ml of 50% sulfuric acid was added. After 1 hr the reaction mixture was diluted with chloroform and washed with sodium bicarbonate and water. The chloroform layer was dried over sodium sulfate and evaporated. The residue was recrystallized from petroleum ether, mp 101°, yield 90%.

24-Oxo-25-ethoxyhomocholane (8).—A solution of diazo ketone **3** (0.5 g) in benzene (3 ml) was diluted with ethanol (30 ml) and stirred. To the resulting solution 0.1 ml of sulfuric acid was added. After 30 hr the reaction mixture was diluted with water, extracted with ether, and washed with water. The ether solution was dried over sodium sulfate and evaporated. The residue when chromatographed on silica gel gave the ethyl ether **8** (60%) (elution with 50% benzene–cyclohexane), the ketol **6** (30%) (elution with 70% benzene–cyclohexane), and cholanic acid (10%) (elution with benzene).

The ethyl ether **8** melted at 56°: ir ν_{CO} 1730–1735 cm^{-1}; mass spectrum *m/e* 402; nmr (CCl_4) 229 (s, 2, CH_2), 207 (q, 2, CH_2), 78 cps (t, 3, CH_3).

Reaction of Diazo Ketone 3 with Sulfuric Acid in Benzene.—To a solution of diazo ketone **3** (300 mg) in benzene (50 ml), H_2SO_4 (0.2 ml) was added. The mixture was stirred for 1 hr and washed with water, and the solvent was removed. The product melted at 130° and could not be stored without decomposition: mass spectrum *m/e* 402; ir 1730 cm^{-1}; nmr ($CDCl_3$) 293 cps (s, 1, CH); nmr (CCl_4) 284 cps.

24-Methoxy-24,25-dihydroxyhomocholane (7).—A solution of ketol **6** (0.5 g) in methanol (30 ml) was treated with hydrogen chloride gas at room temperature. After standing for 24 hr the solvent was removed *in vacuo*. The residue was recrystallized from ether to give **7** (60%): mp *ca.* 200°; nmr ($CDCl_3$) 190 (s, 3, OCH_3), 214, 218 cps (double s, 2, $-CH_2O-$) (two isomers).

Reaction of Ketol Acetate 4, Ketol 6, and Dimeric Compound 5 with Potassium Hydroxide.—To a solution of **4** (5 g) in 10 ml of benzene, a 3% potassium hydroxide–ethanol solution (100 ml) was added and the reaction mixture was stirred for 10 hr, during which period solid material began to precipitate out. The mixture was acidified with dilute hydrochloric acid and extracted with chloroform. The solvent was removed and the residue was chromatographed on silica gel. Elution with benzene and chloroform gave cholanic acid (**1**, 95%) and α-hydroxyhomocholanic acid (**9**, 3%), respectively. The latter compound was oxidized ($NaIO_4$) by a known procedure[6] to the corresponding cholanic aldehyde **11**: mp 105°; nmr ($CDCl_3$) 586 cps (t, 1, –CHO, J = 1.5 cps).

Under nitrogen atmosphere the above reaction afforded beside the above two acids a mixture of nonacidic compounds. Tlc implied that one of them is α-hydroxyhomocholanic aldehyde (**10**). Oxidation with sodium periodate gave the same cholanic aldehyde (**11**), mp 105°. Ketol **6** and the dimeric compound **5** behaved similarly under the same conditions.

Reduction of Ketol Acetate 4 and Ketol 6 with $NaBH_4$ and $LiAlH_4$.—To a boiling solution of **4** (0.15 g) in 30 ml of ethanol a slight excess of $NaBH_4$ was added. After 0.5 hr the mixture was diluted with water and extracted with chloroform, and the solvent was removed. Pure diol **12** was obtained: mp 160°; $[\alpha]^{EtOH}D$ +28.0°; ir 860 (w), 953 (w), 1070 (w), 3400 cm^{-1} (w); nmr ($CDCl_3$) 183 (s), 168 cps (d, J = 6 cps).

A similar treatment of ketol **6** afforded diol **12**. The yield was lower than for ketol **4** due to formation of unidentified less polar by-products.

Contamination of diol **12** also occurred when reduction of **4** was affected at room temperature with either $NaBH_4$ or $LiAlH_4$ in ethanol and ether solutions, respectively.

Reduction of the Dimeric Compound 5 with $NaBH_4$ and $LiAlH_4$.—To a stirred solution of **5** (0.1 g) in 30 ml of methanol a slight

excess of $NaBH_4$ was added. After 15 hr the mixture was diluted with water and extracted with chloroform. Almost pure methyl cholanate (**13**) was obtained: mp 87°; ir ν_{CO} 1740 cm^{-1}; nmr (CCl_4) 215 cps (s, 3, $-OCH_3$).

Reduction of **5** in ether solution with $LiAlH_4$ afforded cholanol (**14**) in high purity: mp 130°; $[\alpha]D$ +24.4 ($CHCl_3$, 1%); ir 3350–3380 (s), 1055 cm^{-1} (w); nmr ($CDCl_3$) 216 cps (t, 2, CH_2, J = 4 cps).

Acetylation of Ketol 6.—The acetylation of ketol **6** to the corresponding ketol acetate **4** could be affected by all known procedures. The dimeric compound **5** resisted acetylation under all conditions.

Registry No.—**3**, 34565-21-4; **4**, 34565-22-5; **5**, 34565-23-6; **6**, 34565-24-7; **7**, 34565-25-8; **8**, 34565-26-9; **11**, 4877-66-1; **12**, 34565-28-1; **13**, 2204-14-0; **14**, 3110-99-4; 24-oxo-25-chlorohomocholane, 34565-31-6.

Mass Spectrometry in Structural and Stereochemical Problems. CCXVIII.[1] The Electron Impact Induced Behavior of Terpenoid Esters of the Juvenile Hormone Class[2]

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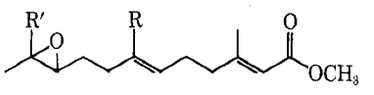
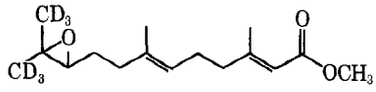
Received November 22, 1971

The 70- and 15-eV mass spectra of methyl 10,11-epoxy-*trans,trans*-farnesoate (III) and three deuterium-labeled analogs, *5,5-d*$_2$ (VI), *8,8,8′,8′,8′-d*$_5$ (V), and *12,12,12,12′,12′,12′-d*$_6$ (IV), have been examined. Generation of the important peaks in the spectra of III at *m/e* 43, 71, 81, 114, and 135 are discussed in light of high resolution and metastable peak data as well as the shift of these peaks in the spectra of the deuterated analogs. The generation of the mass 114 ($C_6H_{10}O_2$) ion by methyl 2,6-dienoates is the subject of further study involving methyl *trans,-trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX), methyl *trans,trans*-3,7-dimethyldeca-2,6-dienoate (XI), their trans,cis isomers, and several specifically deuterium-labeled C-8 or C-8′ analogs. Methyl *trans,trans*-farnesoate (XIII) and several deuterium-labeled analogs are also subjects of investigation. In this latter case, C-12 and C-12′ hydrogen transfer (*via* either a 10-, 12-, or 14-membered transition state) plays a substantial part in the mass 114 ion production.

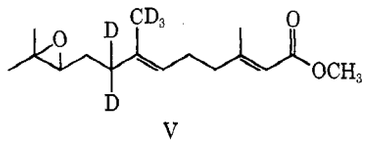
Mass spectrometry played an essential role in the structure elucidation of the first *Cecropria* juvenile hormone I, isolated by Roeller and coworkers,[4] and again in the structure proof of the second hormone II found by Meyer and colleagues.[5] Trost has discussed several of the important mass spectral cleavages of the hormone I in light of the fragments observed in the spectrum of the lower homolog, methyl 10,11-epoxy-*trans,trans*-farnesoate (III),[6] and Meyer, *et al.*,[5] have presented the low-resolution spectrum of the hormone II together with high-resolution mass measurements of some of the fragment ions. The future will see the search for the juvenile hormones of other insects, and, since the acquisition of even a few micrograms of material is very difficult, a clear understanding of the mass spectral behavior of the juvenates[7] is imperative. Because of this and also because of our fundamental interest in the behavior of ionized polyfunctional molecules, we have examined the 70- and 15-eV mass spectra of the methyl 10,11-epoxy farnesoate III and three deuterium-labeled analogs (IV–VI).



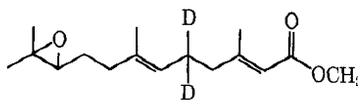
I, R′ = R = C_2H_5
II, R′ = C_2H_5; R = CH_3
III, R′ = R = CH_3



IV



V



VI

Results and Discussion

Peaks in the low mass range dominate the 70-eV spectrum (Figure 1a) of the methyl epoxy farnesoate III; those at *m/e* 43 (66% C_3H_7), 71 (C_4H_7O), 81 (C_6H_9), 114 ($C_6H_{10}O_2$), and 135 ($C_{10}H_{15}$) are particularly intense. None of these fragments arise by simple bond cleavage; as our results show, hydrogen rearrangement is essential in each case. At low ionizing energy (15 eV), fragments in the high mass region of the spectrum (Figure 1b) assume greater importance. One of the more significant peaks is found at *m/e* 248 (M − H_2O) and results from the migration of two hydrogen atoms to the epoxide oxygen. Loss of CH_3OH from the molecular ion generates an ion of mass2 34, which, together with the mass 206 ion [M − (CH_3OH + CO)], serves to identify the ester group. Analysis of the

(1) For preceding paper, see Y. Sheikh, R. J. Liedtke, A. M. Duffield, and C. Djerassi, *Can. J. Chem.*, in press.

(2) Financial assistance by the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged.

(3) National Institutes of Health Predoctoral Fellow, 1968–1971.

(4) H. Roeller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967).

(5) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968).

(6) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970).

(7) Nomenclature suggested by E. E. van Tamelen; see ref 5.