2d in 55 ml of 0.0198 *N* sodium acetate–acetic acid was heated at 90–95° for 42.5 hr. The colorless solution was worked up as in the preceding example. A preliminary attempt to separate the products by chromatography was unsuccessful, hence the entire mixture (indicated by ir to be **4a** and **1b**) was subjected to catalytic hydrogenation. The resulting oil was chromatographed on 20 g of alumina. Elution with 80% benzene–petroleum ether gave 165 mg (40%) of 5-hydroxy-5β-cholestan-6-one which had mp 103–105° after crystallization from methanol. Elution with 15% ether–benzene yielded 210 mg (44.5%) of **1b** which melted at 141–143° when crystallized from methanol.

Registry No.—**1b**, 14956-13-9; **1d**, 6770-44-1; **1e**, 20352-32-3; **2b**, 6580-09-2; **2c**, 20352-49-2; **2d**, 20352-33-4; **2e**, 20398-53-2; **4a**, 20352-34-5; **4b**, 20352-50-5; 5-Hydroxy-5β-cholestan-6-one, 16526-09-3.

The Acid-Catalyzed Rearrangements of *endo,endo*-6,7-Dihydroxy- and *endo,endo*-6,7-Diacetoxycineole

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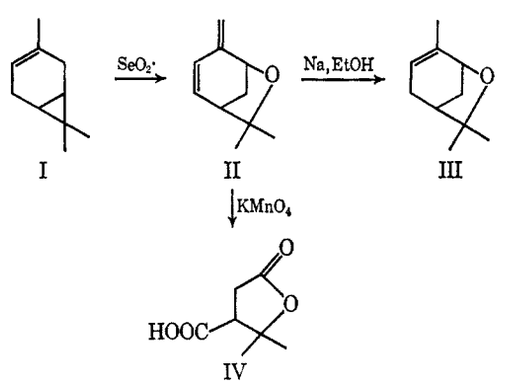
Received December 30, 1968

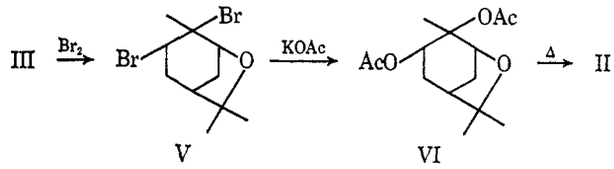
Recently, Arbuzov, Isaeva, and Ratner[2] reported the isolation of the interesting oxabicyclic diene II as one of the products arising from the oxidation of Δ^3-carene (I) with selenium dioxide. The structure assignment was substantiated by the infrared and ultraviolet spectra, the formation of pinol (III) upon reduction with sodium in ethanol, and the production of terebic acid (IV) by permanganate oxidation. Further evidence offered in support of structure II included an independent synthesis from pinol (III) using the steps outlined



I II III IV

in Scheme I based upon the early work of Wallach[3,4] in which "pinol dibromide" and "pinol diacetate" were assigned structures V and VI, respectively. Normal acetate pyrolysis of VI would be expected to afford II. Indeed, one of the pyrolysis products of VI, isolated by column chromatography, had an infrared spectrum "identical" with II (although the ir sample contained a carbonyl impurity) and gave IV upon oxidation with permanganate. Noteworthy was the finding that the pyrolysis was successful only in the presence of a small

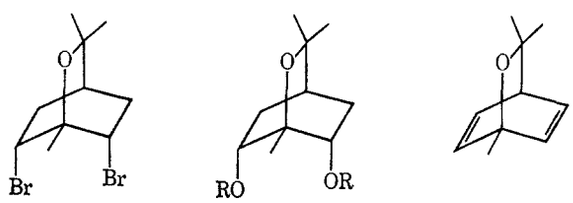
SCHEME I



V VI

amount of acid; attempts to pyrolyze VI alone gave only tar. The Russian workers also reported the presence of a ketone and a hydrocarbon in the reaction mixture, but these were not identified.

Our interest in the above series of reactions stemmed from the recently reported findings[5,6] that, contrary to the early literature,[3,4] pinol reacts with bromine to afford the rearranged dibromide VII (*endo,endo*-6,7-dibromocineole) instead of the reported structure V and that "pinol diacetate" is actually VIII (*endo,endo*-6,7-diacetoxycineole). In view of these revised assignments, regular acetate elimination reactions would be expected to give diene IX, while the conversion of VIII to II, if correct, represents a rather unusual and inter-



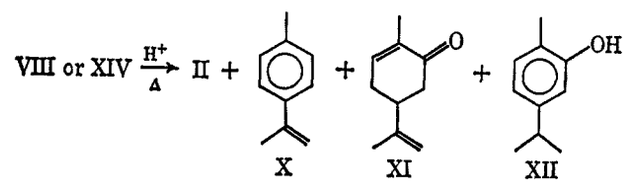
VII VIII, R = Ac XIV, R = H IX

esting rearrangement, certainly not proceeding by a normal acetate pyrolysis mechanism. In order to clear up the above anomalies and to determine the composition of the unidentified hydrocarbon and ketone, we have reinvestigated the acid-pyrolysis reaction of VIII.

Under the same conditions employed by Arbuzov and coworkers, an oily mixture was obtained which was successfully separated by gas–liquid partition chromatography and the four major components (>90% of mixture) identified as the diene II (42.2%), *p*-isopropenyltoluene (X, 36%), carvone (XI, 13.9%), and carvacrol (XII, 7.9%). The data are tabulated in Table I.

TABLE I

ACID PYROLYSIS OF *endo,endo*-6,7-DIACETOXY- AND DIHYDROXYCINEOLE



X XI XII

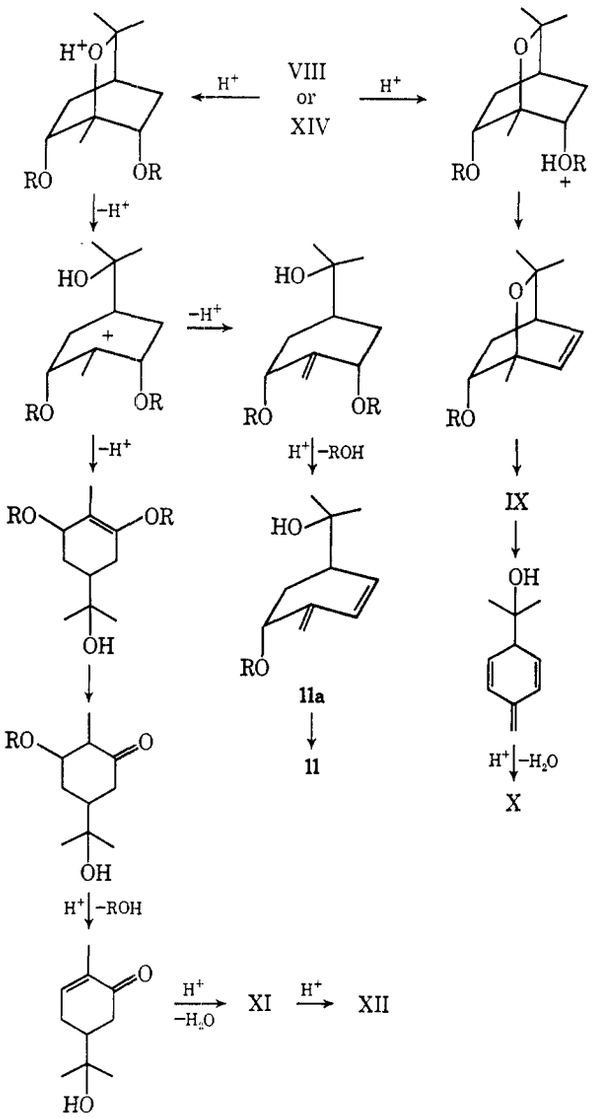
Compd	% II[a]	% X	% XI	% XII
VIII	42.2	36.0	13.9	7.9
XIV	8.2	8.5	65.0	18.3

[a] The percentages reflect only the relative amounts of the four major products (*ca.* 90% of the total volatile material) and are approximate, since differences in glpc detector responses were not measured.

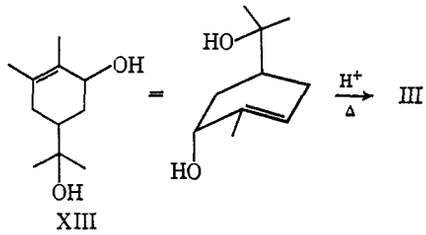
(1) Undergraduate research participant, 1968–1969.
(2) B. A. Arbuzov, Z. G. Isaeva, and V. V. Ratner, *Zh. Org. Khim.*, **2**, 1401 (1966); *J. Org. Chem. USSR*, 1391 (1966).
(3) O. Wallach and A. Otto, *Ann.*, **253**, 249 (1889).
(4) O. Wallach, *ibid.*, **259**, 309 (1890).
(5) R. O. Hutchins, Ph.D. Thesis, Purdue University, Jan 1967.
(6) J. Wolinsky and R. O. Hutchins, presented at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

Identification of X, XI and XII was accomplished by glpc and spectral comparisons with authentic samples or literature values. The data obtained for the diene II agreed well with that reported[2] and, furthermore, the nmr spectrum was in complete accord with II and inconsistent with structure IX (see Experimental Section). The mechanistic pathways for the observed transformations must be complex, but probably involve a series of acid-catalyzed elimination and isomerization reactions similar to those depicted in Scheme II.

SCHEME II



The formation of the rearranged diene II most likely occurs by initial ring opening followed by an acid-catalyzed ring closure of a labile allylic intermediate as IIa. Such a closure is similar to that observed in the acid-catalyzed formation of III from pinol hydrate



(XIII);[4,5] this suggested that the corresponding diol (XIV, *endo,endo*-6,7-dihydroxycineole) should also afford similar products upon heating with acid and, indeed, treatment of XIV under the same reaction conditions produced the same four products although the relative amounts of each were different (Table I). No evidence for the isomeric cineole diene IX was obtained from either reaction, but trace amounts of several other products were detected by glpc in both cases (<10% total) so that presumably one of these might be IX. Even if IX were initially formed in substantial quantity, it probably would not survive the acidic reaction conditions, since the compound is a diallylic ether. In fact, the expected product from ring opening of IX, *p*-isopropenyltoluene (X), may arise, at least in part, from this source. Carvacrol (XII) most probably arises from the well known acid catalyzed isomerization of XI.[5,7]

The conversion of VIII and XIV into the rearranged diene II somewhat parallels the corresponding transformation of *endo,endo*-6,7-dibromocineole (VII) to pinol (III) upon reaction with sodium in refluxing toluene or with hot alcoholic potassium hydroxide.[4,5] Finally, it is noteworthy that the successful conversion of III to diene II by Arbuzov and coworkers involved a combination of two skeletal rearrangements, unknown to them, which fortuitously cancelled and generated the desired product.

Experimental Section[8]

endo,endo-**6,7-Dibromocineole (VII).**—Bromination of pinol[4,5] in methylene chloride as previously described[3,5] afforded colorless prisms (from cyclohexane), mp 92–94° (lit. mp 92–94°, 94°).[3]

endo,endo-**6,7-Diacetoxycineole (VIII).**—Treatment of VII with silver acetate in glacial acetic acid in the reported manner[4,5] gave diacetate VIII in 78% yield. Recrystallization from *n*-pentane and sublimation gave white needles, mp 94–96° (lit. mp 97°,[4] 95.5–96.5°,[2] 92°[5]).

endo,endo-**6,7-Dihydroxycineole (XIV).**—Reaction of III with aqueous performic acid followed by hydrolysis of the resulting formate ester with sodium hydroxide[5] gave XIV. Recrystallization from *n*-hexane–ethyl acetate and sublimation afforded colorless needles, mp 121–124° (lit.[4,5,9] mp 122–124°).

Acid-Pyrolysis Reactions. A. VIII.—Following the procedure of Arbuzov,[2] a mixture of 5.01 g of VIII, 0.10 g of β-naphthalenesulfonic acid, and 20 ml of di-*n*-butyl phthalate was slowly heated with a Wood's metal bath to *ca.* 280° under a 90-mm nitrogen atmosphere. The distillate (bp *ca.* 60–173°) was diluted with 5 ml of ether, washed with 10 ml of water and twice with 10-ml portions of 5% sodium bicarbonate, and dried ($MgSO_4$). Distillation in a short-path apparatus at 11 mm afforded 0.74 g of yellow oil. Analysis by glpc[10] demonstrated the presence of four major constituents which were isolated by preparative glpc.[10] In order of increasing retention times, the following components were identified. (1) Diene II: $n^{25}D$ 1.5004 (lit.[2] $n^{20}D$ 1.5020, 1.5030); ir (neat) 1630, 1587, 1374, 1359, 1271, 1046, 993, and 880 cm^{-1} (lit.[2] 1636, 1592, 1378,

(7) H. Rupe and P. Schlochoff, *Ber.*, **38**, 1719 (1905).

(8) All boiling points and melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrometer or a Perkin-Elmer Model 621 spectrometer. Nmr spectra were measured with a Varian Associates A-60 spectrometer; chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard. Ultraviolet spectra were obtained with a Perkin-Elmer ultraviolet–visible spectrometer, Model 202. Gas–liquid partition chromatography was performed with a Perkin-Elmer Model 900 gas chromatograph or an Aerograph A-700 preparative chromatograph, both equipped with thermal conductivity detectors.

(9) G. Wagner and K. Slawinski, *Ber.*, **32**, 2064 (1899).

(10) Analysis was accomplished using a 10 ft × 1/8 in. 20% Apiazon L on Chromosorb W column at 160°. Preparative isolations were performed using a 20 ft × 1/8 in. 15% Bentone, 5% SE-52 on Chromosorb W column at 160°. A 20 ft × 3/8 in. 20% DEGS on Chromosorb W column also separated the components, but in this case the elution order of II and X was reversed.

1362, 1278, 1052, 1000, and 887 cm^{-1}); uv λ_{max} (cyclohexane) 232 mμ (log ε 4.17) [lit.[2] λ_{max} 233 (log ε 4.2)]; (C_2DCl_3) δ 1.27 [s, 6 H; $(CH_3)_2CO$], 1.7–2.6 (m, 3 H), 4.52 (broad d, 1 H, C=CCHCO, bridge H), *ca.* 4.81 (m, 2 H; C=CH_2), *ca.* 6.10 (m, 2 H; conj CH=CH). (2) *p*-Isopropenyltoluene (X): $n^{25}D$ 1.5325 (lit. $n^{25}D$ 1.5290,[11] $n^{20}D$ 1.5350[12]); uv λ_{max} (cyclohexane) 245 mμ (log ε 4.08) [lit.[13] λ_{max} 245 mμ (log ε 4.13)]; nmr ($CDCl_3$) δ 2.14 (d, 3 H, J = *ca.* 1 cps; CH_3C=C), 2.34 (s, 3 H; CH_3Ar), 5.10 and 5.34 (two m, 2 H; CCH_2), *ca.* 7.26 (m, 4 H; ArH); ir spectrum identical with that reproduced in the literature.[13] (3) Carvone (XI) was identified by glpc retention time and ir and nmr spectral comparisons with an authentic sample. (4) Carvacrol (XII) was identified by ir and nmr spectral comparisons with an authentic sample. In a second experiment, 5.0 g of VIII gave 1.22 g of the product mixture.

B. XIV.—In the same manner described for VIII, a mixture of 2.68 g of XIV and 0.06 g of β-naphthalenesulfonic acid in 20 ml of di-*n*-butyl phthalate was heated at 100-mm pressure under nitrogen. Work-up and distillation gave 0.58 g of yellow oil. Analysis by glpc indicated the oil to be primarily XI (65%) with lesser amounts of II (8.2%), X (8.5%), and XII (18.3%).

Registry No.—VIII, 20178-11-4; XIV, 20178-12-5.

(11) G. B. Bachman and H. M. Hellman, *J. Amer. Chem. Soc.*, **70**, 1772 (1948).
(12) V. N. Ipatieff, H. Pines, and R. C. Olberg, *ibid.*, **70**, 2123 (1948).
(13) M. J. Murray and W. S. Gallaway, *ibid.*, **70**, 3867 (1948).

A Novel Procedure for the Removal of *o*-Nitrophenoxyacetyl Amino-Protecting Groups[1]

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Received January 20, 1969

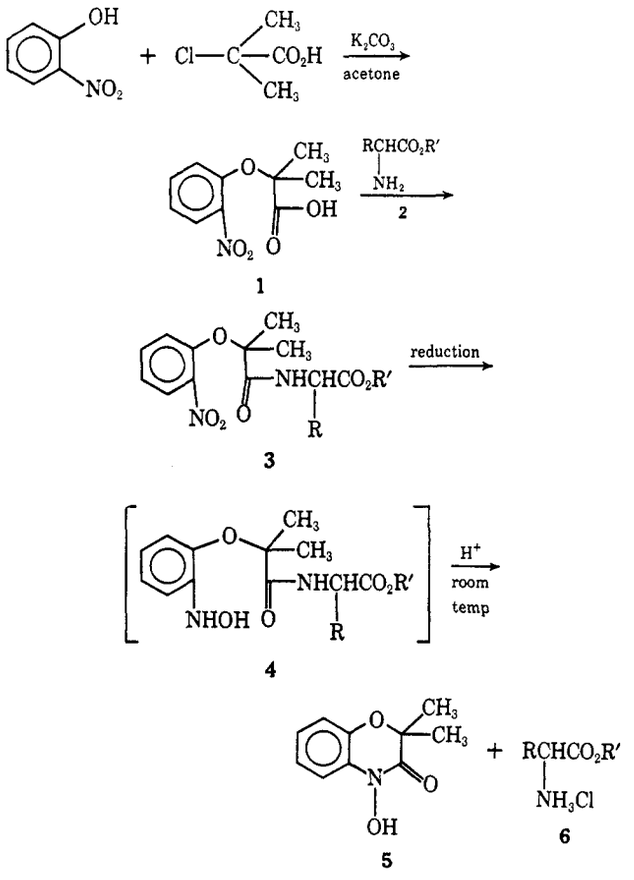
Several years ago, Holley and Holley[2] introduced the *o*-nitrophenoxyacetyl moiety as an amino-protecting group during the synthesis of peptides. They reported that this type of blocking group is removed by thermal cyclization of the corresponding *o*-aminophenoxyacetyl derivative which is obtained by catalytic reduction. Formation of the lactam of *o*-aminophenoxyacetic acid occurs with concomitant liberation of the amino group on the peptide.

We have found that the removal of the *o*-nitrophenoxyacetyl protecting group is facilitated by partial reduction of the nitro group to a hydroxylamino moiety. The deblocking is accomplished at room temperature, does not require a noble metal catalyst, and is unaffected by sulfur-containing amino acids. The procedure is illustrated in Scheme I.

The specific blocking group used in this work was derived from α-methyl-α-(*o*-nitrophenoxy)propionic acid (**1**).[3] It is easily coupled to an amino acid ester (**2**) *via* either the acid chloride or carbodiimide procedure. The amino-protected derivative (**3**) was named an MNP-amino acid ester. It has an infrared spectrum which contains a very characteristic peak at 1600 cm^{-1} (apparently an aromatic stretching band) among the other expected absorptions.

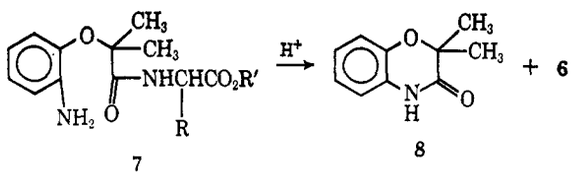
(1) Presented at the 20th Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 4, 1968.
(2) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 3069 (1952).
(3) D. A. Johnson, C. A. Panetta, and R. R. Smith, *J. Org. Chem.*, **31**, 2560 (1966).

SCHEME I



The reduction of the MNP-amino acid ester **3** to the *o*-hydroxylamino derivative (**4**) is accomplished using either aluminum amalgam or zinc and ammonium chloride in aqueous tetrahydrofuran. The former method was the less preferred one because it appeared, by tlc, to give a much larger amount of the *o*-aminophenoxyacetyl derivative (**7**) than did the latter. α-Methyl-α-(*o*-aminophenoxy)propionyl glycine ethyl ester (**7**, R = H, R′ = Et) was prepared by using a 10:1 molar ratio of aluminum amalgam to **3** (R = H, R′ = Et) and was characterized. According to tlc, **7** (R = H, R′ = Et) was found to deblock (Scheme II) much

SCHEME II



more slowly than did the ferric chloride positive[4] reduction product which is apparently the corresponding hydroxylamino derivative **4**, (R = H, R′ = Et). A proportionately smaller amount of aluminum amalgam afforded a larger yield of **4** (R = H, R′ = Et) from **3** (R = H, R′ = Et).

Compound **4** was not isolated, but a solution of it was acidified with alcoholic hydrogen chloride solution and stored at room temperature. The hydrochloride of the amino acid ester (**6**) crystallized and was separated

(4) R. L. Shriner, R. C. Tuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 135.