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THE JOURNAL OF Organic Chemistry

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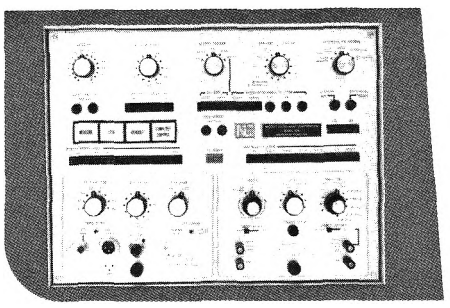

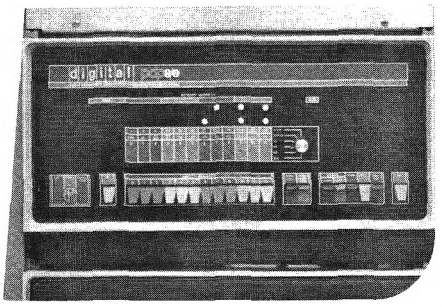

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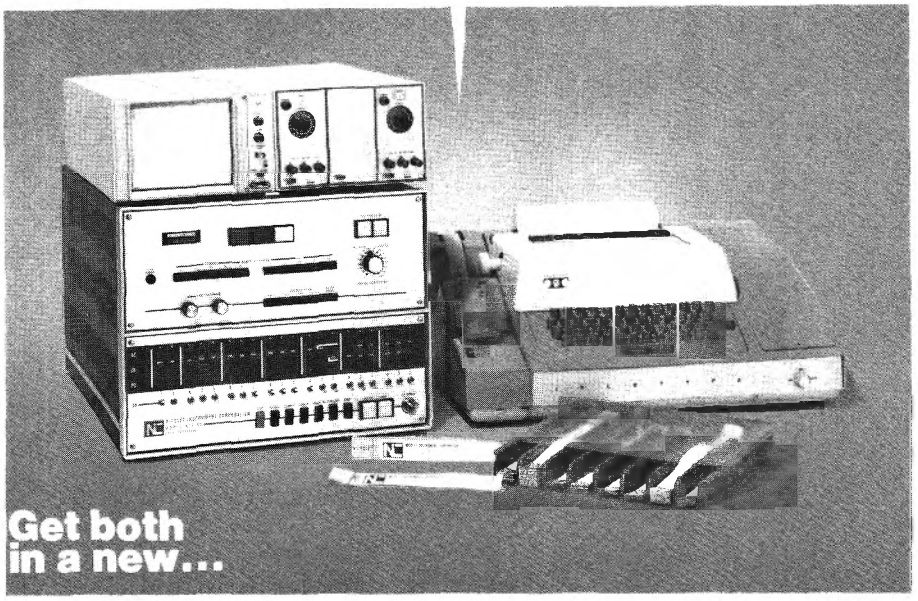

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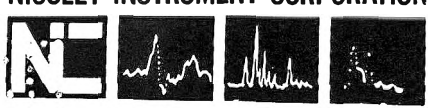

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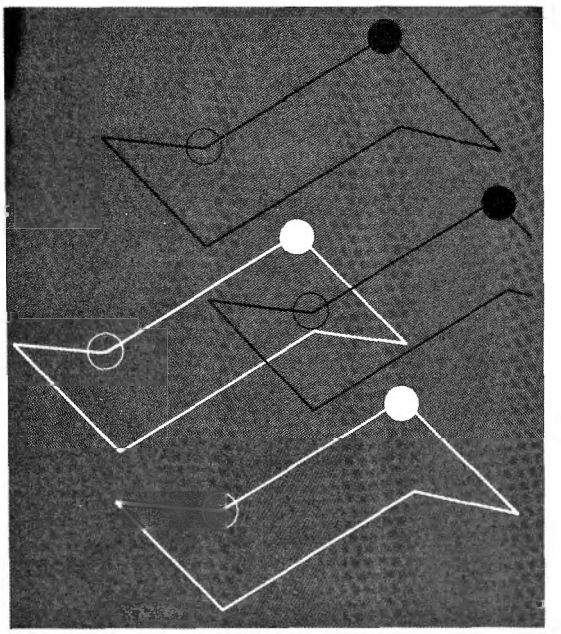

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Preparations of Some 1,2- and 1,4-Disubstituted Adamantanes

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From readily available 1-carboxyadamantan-2-one (**1**), nine 1,2-disubstituted adamantanes (**2**–**10**) were prepared. Photoacetylation of 2-acetoxyadamantane resulted in the exclusive formation of 1-acetyl-4-acetoxyadamantane (**13**), from which seven 1,4-disubstituted adamantanes (**14**–**20**) were derived. In some cases, novel dibromocarbene bromination was applied to the oxy esters (**3** and **15**). By the protoadamantane route was prepared 1-ethyl-2-bromoadamantane (**23**). Autoxidation of 1-fluoroadamantane gave the 4 and 2 ketones **26** and **27** besides the bridgehead alcohol **25**. α methine proton chemical shifts of some 1,2- and 1,4-disubstituted adamantanes are discussed from the viewpoint of additivity relationship based on the chemical shifts of monosubstituted adamantanes.

Because of its high rigidity and unique geometry, the chemistry of adamantanes has received much interest in recent years both from theoretical and synthetic viewpoints. The high symmetry of adamantane allows only two monosubstituted derivatives to exist. The situation is more complicated for disubstituted adamantanes ($C_{10}H_{14}XY$). When $X \neq Y$, 13 isomers (seven chiral and six achiral) are possible. This number is reduced to nine (six achiral and three chiral) when $X = Y$. Regioselective difunctionalization of adamantane may be one of the most exciting synthetic challenges for adamantane chemists.

A 1,3-disubstituted adamantane may be prepared rather easily *via* direct bridgehead substitutions such as ionic substitutions,[1] dichlorocarbene insertion,[2] and photoacetylation.[3] Some elegant procedures (based on intramolecular processes[4,5] or the protoadamantane route[6]) have been established for the preparations of 1,2-disubstituted adamantanes. A number of 2,4-disubstituted adamantanes have also been prepared by the direct substitution of adamantanone,[7] addition reactions to 2,4-dehydroadamantane,[8] the so-called π route ring closures of bicyclo[3.3.1]non-3-ene systems,[9,10] or the protoadamantane route.[6a,11] On the other hand, only limited works have been reported on the 1,4 difunctionalization of adamantane. The sulfuric[12–14] or nitric acid[15] oxidation or oxidative rearrangement of 1- or 2-adamantyl derivatives gave some 1,4-disubstituted adamantanes. The aluminum bromide catalyzed bromination of adamantanone has been reported to give 1-bromoadamantan-4-one almost exclusively.[9] A unique microbiological oxidation of 1-acetamido- or benzamidoadamantane has been reported to give the anti 4-hydroxy derivatives.[16] The present paper describes the preparations of 1,2- and 1,4-disubstituted adamantanes utilizing some novel together with known techniques.

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(3) I. Tabushi, Z. Yoshida, and S. Kojo, *Tetrahedron Lett.*, 2329 (1973).

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(15) (a) H. W. Geluk, *Tetrahedron Lett.*, 4473 (1971); (b) *Synthesis*, 374 (1972).

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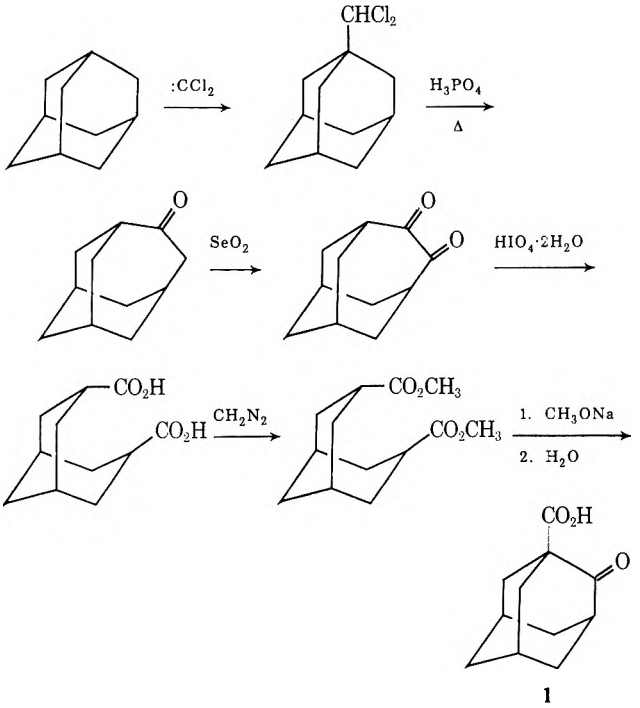
Results and Discussion

Preparations of Some 1,2-Disubstituted Adamantanes Derived from 1-Carboxyadamantan-2-one (1).—1-Carboxyadamantan-2-one (1) was prepared by a modification of the procedure of Peters, *et al.*[17] (Chart I). The modification was made for the preparation

CHART I

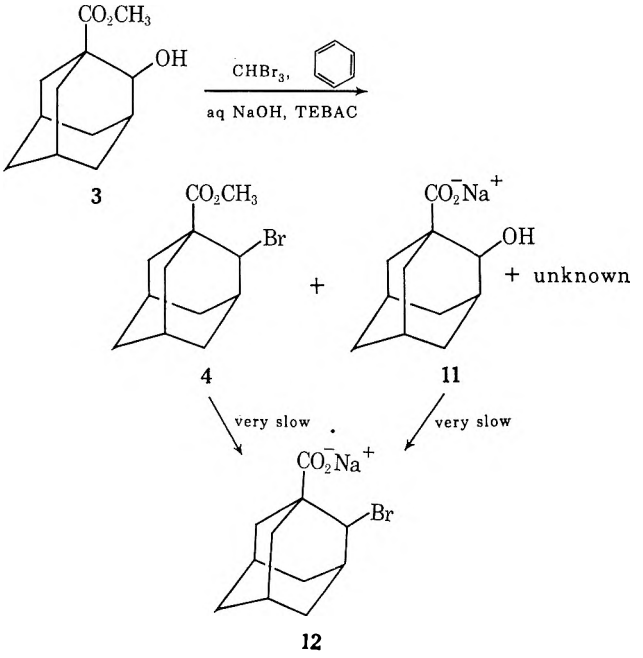


1

of homoadamantanone, which was obtained by the hydrolytic rearrangement of 1-dichloromethyladamantane[2] in our study instead of diazomethane ring homologation of adamantanone.

Some 1,2-disubstituted adamantanes derived from the keto acid **1** are summarized in Chart II. The sodium borohydride reduction of the keto acid **1** gave, in a quantitative yield, the oxy acid **2**, which was esterified with diazomethane in a quantitative yield.

Some unexpected difficulties have been encountered in the next step, the replacement of the hydroxy to bromine giving the bromo ester **4**. Common procedures such as treating the oxy ester **3** with thionyl bromide or triphenylphosphine dibromide did not give satisfactory results. In analogy with the successful chlorination of an alcohol by dichlorocarbene in an alkaline emulsion,[18] the dibromocarbene bromination of the alcohol was the final choice for this conversion.[19] Thus, the reaction of the oxy ester **3** with dibromocarbene generated from bromoform in 50% aqueous sodium hydroxide containing a small amount of benzene emulsified by triethylbenzylammonium chloride (TEBAC) gave the expected bromo ester **4** (10–15% yield) together with unknown tarry materials and the hydrolyzed oxy carboxylate **11**, which was subjected to a cycle of reesterification–dibromocarbene bromination to complete the conversion.



Interestingly, there was found no bromo carboxylate **12**, suggesting that neither the hydrolysis of the bromo ester **4** nor the bromination of the oxy carboxylate **11** took place under the present condition.

The bromo ester **4** was hydrolyzed to the bromo acid **5**, which was converted to the bromo amide **6** *via* the acid chloride in a 60% yield. Finally the bromo nitrile **7** was obtained by the triphenylphosphine–triethylamine dehydration of the bromo amide **6**.[20] Similarly the keto amide **8** in a yield of 73% and the keto nitrile **9** in a yield of 85% were obtained starting from the keto acid **1**. The sodium borohydride reduction of the keto nitrile **9** gave the oxy nitrile **10** in a yield of 99%.

Preparation of 1-Acetyl-4-acetoxyadamantane and Derived Compounds.—Principally, a 1,4-disubstituted adamantane may be prepared either by a selective γ (bridge) substitution of a 1-substituted adamantane (process a) or by a selective γ (bridgehead) substitution of a 2-substituted admantane (process b). Process a would be less accessible. Even in the simple free-radical substitution of a 1-substituted adamantane, attack at the γ (4) position was the minor reaction compared with the attack at the β (3) position.[22] In addition the stereoselectivity in the atom transfer step to the thus formed γ (4) radical was very low.[23] Process b, on the other hand, seems more promising because of a number of known examples of selective

(17) J. A. Peters, J. D. Remijnnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Lett.*, 3065 (1971).

(18) I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **93**, 1820 (1971).

(19) Mechanistic and stereochemical details of this novel procedure for the bromination of an alcohol will be published later: I. Tabushi and Y. Aoyama.

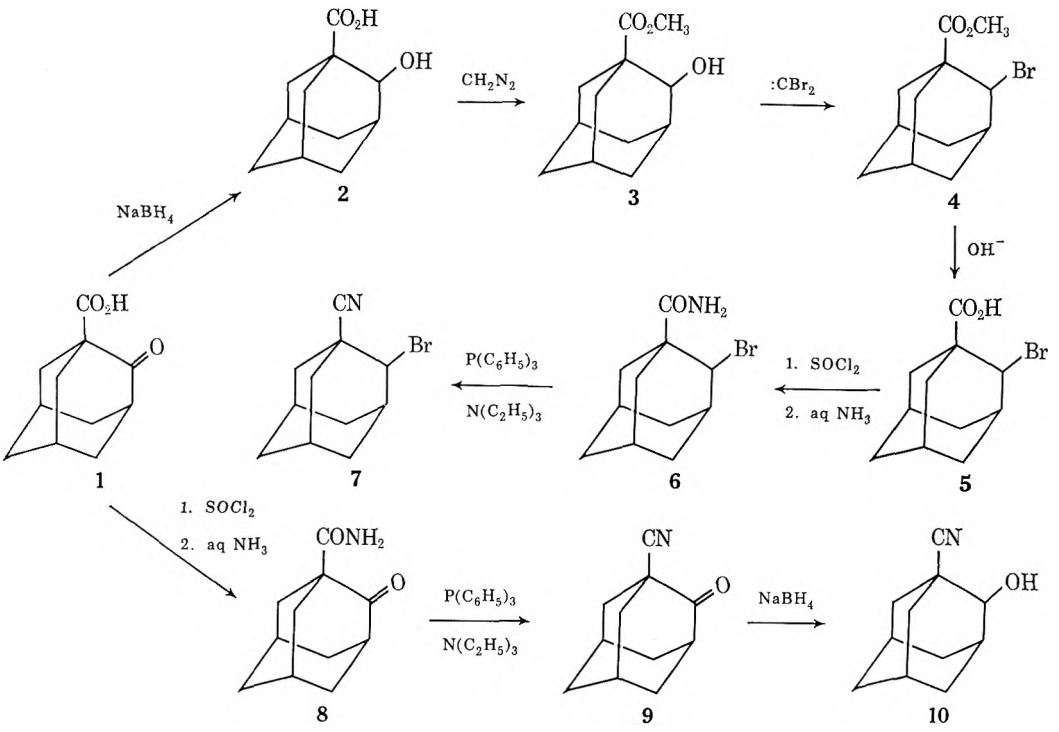
(20) The procedure was practically the same as that of Snatzke[21] for the preparation of 4-cyano-2,6-adamantanedione.

(21) G. Snatzke, *Chem. Ber.*, **105**, 244 (1972).

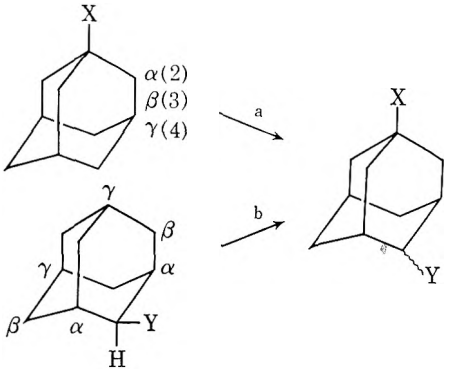
(22) (a) I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 1605 (1969); (b) G. J. Gleicher, T. L. Jackson, P. H. Owens, and J. D. Unruh, *ibid.*, 833 (1969); (c) P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, **90**, 4122 (1968).

(23) Nearly a 1:1 stereoisomer ratio of 1,4 syn and 1,4 anti products was obtained in the NBS bromination of 1-*tert*-butyladamantane or the chlorocarbonylation of 1-methyladamantane: I. Tabushi, Y. Aoyama, and T. Okada, unpublished results.

CHART II

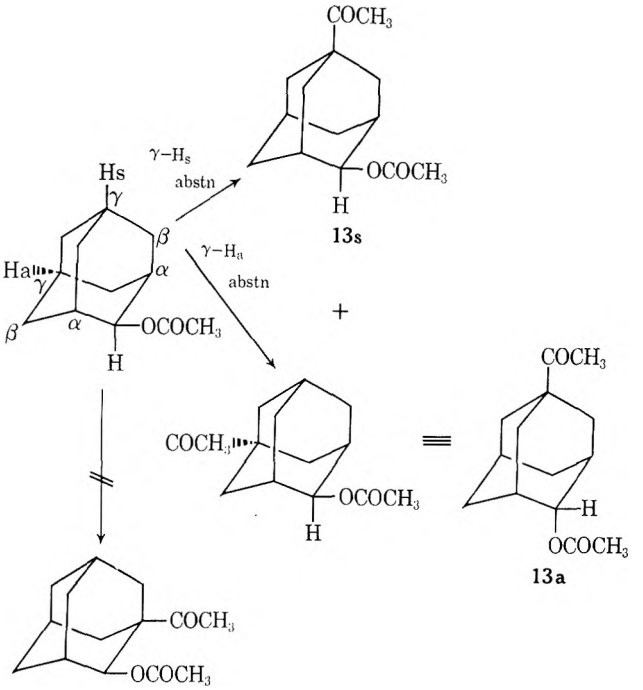


bridgehead reactions such as many ionic substitutions,[1] dichlorocarbene insertion,[2] and photoacetylation.[3]



The nonionic,[24] regioselective γ substitution of a 2-substituted adamantane was realized, for the first time, for 2-acetoxyadamantane in the photoacetylation, which was originally applied to adamantane to give rise to an exclusive formation of bridgehead acetyladamantane and was characterized by hydrogen abstraction by the photoexcited biacetyl triplet followed by the acetyl transfer from biacetyl to the thus formed adamantyl radical.[3]

High-pressure mercury lamp irradiation of a methylene chloride solution of 2-acetoxyadamantane and excess biacetyl resulted in the formation of, besides a large amount of the unreacted materials and undesired biacetyl-derived products, two bridgehead acetylated products (**13s** and **13a**) (*ca.* 10% after purification based on used 2-acetoxyadamantane, more than 40% based on consumed 2-acetoxyadamantane[26]) in a ratio of *ca* 1.7:1, although it was not yet decided which was which. That no appreciable bridge acetylation took place was confirmed by the lack of a signal assignable to the α proton of acetyl in the nmr spectra, in accord with the photoacetylation of adamantane.[3] The acetyl acetates **13s** and **13a** had by nmr (CCl_4, TMS) a sharp singlet at τ 8.00 (acetyl and acetoxy) and



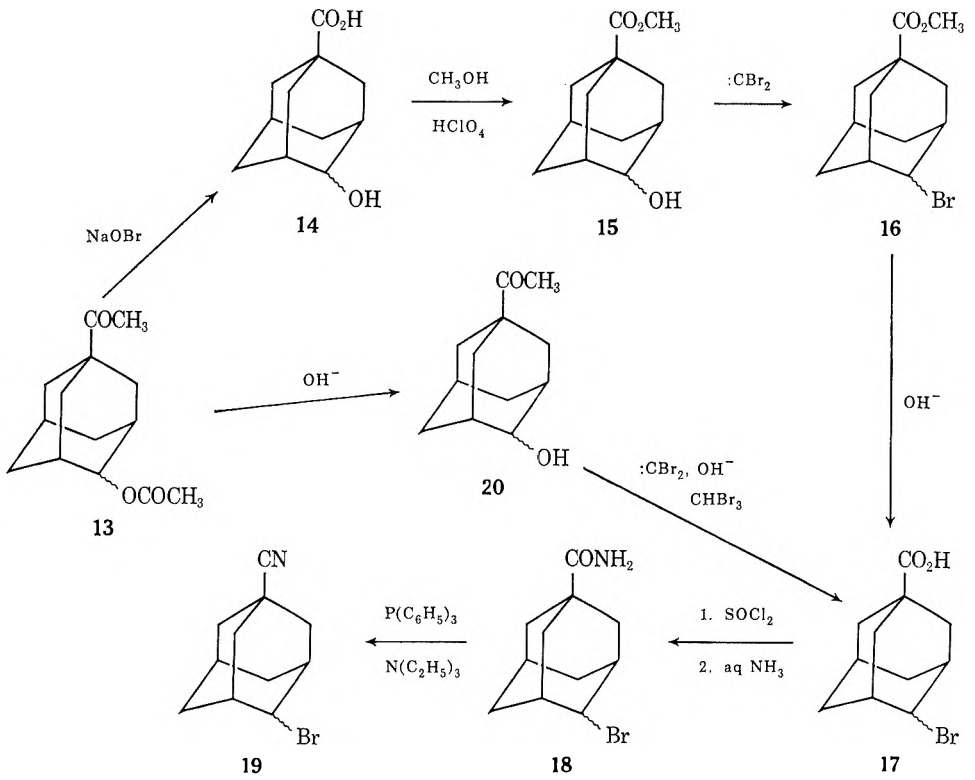
a broad singlet at τ 5.22 (acetoxy methine); ir 1705 (acetyl) and 1740 cm^{-1} (acetoxy). The acetyl acetates were converted to the oxy ester **15** (Chart III), different from the known 2-oxy-1-carbomethoxyadamantane (**3**). On this basis, it was concluded that the present photoacetylation took place exclusively at the γ bridgehead. This result may interestingly be compared with the less selective free-radical halogenation

(24) Almost regioselective γ-bromination (ionic) of adamantanone was reported.[9] Free-radical bromination of adamantanone, however, was less selective, giving all possible monobromoadamantanones.[25]

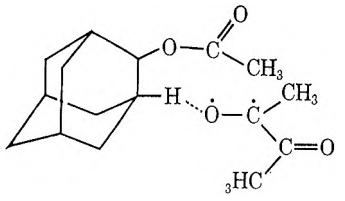
(25) I. Tabushi, Y. Aoyama, and Z. Yoshida, *J. Amer. Chem. Soc.*, **93**, 2077 (1971).

(26) Although a large amount of 2-acetoxyadamantane still remained at the end of the reaction, prolonged irradiation coupled with additional supply of biacetyl did not cause an appreciable improvement of the yield of **13**, presumably because of the accumulation of a biacetyl-derived product which had readily abstractable hydrogens.

CHART III



of adamantanone ethylene ketal,[27] 1,2-dimethyladamantane,[27] or adamantanone,[25] where the γ to α reactivity ratio ranged from 4 to 9. Although the electronic effect of the acetoxy group can never be neglected, the steric repulsion between the acetoxy group and the bulky photoexcited biacetyl in the hypothetical transition state of the α-hydrogen abstraction

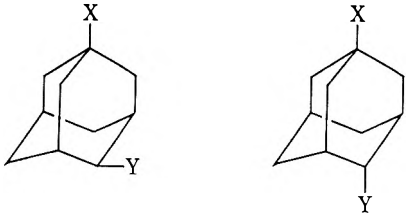


may be the best candidate for the origin of the observed high selectivity of γ-acetylation. This viewpoint is in accord with the conclusion drawn about the photoacetylation of adamantane derivatives, including diamantane.[28]

Contrary to the above-described high regioselectivity, a modest selectivity was observed for the abstraction of two kinds of γ hydrogens, one (H_s) which was syn to the acetoxy and the other (H_a) which was anti to the acetoxy. Abstraction of H_s or H_a would lead to the syn (**13s**) or anti (**13a**) acetylacetoxy derivative, respectively. This kind of "stereoselectivity"[29] will be discussed after the structural assignment is completed.

Some 1,4-disubstituted adamantanes derived from the acetylacetoxyadamantane (**13**) are summarized in Chart III.

Because an attempt to separate the two stereoisomers **13s** and **13a** in a preparative scale was not successful, all of the derived compounds (**14**–**20**) were obtained as mixtures of 1,4 syn and 1,4 anti derivatives. The



1,4 syn 1,4 anti

bromoform reaction of acetylacetoxyadamantane (**13**) in dioxane–water gave the oxy acid **14** in a 50% yield, which was quantitatively esterified to the oxy ester **15** and then converted to the bromo ester **16** *via* the dibromocarbene bromination in a yield of *ca.* 20%. The dibromocarbene bromination was accompanied with appreciable hydrolysis of the starting ester. The bromo acid **17**, bromo amide **18**, and bromo nitrile **19** were obtained in similar ways as their 1,2 counterparts (**5**, **6**, and **7**).

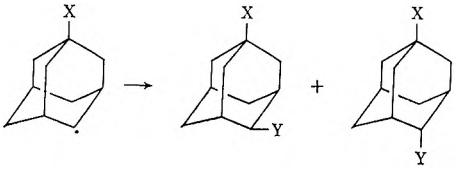
Interestingly, the dibromocarbene bromination of 4-oxy-1-acetyladamantane (**20**), obtained in a yield of 84% by the hydrolysis of acetylacetoxyadamantane (**13**), gave the bromo acid **17** in a yield of 37%. The observed conversion of acetyl to carboxyl seems to be the result of the bromoform reaction or some unknown reaction of that kind.

Glpc separation of 1,4 syn and 1,4 anti isomers was satisfactory for the bromo ester **16** and bromo nitrile

(27) I. Tabushi, Z. Yoshida, A. Togashi, M. Ozawa, and Y. Aoyama, unpublished results.

(28) I. Tabushi, Z. Yoshida, S. Kojo, and O. Fukunishi, unpublished results.

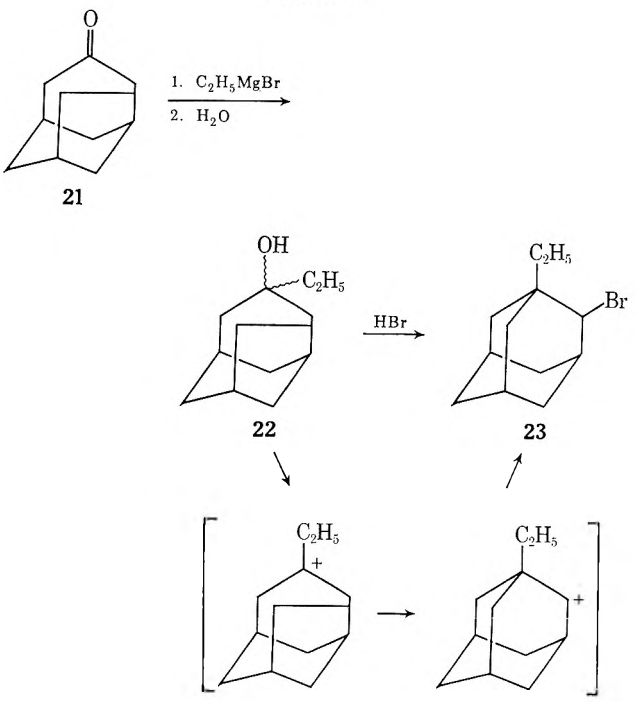
(29) It should be emphasized that this kind of "stereoselectivity" is essentially different from the more familiar stereoselectivity of an atom transfer process such as shown below.



19, where the observed stereoisomer ratios were *ca.* 2:1 and *ca.* 1:1, respectively, which were somewhat larger or smaller than the stereoisomer ratio of 1.7:1 of acetylacetoxyadamantane (13).

Preparation of 1-Ethyl-2-bromoadamantane *via* the Protoadamantane Route.—1-Ethyl-2-bromoadamantane (23) was prepared *via* the protoadamantane route[6] (Chart IV). Thus, readily available 4-proto-

CHART IV

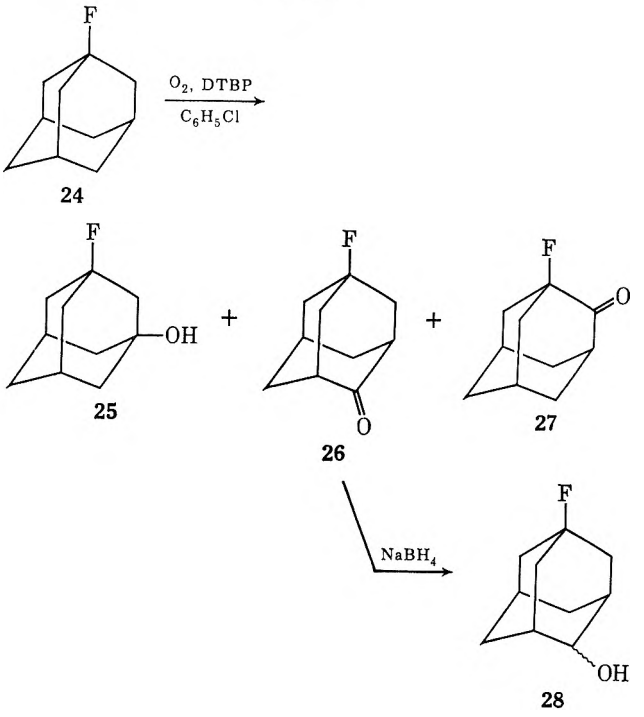


adamantanone (21)[30] was converted in 91% yield to the ethylhydroxy derivative 22 by reaction with ethylmagnesium bromide. Treatment of 22 with ethereal hydrogen bromide resulted in the formation of 1-ethyl-2-bromoadamantane (23) (61%).

Di-*tert*-butyl Peroxide Initiated Autoxidation of 1-Fluoroadamantane.—Autoxidation of 1-fluoroadamantane (24) in chlorobenzene was carried out using di-*tert*-butyl peroxide as an initiator under the vigorous flow of oxygen at 110–120°. As oxidates, there were obtained 1-fluoroadamantan-3-ol (25), 1-fluoroadamantan-4-one (26), and 1-fluoroadamantan-2-one (27) (in the order of glpc elution from a silicone column) in a ratio of *ca.* 6:2:1 (Chart V), which were readily separated by means of silica gel column chromatography. The order of glpc elution of the two ketones 26 and 27 was as expected from that of the corresponding 1,2- and 1,4-bromoadamantanones.[25] The expected upfield shift of the carbonyl stretching frequency of the 2 ketone 27 (1750 cm^{-1}) compared with that of the 4 ketone 26 (1740 cm^{-1}) was a further support for these structural assignments. From the major ketone 26 was obtained the oxy fluoride 28 by the sodium borohydride reduction in DMF (87%).

Except for some regioselective substitutions such as dichlorocarbene insertion or photoacetylation, more common free-radical substitutions are not recommendable for the second (or further) functionalization because of the low selectivities of attacking radicals re-

CHART V



sulting in the formation of tedious-to-separate mixtures of isomers.[22,31] A synthetic merit of the oxidation of a 1-substituted adamantane lies in the ease with which the products (an alcohol from the bridgehead attack and ketones from the bridge attack) are separated. Thus, despite low selectivity, autoxidation may sometimes still be an effective procedure for the preparation of adamantane derivatives such as fluoroadamantanones which otherwise are less accessible.

α Methine Proton Chemical Shifts of 1,2- and 1,4-Disubstituted Adamantanes.—Because of its rigidity, adamantane may be one of the most ideal models for the investigation of the effects of a substituent on the chemical shifts of protons which are fixed at definite angle and distance from a substituent. An especially interesting problem would be whether or not the effects of substituents are additive in di- or polysubstituted adamantanes. The nmr spectra of bridgehead-polysubstituted adamantanes[32] and 2,4-disubstituted adamantanes[33] have been studied along this line.

For a 1,2 or 1,4 derivative, a characteristic absorption of the α methine (geminal to the 2 or 4 substituent) proton was easily detected and is shown in Table I. The nmr spectrum of a 1,4 derivative (mixture of 1,4 syn and 1,4 anti isomers) except the oxy fluoride 28 showed single α proton absorption with some broadening, indicating that syn or anti orientation had little effect on the chemical shift. This result was in accord with the fact that no appreciable difference was observed in the chemical shifts of 4-axial and 4-equatorial protons of a 1-substituted adamantane.[32] In Table I are also shown the chemical shifts predicted from the additivity relationship based on the chemical

(30) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970).

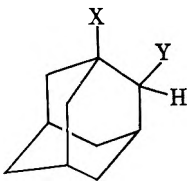
(31) Perfect determination of the product distribution of the free-radical bromination of 1-substituted adamantanes will be published soon: I. Tabushi and Y. Aoyama.

(32) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

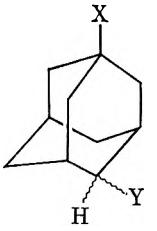
(33) F. W. van Deursen and P. K. Korver, *Tetrahedron Lett.*, 3923 (1967); (b) F. W. van Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas*, **87**, 1243 (1968); (c) F. W. van Deursen and J. Bakker, *Tetrahedron*, **27**, 4593 (1971).

TABLE I

CHEMICAL SHIFTS OF THE α METHINE PROTONS OF SOME 1,2- AND 1,4-DISUBSTITUTED ADAMANTANES[a]



X	CH_3	CH_3	C_2H_5	CO_2H	CO_2CH_3	CO_2CH_3	Cl	CN	CN
Y	OH	Br	Br	OH	OH	Br	Cl	OH	Br
Chemical shift, τ									
Obsd	6.52[b,c]	5.60[b,c]	5.67	5.90[b]	6.02	5.33	5.50[b,c] 5.65[b,e]	6.10	5.50
Calcd	6.42[d]	5.63[d]	5.72	5.96[d]	6.10	5.34	5.23[d]	5.90	5.15



X	$COCH_3$	$COCH_3$	CO_2CH_3	CO_2CH_3	Cl	F	CN
Y	$OCOCH_3$	OH	OH	Br	Cl	OH	Br
Chemical shift, τ							
Obsd	5.22	6.23	6.23	5.51	5.72[b,f,g]	6.32[f]	5.47
Calcd	5.26	6.18	6.27	5.51	5.69[d]	6.36	5.45

[a] In carbon tetrachloride with TMS as a standard. [b] In deuteriochloroform. [c] Reference 6b. [d] Calculated from the substituent shifts in deuteriochloroform. [e] Reference 6a. [f] Average of the chemical shifts of 1,4 syn and 1,4 anti isomers. [g] Reference 14.

shifts of monosubstituted adamantanes.[32] A marked difference in 1,2- and 1,4-disubstituted adamantanes may easily be seen in Table I. Without exception, the α methine proton chemical shifts of all of the 1,4-disubstituted adamantanes examined could be reproducible within 0.05 ppm by the additivity relationship, whereas such an additivity rule no longer held for 1,2-disubstituted derivatives, especially for 1-cyano-2-bromoadamantane, where a deviation as large as 0.35 ppm was observed. 1,2-Disubstituted derivatives having less electron-withdrawing groups such as alkyl or carbomethoxy had the α methine proton chemical shifts predictable from the additivity rule. Although only a limited set of substituents allows no decisive conclusion, a success or a failure of the additivity rule prediction about the α methine proton chemical shift of a 1,2-disubstituted adamantane may be dependent on the nature of the 1 substituent (alkyl, carbomethoxy, halo, or cyano) rather than on that of the 2 substituent (hydroxy or bromine).

Contrary to the bridgehead-polysubstituted adamantanes,[32] it was reported[33] that the α methine proton chemical shifts of some 2,4-disubstituted adamantanes were not predictable from the substituent shift additivity. No reasonable explanation, however, was made anywhere. Although we also hesitate to present a full interpretation of the present results, some specific interaction (steric or electronic) between the 1 and 2 substituents may be responsible for the failure of the additivity rule prediction about the α methine proton chemical shifts of some 1,2-disubstituted adamantanes.

Experimental Section

General.—Melting points (sealed capillary) and boiling points were uncorrected. Ir spectra were obtained with a Hitachi 215 spectrophotometer. Unless otherwise indicated, nmr spectra were taken in carbon tetrachloride with TMS and were recorded with a Varian T-60 spectrometer. Mass spectra were obtained with a Hitachi mass spectrometer. Microanalyses were performed either at the Microanalysis Center of Kyoto University or at the Faculty of Pharmaceutical Science of Kyushu University.

1-Carboxyadamantan-2-one (1).—According to the procedure of Peters, *et al.*,[17] 1 was prepared from homoadamantanone *via* four steps (selenium dioxide oxidation, periodic acid oxidative cleavage, esterification, and ester condensation followed by hydrolysis). Homoadamantanone was obtained by the hydrolytic rearrangement in polyphosphoric acid of 1-dichloromethyladamantane,[2] which was prepared by the dichlorocarbene insertion into adamantane in an emulsifying system.[2]

1-Carboxyadamantan-2-ol (2).—A mixture of 2.93 g of 1 and 320 mg of sodium borohydride in 10 ml of DMF was stirred for 1 hr in an ice bath and then for 18 hr at room temperature. Most of the DMF was removed *in vacuo* (140 mm) and, after acidification with hydrochloric acid, the mixture was extracted with three portions of 100 ml of ether. The combined ether extract was washed with water and dried over sodium sulfate. Evaporation of ether gave 2.96 g (quantitative) of 2 as a white solid: mp 125.5–126.5° (from 30% aqueous methanol); ir (KBr) 3345, 1705, 1280, 1252, 1208, and 1046 cm^{-1}; nmr ($CDCl_3$) τ 2.43 (broad s, 2 H, CO_2H and OH, disappeared on deuteration), 5.90 (broad s, 1 H, CHOH), and 7.6–8.6 (m, 13 H, remaining adamantyl protons).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.21. Found: C, 67.31; H, 8.19.

1-Carbomethoxyadamantan-2-ol (3).—To 800 mg of 2 was added an ether solution of excess diazomethane. The solution was stirred for 1 hr at room temperature. Evaporation of ether and excess diazomethane gave an oil which was distilled at 114–115° (0.4 mm) to give 3 in an almost quantitative yield: ir (neat) 3500, 1735, 1245, 1105, 1080, and 1053 cm^{-1}; nmr τ 6.02

(broad s, 1 H, CHOH), 6.33 (s, 3 H, CH_3), *ca.* 6.4 (broad s, 1 H, OH, disappeared on deuteration), and 7.7–8.6 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 210 (M^+, 3.5), 192 (4.3), 182 (36), 151 (36), and 150 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.84.

1-Carbomethoxy-2-bromoadamantane (4).—To a vigorously stirred mixture of 2.7 g of **3**, 7 ml of benzene, 60 ml of 50% (w/w) aqueous sodium hydroxide, and 400 mg of triethylbenzylammonium chloride was added at room temperature 25 ml of bromoform in a period of 2 hr. The mixture was stirred for a further 2 hr, then 30 ml of water was added and the mixture was extracted with five portions of 70 ml of ether. Usual work-up (washing, drying, and evaporation) on the ether extract gave a brown, tarry material (1.9 g), which was chromatographed on a silica gel column. Elution with benzene–hexane (1:1) gave a yellow oil (0.96 g) which was distilled at 115–120° (0.3 mm) to give 360 mg (10%) of **4**: ir (neat) 1750, 1255, and 1092 cm^{-1}; nmr τ 5.33 (broad s, 1 H, CHBr), 6.36 (s, 3 H, CH_3), and 7.4–8.4 (complex m with peaks at 7.60, 7.77, 8.03, and 8.30, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 272 and 274 (M^+, 27.6), 241 and 243 (3.5), 213 (11), and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.63; H, 6.04.

Further elution with benzene gave a tarry material (*ca.* 1 g), the nmr spectrum of which showed no methyl signal. The structure was not further investigated.

The aqueous layer was acidified with hydrochloric acid and then extracted with three portions of 30 ml of methylene chloride. After evaporation of methylene chloride, the residue was esterified as above. Glpc analysis showed a single peak which was identified as the starting material **3** by means of glpc coinjection and spectral behavior. Thus recovered oxy ester **3** was further subjected to the dibromocarbene bromination.

1-Cyano-2-bromoadamantane (7).—A mixture of 159 mg of **4** and 80 mg of powdered sodium hydroxide in 20 ml of methanol containing 1 ml of water was refluxed for 5 hr. At the end of the reaction, 70 ml of water was added and the mixture was extracted with ether. From the ether extract was recovered a small amount of the unreacted ester. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. Drying and evaporation gave 100 mg (69%) of 1-carboxy-2-bromoadamantane (**5**) as an oil, which was dissolved in 2 ml of thionyl chloride. The mixture was refluxed for 2 hr, then thionyl chloride was evaporated *in vacuo* and the residue was dissolved in 0.5 ml of dry tetrahydrofuran. The tetrahydrofuran solution was added to 3 ml of 28% aqueous ammonia with stirring. The mixture was stirred at room temperature for 1 hr and extracted with methylene chloride. From the methylene chloride extract was obtained 61 mg (61% from **5**) of 1-carbamoyl-2-bromoadamantane (**6**), ir 1680 cm^{-1}. A solution of 30 mg of crude **6**, 60 mg of triphenylphosphine, 0.046 ml of triethylamine, and 35 mg of carbon tetrachloride in 3 ml of methylene chloride was refluxed for 15 hr. Water was added and the mixture was shaken. The organic layer was dried over sodium sulfate and evaporated to dryness and the residue was chromatographed on a silica gel column. After elution with hexane, **7** was eluted with hexane–benzene (1:1). Pure **7** was obtained by means of preparative glpc (silicone DC 550): ir (KBr) 2250, 970, and 735 cm^{-1}; nmr τ 5.50 (broad s, 1 H, CHCN), 7.5–8.5 (complex m with peaks at 7.60, 7.79, 8.05, and 8.30, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 239 and 241 (M^+, 2.35) and 161 (100).

1-Carbamoyladamantan-2-one (8).—A solution of 850 mg of **1** in 10 ml of thionyl chloride was refluxed for 2 hr, then excess thionyl chloride was removed *in vacuo*. The residue was dissolved in 6 ml of dry tetrahydrofuran and the tetrahydrofuran solution was added dropwise at 0° to 12 ml of 28% aqueous ammonia with stirring. Stirring was continued for 3 hr at room temperature. Water was added and the mixture was extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated to dryness to give 620 mg (73%) of **8**: mp 177–177.5° (from cyclohexane); ir (KBr) 3425, 3345, 3293, 3195, 1713, 1663, 1619, and 1056 cm^{-1}; nmr ($CDCl_3$) τ 2.0–2.5 and 3.8–4.6 (very broad, each corresponded to 1 H, NH_2, disappeared on deuteration), and 7.2–8.3 (m with peaks at 7.38, 7.60, and 7.90, 13 H, adamantyl protons); mass spectrum *m/e* (rel intensity) 193 (M^+, 8.0), 164 (27.0), and 150 (100).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 8.01; N, 7.23.

1-Cyanoadamantan-2-one (9).—Practically the same procedure for the preparation of **7** was applied to **8** to give **9** in a yield of 85%: mp 199.5–200.5° (from cyclohexane); ir (KBr) 2250, 1730, and 1062 cm^{-1}; nmr ($CDCl_3$ + CCl_4) τ 7.32 (broad s, 1 H, bridgehead proton vicinal to C=O), 7.67 (broad s, 4 H, methylene protons vicinal to CN), and 7.7–8.2 (m, 8 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 175 (M^+, 51.8), 149 (22), 147 (100), and 146 (23.2).

Anal. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.50; H, 7.23; N, 7.75.

1-Cyanoadamantan-2-ol (10).—A mixture of 300 mg of **9** and 35 mg of sodium borohydride in 10 ml of DMF was stirred at room temperature for 20 hr. Usual work-up gave 300 mg (99%) of **10** as a white crystal: mp 215.5–216° (from cyclohexane); ir (KBr) 2234, 1102, 1056, and 1031 cm^{-1}; nmr τ 6.10 (broad s, 1 H, CHOH) and 7.4–8.5 (complex m with peaks at 7.43, 7.70, 7.99, 8.20, and 8.27, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 177 (M^+, 6.6), 150 (14.7), and 149 (100).

Anal. Calcd for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.68; H, 8.62; N, 7.81.

1-Acetyl-4-acetoxyadamantane (13).—A solution of 6.3 g of 2-acetoxyadamantane and 40 ml of biacetyl in 400 ml of methylene chloride was irradiated by a 450-W high-pressure mercury lamp for 35 hr in an ice bath. The methylene chloride was removed *in vacuo* and the residue was distilled. Distillation at *ca.* 90° (3 mm) gave a yellow to brown oil (*ca.* 13 g), which consisted mainly of 2-acetoxyadamantane and the pinacol derived from reductive dimerization of biacetyl.[34] About 5 g of 2-acetoxyadamantane was recovered by distillation after the removal of the pinacol *via* washing with water followed by adsorption on powdered calcium chloride. Further distillation at *ca.* 200° (3 mm) gave an oil (4 g), which was washed with water. A large amount of powdered calcium chloride was added and the mixture was allowed to stand for 3 days. Distillation at 130–150° (0.4 mm) gave a yellow oil (1.4 g), which was chromatographed on a silica gel column. About 600 mg of crude **13** was obtained by elution with benzene. A pure sample for analytical purposes was obtained by preparative glpc followed by distillation: ir (neat) 1740 ($OCOCH_3$), 1705 ($COCH_3$), and 1260 cm^{-1}; nmr τ 5.22 (broad s, 1 H, $CHOCOCH_3$), 8.00 (s, 6 H, $COCH_3$ and $OCOCH_3$), and 7.8–8.4 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 236 (M^+, 5.3), 193 (85.6), 151 (100), and 133 (100).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.39.

1-Carboxyadamantan-4-ol (14).—To a vigorously stirred solution of 2 g of sodium hydroxide and 1 ml of bromine in 12 ml of water was added a solution of 250 mg of **13** dissolved in 12 ml of dioxane in a period of 1 hr at 0°. The mixture was stirred at room temperature for 4 hr. Water (200 ml) was added and the mixture was extracted with ether. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. From the extract was obtained 110 mg (45%) of **14**, ir 1705 cm^{-1} (broad).

1-Carbomethoxyadamantan-4-ol (15), 1-Carbomethoxy-4-bromoadamantane (16), 1-Carboxy-4-bromoadamantane (17), 1-Carbamoyl-4-bromoadamantane (18), and 1-Cyano-4-bromoadamantane (19).—These compounds were prepared by similar procedures to those described for the preparations of their 1,2 counterparts (**3**, **4**, **5**, **6**, and **7**).

15 had ir (neat) 1737, 1250, and 1085 cm^{-1}; nmr τ 6.23 (broad s, 1 H, CHOH), 6.40 (s, 3 H, CH_3), and 7.7–8.4 (m, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 210 (M^+, 4.3), 192 (34), 151 (100), and 133 (81).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.60.

16 had ir (neat) 1735, 1250, 1080, and 733 cm^{-1}; nmr τ 5.51 (broad s, 1 H, CHBr), 6.40 (s, 3 H, CH_3), and 7.3–8.2 (m, 13 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 213 and 215 (12.5) and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.93; H, 6.14.

19 had ir (KBr) 2270, 2250 (shoulder), 978, 925, and 740 cm^{-1}; nmr τ 5.47 (broad s, 1 H, CHCN) and 7.3–8.5 (m with peaks at 7.7 and 8.1, 13 H, remaining adamantyl protons), mass spectrum *m/e* (rel intensity) 239 and 241 (M^+, 0.2) and 161 (100).

1-Acetyladamantan-4-ol (20).—A solution of 700 mg of **13** and

(34) W. D. Cohen, *Chem. Weekblad.*, **13**, 590 (1916).

500 mg of powdered sodium hydroxide in 50 ml of methanol containing 1.5 ml of water was refluxed for 0.5 hr. Water (300 ml) was added and the mixture was extracted with four portions of 30 ml of ether. The ether extract was washed with water and dried over sodium sulfate. Glpc analysis showed that the yield of **20** was 84%. The ether was evaporated and the residue was distilled at 114–115° (0.4 mm) to give **20**: ir (neat) 3450, 1703, 1070, and 1040 cm^{-1}; nmr τ 6.23 (broad s, 1 H, CHOH), 7.94 (s, 3 H, CH_3), and 7.6–8.9 (complex m with peaks at 7.70, 8.23, 8.45, and 8.68, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 194 (M^+, 6.7), 151 (100), and 133 (52).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.33. Found: C, 73.83; H, 9.37.

Dibromocarbene Bromination of 20.—The reaction of **20** (270 mg) with dibromocarbene was carried out in a similar way as described for the preparation of **4**. From the alkaline layer was obtained 130 mg (37%) of **17**.

1-Ethyl-2-bromoadamantane (23).—To 10 ml of ether solution of ethylmagnesium bromide prepared from 146 mg of magnesium and 670 mg of ethyl bromide was added a solution of 308 mg of 4-protoadamantanone (**21**)[30] in 10 ml of ether. The mixture was refluxed for 2 hr. A saturated ammonium chloride solution (10 ml) was added and the ether layer was separated. The aqueous layer was extracted with 20 ml of ether. The combined ether extract was washed with water, dried over sodium sulfate, and evaporated to give 335 mg (91%) of 4-ethyl-4-hydroxyprotoadamantane (**22**) as an oil. No further purification was attempted on **22**. A solution of 115 mg of **22** in 10 ml of ether saturated with hydrogen bromide was refluxed for 0.5 hr. Evaporation of ether gave an oil, which was distilled to give 100 mg (61%) of **23**: ir (CCl_4) 962, 924, 890, 648, and 617 cm^{-1}; nmr τ 5.67 (broad s, 1 H, CHBr), 7.58 (broad s, 1 H, bridgehead proton adjacent to Br), 7.74 (broad s, 2 H, other bridgehead protons), 8.17, 8.27 (m, 10 H, remaining adamantyl protons), 8.4–9.0 (2 H, CH_2CH_3), and 9.0–9.4 (3 H, CH_2CH_3); mass spectrum *m/e* (rel intensity) 242 and 244 (M^+, 2.5), 213 and 215 (3.0), and 163 (100).

Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.87. Found: C, 59.50; H, 8.04.

Autoxidation of 1-Fluoroadamantane.—A solution of 2.6 g of 1-fluoroadamantane (**24**) in 18 ml of chlorobenzene was heated at 120°. To this solution was added, under vigorous flow of oxygen, a mixture of 20 ml of di-*tert*-butyl peroxide and 8 ml of chlorobenzene in a period of 7 hr. The mixture was heated at the same temperature for 6 hr. After cooling, a small amount of ferrous oxide was added and the mixture was allowed to stand overnight. Chlorobenzene was distilled *in vacuo* (50 mm) and the residue was chromatographed on a silica gel column. Elution with pentane (300 ml) gave 343 mg of the recovered 1-fluoroadamantane. Elution with benzene (200 ml) gave white solid (350 mg), which consisted of 1-fluoroadamantan-4-one (**26**), 1-fluoroadamantan-2-one (**27**), and 1-fluoroadamantan-3-ol (**25**). Further elution with benzene (1000 ml) gave **25** (490 mg). The ketone fraction was rechromatographed on a silica gel column to complete the separation of **26** and **27** using hexane–benzene (1:1) as an eluent. By a controlled elution, there were obtained 27 mg of pure **27**, 90 mg of pure **26**, 80 mg of a mixture of these, and 150 mg of **25**.

26 had mp 170–171° (after sublimation *in vacuo*); ir (KBr) 1740, 1090, 1065, 1055, 965, and 920 cm^{-1}; nmr τ 7.40 (broad s, 2 H, bridgehead protons adjacent to C=O) and 7.4–8.6 (m with peaks at 7.83, 8.06, and 8.30, 11 H, remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 168 (M^+, 100), 149 (16.7), 140 (11.7), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.57; H, 8.06.

27 had mp 213–216° (after sublimation *in vacuo*); ir (KBr) 1750, 1123, 1097, 1060, 970, 880, and 838 cm^{-1}; mass spectrum *m/e* (rel intensity) 168 (M^+, 55.0), 149 (28.6), 140 (28.6), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.11; H, 7.75.

1-Fluoroadamantan-4-ol (28).—A mixture of 153 mg of **26** and 17 mg of sodium borohydride in 3 ml of DMF was stirred at room temperature for 15 hr, then 3 ml of water was added and the mixture was stirred for 10 min. Water was added and the product was extracted into three portions of 50 ml of ether. Washing, drying, and evaporation of the combined ether extract gave 133 mg (87%) of **28**: ir (KBr) 1103, 1078, 1057, and 910 cm^{-1}; nmr τ 6.23, 6.40 (broad s, 1 H, CHOH), and 7.4–8.6 (m with peaks at 7.87, 8.20, and 8.36, 14 H, OH and remaining adamantyl protons); mass spectrum *m/e* (rel intensity) 170 (M^+, 8.7) and 151 (100).

Acknowledgment.—The authors are very grateful to Professor Yoshida, Kyoto University, for his helpful discussions.

Registry No.—**1**, 40556-86-3; **2**, 40556-88-5; **3**, 41171-74-8; **4**, 41171-75-9; **7**, 41171-76-0; **8**, 41171-77-1; **9**, 41171-78-2; **10**, 41171-79-3; *syn*-**13**, 41163-62-6; *anti*-**13**, 41163-63-7; *syn*-**14**, 41163-64-8; *anti*-**14**, 41163-65-9; *syn*-**15**, 41163-66-0; *anti*-**15**, 41163-67-1; *syn*-**16**, 41163-68-2; *anti*-**16**, 41163-69-3; *syn*-**20**, 41163-70-6; *anti*-**20**, 41163-71-7; **21**, 27567-85-7; **23**, 41171-81-7; **24**, 768-92-3; **26**, 41171-83-9; **27**, 41171-84-0; *syn*-**28**, 41163-72-8; *anti*-**28**, 41163-73-9; homoadamantanone, 24669-56-5; 1-dichloromethyladamantane, 41171-86-2; bromoform, 75-25-2; 2-acetoxyadamantane, 19066-22-9; biacetyl, 431-03-8; ethyl bromide, 74-96-4.

Ring Enlargements by Thallium(III) Oxidation of Double Bonds. Applications to Adamantane Systems

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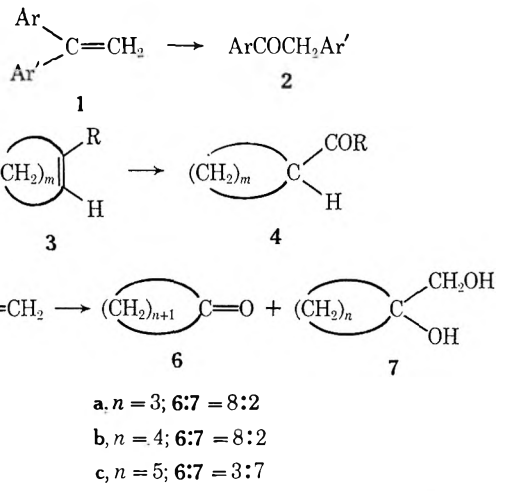
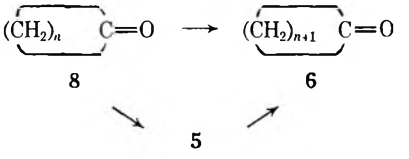
The synthetic potential of a new homologization procedure based on the thallium(III) oxidation of exocyclic olefins was explored. The four- and five-membered ring systems, **9**, **10**, **11**, and **13**, gave moderate yields of ring-expanded ketones. The method was found to suffer from incompleteness of oxidation on one hand and the sensitivity of the ketone products toward further oxidation on the other. In the case of 2-methyleneadamantane, a six-membered system less prone to ring expansion, side reactions predominated, and unsatisfactory yields of 4-homodiamantanone (**15**) were obtained. The high ratio of methylene over methine migration (85:1) in the oxidation of 2-methylenenorbornane (**13**) to **29** and **30** suggests the intermediacy of 2-*exo*-hydroxy-2-thallomethylnorbornane (**35**) rather than its endo epimer, **36**.

Rearrangements characterize the reaction of olefins with thallium(III) salts.[2-6] Deoxybenzoins (**2**) are obtained from 1,1-diarylethylenes (**1**),[3] and cycloalkanes (**3**) give ring-contracted aldehydes and ketones (**4**).[3-6] Recently, Abley, Byrd, and Halpern have shown that exocyclic olefins (**5**) undergo ring expansion by thallic oxidation in aqueous solution.[6]

We wished to explore the potential of this reaction as an alternative method for ring enlargement of cyclic ketones, **8** → **6**. Of the homologation methods normally employed, the reaction with diazomethane[7] is the most direct, but often gives poor results with cyclobutanones[8,9] and cyclopentanones.[10,11] These either are unreactive, or give complex mixtures of mono- and polyhomologated products.[7,8,10,11] The Tiffeneau–Demyanov procedure involves three steps: cyanohydrin formation, reduction to an amino alcohol, and nitrous acid deamination.[12] Because of unfavorable equilibria, the formation of cyanohydrins from ketones is often unfavorable. While methods are now available which overcome this drawback,[13,14] the overall yields of homologated ketones (**8** → **6**) are seldom good.[12-14]





Since the methylenecycloalkanes (**5**) can be obtained from ketones **8** by the Wittig reaction,[15] the conversion **8** → **6** using thallium oxidation would be a two-step process. However, the procedure used by Halpern, *et al.*[6] (oxidation of olefin with thallic perchlorate in 0.1–1 *M* aqueous perchloric acid) was designed for analytical and kinetic purposes and is unsuitable for synthetic work on larger systems with very low water solubility.

Results

Five representative olefins, **9**–**13**, were chosen for study. These included 3-methylenecyclobutanecar-

(1) Sabbatical leave at Princeton University, 1971–1972.

(2) A. McKillop and E. C. Taylor, *Chem. Brit.*, 4 (1973).

(3) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970); A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Amer. Chem. Soc.*, **95**, 3635 (1973).

(4) J. E. Byrd, L. Cassar, P. E. Eaton, and J. Halpern, *Chem. Commun.*, 40 (1971).

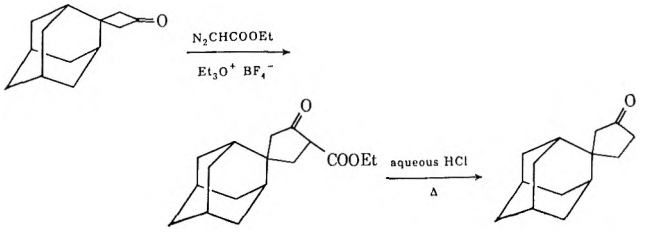
(5) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971).

(6) P. Abley, J. E. Byrd, and J. Halpern, *J. Amer. Chem. Soc.*, **95**, 2591 (1973); also see J. E. Byrd and J. Halpern, *ibid.*, **95**, 2586 (1973).

(7) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, Chapter IV.

(8) J. Jaz and J. P. Davreux, *Bull. Soc. Chim. Belg.*, **74**, 370 (1965).

(9) This problem can be circumvented by employing diazoacetic ester and triethyloxonium fluoroborate catalyst: W. L. Mock and M. E. Hartman, *J. Amer. Chem. Soc.*, **92**, 5767 (1970). The ring-expanded β-keto ester can be hydrolyzed and decarboxylated to the parent ketone. By this procedure, we have carried out the following homologation in 94% yield.



(10) A. P. Giraitis and J. L. Bullock, *J. Amer. Chem. Soc.*, **59**, 951 (1937); J. T. Lumb and G. H. Whitham, *Tetrahedron*, **21**, 499 (1965).

(11) (a) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963); (b) G. Fachinetti, F. Pietra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971).

(12) P. A. S. Smith and D. R. Baer, *Org. React.*, **11**, 157 (1960); ref 7b, Chapter III.

(13) U. Schöllkopf and F. Gerhart, *Angew. Chem., Int. Ed. Engl.*, **7**, 805 (1968); *Tetrahedron Lett.*, 6231 (1968).

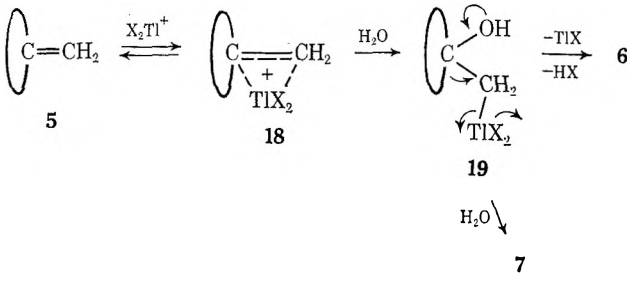
(14) H. Gerlach, *Helv. Chim. Acta*, **55**, 2962 (1972).

(15) U. Schöllkopf in "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 111; A. Maercker, *Org. React.*, **14**, 270 (1965).

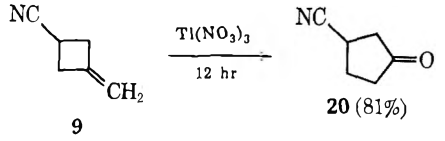
bonitrile (**9**)[16] and 2-methylenenorbornane (**13**)[17] as model substrates for four- and five-membered ring systems. 2-Methyleneadamantane (**12**),[18] a six-membered ring example, was expected to be less prone toward ring expansion. The conversion of adamantanone (**14**) to 4-homoadamantanone (**15**) has already been carried out by diazomethane[19] and Tiffeneau–Demyanov[20] procedure, so that a direct comparison of all three methods was possible. The ring-expanded ketones, **16** and **17**, from the two tetracyclic adamantane derivatives, **10** and **11** (obtained from the ketones **21**[21] and **22**[22]), were desired in order to prepare the parent hydrocarbons.

1,2-Dimethoxyethane was chosen as cosolvent to increase olefin solubility and decrease reaction time,[23] but studies of the reaction conditions indicated that a mixed solvent containing a large excess of water gave better results. The effect of other parameters, like acidity and reaction time, was also investigated, but a truly comprehensive search for the best reaction conditions was not carried out; it might be possible to improve the results reported here. However, our experience in difficult cases was not encouraging in this respect.

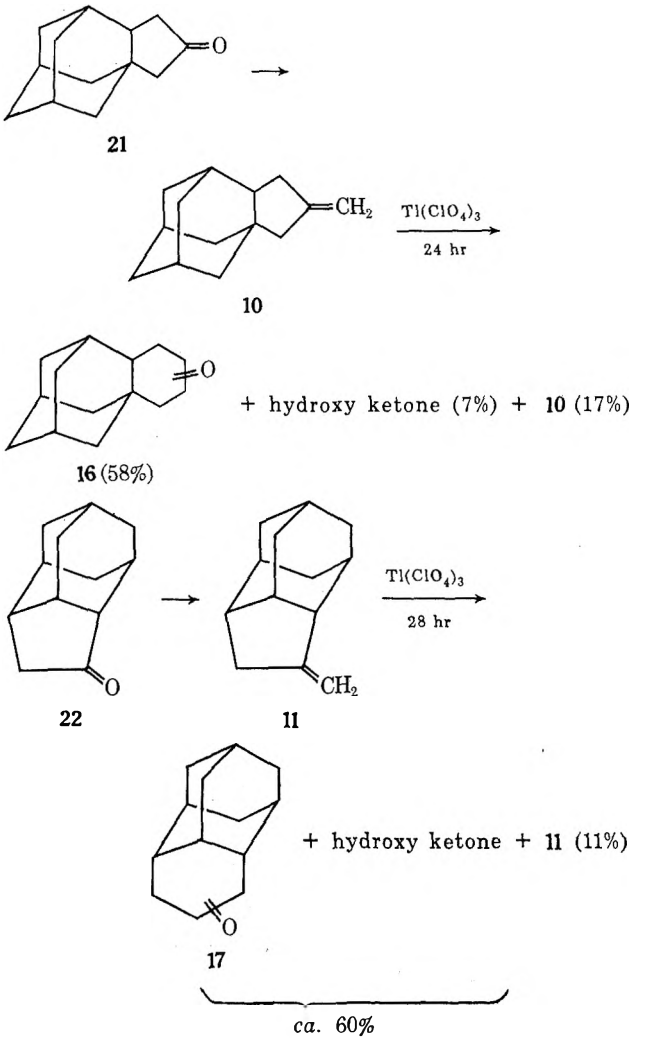
The mechanism of these reactions generally involves initial formation of a cyclic thallonium ion (**18**), followed by trans attack by water to give an intermediate **19** in which the thallium can function as leaving group.[4,6,24]



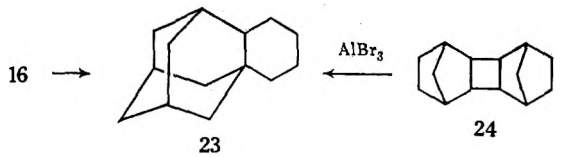
Nucleophilic displacement by water on **19** can give diol **7**, but, in favorable instances where ring strain can be relieved, rearrangement to ring-expanded ketone **6** predominates. Thus, methylenecyclobutanecarbonitrile (**9**) gave 3-cyanocyclopentanone (**20**) as the only product observed.



The expansion of methylenecyclopentanes to cyclohexanones is still favorable thermodynamically, and this is reflected in our results with **10** and **11**; no unrearranged oxidation products were observed. However, the reactions were rather slow, evidently owing to the poor solubility of these compounds, and starting olefin was recovered. At the same time, some overoxidation to the corresponding α-hydroxy ketones occurred.[25] It is probably significant that **11** reacted more slowly than **10** and gave the larger amount of



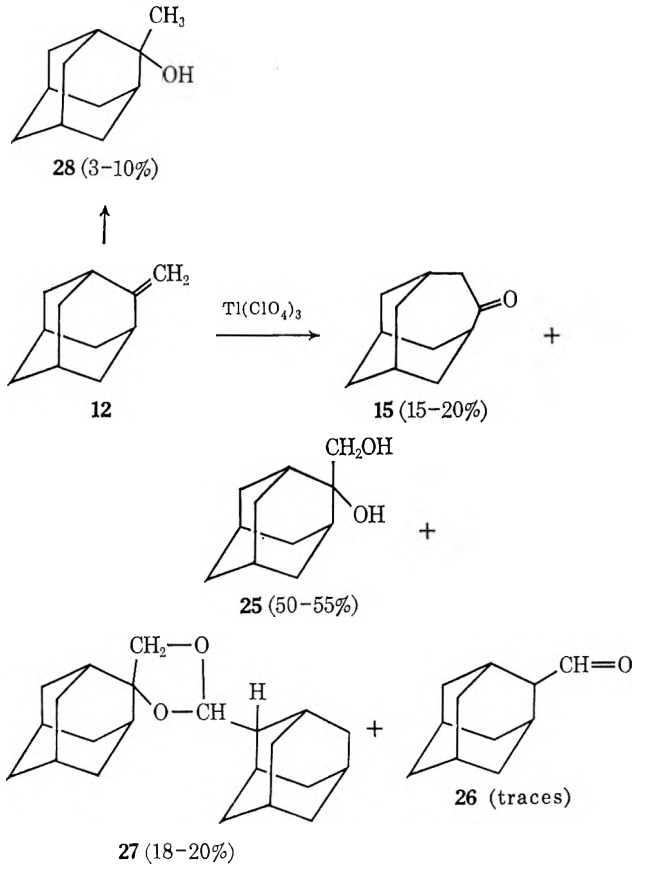
α-hydroxy ketone. We found no way of avoiding incomplete oxidation without increasing overoxidation. The Wolff–Kishner reduction of ketone **16** gave the parent hydrocarbon, **23**, identical with that obtained by disproportionation from the [2 + 2] norbornene dimer, **24** (precursor of diamantane).[26]



In 2-methyleneadamantane (**12**)[18] the double bond is exocyclic to a six-membered ring, and ring expansion would increase strain. Oxidation with Tl(III) gave a mixture of 4-homoadamantanone (**15**)[19,20] (15–20%), 2-

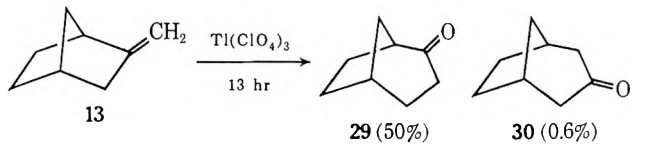
(16) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **80**, 751 (1958); **81**, 2723 (1959).
(17) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **470**, 62 (1929).
(18) P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 182 (1961).
(19) P. v. R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, **91**, 3965 (1969); R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970).
(20) J. E. Nordlander, F. Y. H. Wu, and S. P. Jindall, *J. Amer. Chem. Soc.*, **91**, 3962 (1969); J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970).
(21) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970). The same ketone was obtained in better yield from 2-adamantylmethyl diazomethyl ketone: D. Fărcaşiu, unpublished observations.
(22) W. Thielecke and D. Fărcaşiu, unpublished observations.
(23) E. C. Taylor, personal communication.
(24) P. M. Henry, *J. Amer. Chem. Soc.*, **87**, 990 (1965).
(25) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, **37**, 3381 (1972).
(26) T. M. Gund, V. Z. Williams, Jr., E. Osawa, and P. v. R. Schleyer, *Tetrahedron Lett.*, 3877 (1970); *cf.* E. Engler and P. v. R. Schleyer, *MTP Rev. Sci.*, in press. Also see ref 37.

hydroxy-2-hydroxymethyladamantane (**25**)[27] (50–55%), a trace of 2-adamantanecarboxaldehyde (**26**),[27] the acetal of **25** with **26** (**27**) (18–20%), and 2-methyl-2-adamantanol (**28**)[18] (3–10%). The carbinol **28** is formed by the concurrent hydration of the double bond, as proved by allowing **12** to react with aqueous



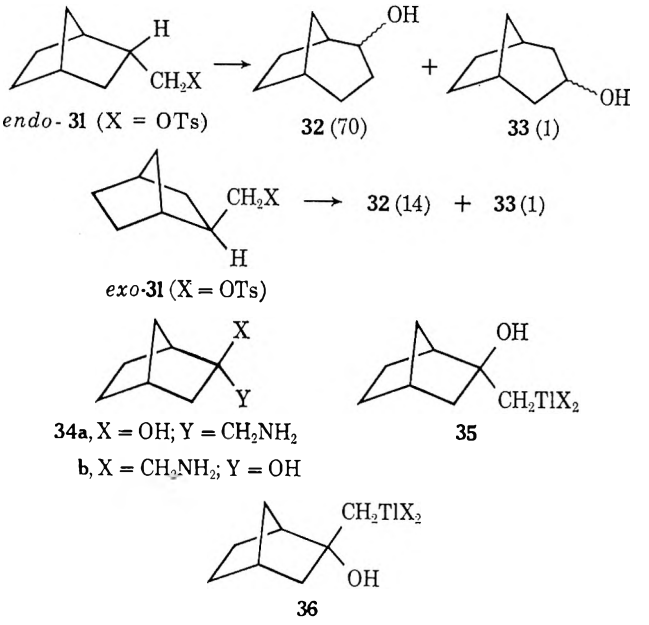
perchloric acid under the same conditions. Thus, the products in which the polycyclic skeleton is preserved (**25**–**27**) are favored over the ring-expanded product (**15**) by a factor of about 4 (compare **5c** → 30% **6c** + 70% **7c**).[6] In this case, the alternative diazomethane[19] and cyanohydrin reduction–deamination[20] homologation procedures are preferable.

The positions of the keto groups in **16** and **17** were not established. The oxidation of **11** gave a mixture of **17** and hydroxy ketone which was only incompletely separated by column chromatography, and the nmr spectrum was complex. However, the question of regiospecificity of the ring-expansion step, **19** → **6**, was investigated with 2-methylenenorbornane (**13**).[17] The oxidation products from **13**, bicyclo[3.2.1]octan-2-one (**29**) and bicyclo[3.2.1]octan-3-one (**30**), were identified by comparison of the ir spectra (**29**) and glc retention times (**30**) with those of authentic samples.[28,29] No diol was obtained, and hydration of **13** appeared to be the only side reaction.

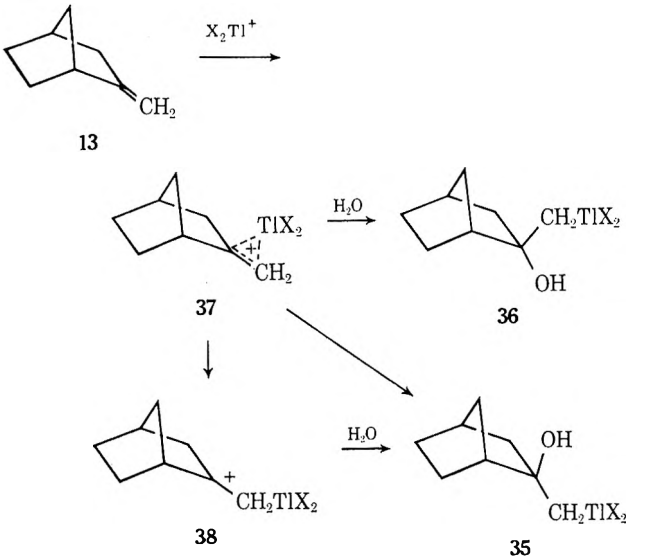


(27) Identical with a sample prepared from 2-epoxymethyleneadamantane: (a) D. Fărcaşiu, *Synthesis*, 615 (1972); (b) J. A. Bone, J. R. Pritt, and M. C. Whiting, *J. Chem. Soc., Perkins Trans. 1*, 2644 (1972).

The high ratio of methylene over methine migration in the oxidation of **13** (**29**:**30** 85:1) is near to that found for the solvolysis of *endo*-2-norbornylmethyl tosylate (*endo*-**31**) {ratio of bicyclo[3.2.1]octan-2-ol (**32**): bicyclo[3.2.1]octan-3-ol (**33**) = 70} and significantly larger than the ratio obtained from *exo*-**31** (**32**:**33** = 14).[11a] Similar differences were observed in the deamination of *exo*- and *endo*-2-norbornylmethylamines (**31**, X = NH_2)[30] and particularly in the deamination of amino alcohols **34a** and **34b**, which gave ratios of **29**:**30** of 20 and 2, respectively.[31] These data suggest that the rearrangement step of thallic oxidation takes place from intermediate **35** rather than **36**.



Since the attack of the double bond in **13** by Tl(III) takes place most probably from the exo side,[32] trans attack by a water molecule (as represented in **18** → **19**)[6,24] should give rise to **36**. Formation of **35**



(28) W. Kraus, *Justus Liebigs Ann. Chem.*, **685**, 97 (1965); we are indebted to Dr. Kraus for the ir spectrum of authentic **29**.

(29) C. W. Jefford, J. Gunsher, D. T. Hill, P. Brun, J. LeGras, and B. Waegell, *Org. Syn.*, **51**, 60 (1971); we are indebted to Professor Jefford for a sample of **30**.

(30) J. A. Berson and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, **86**, 595 (1964); J. A. Berson and D. Willner, *ibid.*, **86**, 609 (1964).

(31) E. Volpi and F. Pietra, *Tetrahedron Lett.*, 4867 (1972).

(32) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, p 181 ff.

suggested by the high ratio of **29**:**30** agrees better with the intermediacy of an "open" ion, **38**, which, even if classical (like the 2-methyl-2-norbornyl cation), is attacked by a water molecule from the exo side;[33] alternatively, a referee has suggested that **37** might be attacked by water directly from the front side to give **35**.

In conclusion, we found thallic oxidation useful for ring expanding cyclic systems in which a double bond is exocyclic to a four- or five-membered ring, but not to a six-membered ring. Even for five-membered rings, the yields are limited by side reactions and the method does not appear to be so promising a general synthetic procedure as we had hoped based on results for the simple methylenecycloalkanes.[6]

Experimental Section

The ir spectra were determined using a Perkin-Elmer 237 B spectrometer. The nmr spectra were recorded on a Varian A-60A instrument. Chemical shifts are given in δ units from internal TMS. Mass spectra were determined at 70 eV on an AEI-MS9 spectrometer. Microanalyses were performed at Hoffmann-La Roche, Nutley, N. J.

Wittig Reactions.—The literature procedure[34] was followed, except for the manner of drying the DMSO[27a] and the amount of methylenetriphenylphosphorane employed (2:1 molar ratio to the ketone). After reaction, the mixture was poured into ice–water and extracted with pentane, and the crude product was purified by chromatography on silica gel with pentane. 2-Methyleneadamantane (**12**) (70% yield) and the following olefins were prepared in this manner.

3-Methylenetetracyclo[6.3.1.1^{6,10}.0^{1,5}]tridecane (**10**) was a liquid: yield 87% from **21**;[21] nmr (CCl_4) δ 4.82 (2 H, m, CH_2=), 2.55–1.00 (18 H, complex); ir (neat) 3051, 1656, 873 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.04; H, 10.63.

3-Methylenetetracyclo[6.3.1.0^{2,6}.0^{5,10}]dodecane (**11**) was a liquid: yield 78% from **22**;[22] nmr δ 4.83–4.63 (2 H, broad, CH_2=), 2.57–2.21 (3 H, complex), 2.21–1.10 (13 H, complex); ir (neat) 3045, 1650, 874 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.29; H, 10.36.

Thallic Oxidations. Method A.—A solution of $Tl(ClO_4)_3$ in $HClO_4$ [made by dissolving 9.2 g (20 mmol) of Tl_2O_3 in 50 ml of 71% $HClO_4$ and 25 ml of water with heating] was added in small portions at room temperature to 5 mmol of alkene suspended in a magnetically stirred mixture of 20–30 ml of 1,2-dimethoxyethane, 220–230 ml of water, and 2–3 ml of 71% $HClO_4$. Each aliquot (1–2 ml) of Tl(III) solution was added when the previous one had reacted completely (KI–starch paper). The reaction was discontinued when the rate of Tl(III) consumption decreased markedly [usually a little less than the calculated amount of Tl(III) was used]. The total reaction time varied from 10 to 30 hr for different compounds. Solid Na_2CO_3 (30 g) was added and the reaction mixture was extracted with pentane. The crude product was chromatographed on silica gel (80 g). Elution with pentane gave the unreacted alkene; the oxidation products were then eluted with ether.

Method B.[35]—To a solution of 1 g (10.9 mmol) of 3-methylenecyclobutanecarbonitrile (**9**)[16] in 20 ml of dimethoxyethane, $Tl(NO_3)_3 \cdot 3H_2O$ (5.8 g, 12 mmol) dissolved in water (20 ml) was added dropwise with stirring. The reaction was slightly exothermic and after 20 min a white precipitate appeared [Tl(I) salt]. The reaction mixture was stirred overnight, poured into saturated aqueous NaCl, and extracted three times with chloroform. The chloroform solution was washed with 5% aqueous sodium bicarbonate, dried (Na_2SO_4), and eluted through a short (5 cm) column with silica gel to remove any inorganic salts. The residue after evaporation of solvent (1.2 g still containing some solvent) contained only one product, 3-cyanocyclopentanone (**20**) (glc on a 5% Carbowax column, 3 m × 6 mm o.d., at 175°). Preparative glc gave a product showing ν 2240 (C≡N), 1755 cm^{-1} (C=O) (in $CDCl_3$); nmr ($CDCl_3$) δ 3.43–2.95 (complex, 1 H, CHCN), 2.65–2.14 (complex, 6 H). Integration of the gas chromatogram of the crude reaction mixture indicated a yield of 81% of **20**.

Oxidation of 10 (0.78 g, 4.15 mmol) was conducted by method A as above. The residue from the pentane extract weighted 0.70 g. Extraction with $CHCl_3$ of the residual water solution (*vide infra*) gave no additional organic material (diol). The crude product was chromatographed on silica gel. Elution with pentane gave 0.135 g (17.5%) of **10**. Elution with pentane–ether (25:75) gave 0.50 g (58%) of **16**, ir (CCl_4) 1715 cm^{-1}, nmr complex pattern at δ 2.55–1.10. Further elution gave (after 0.051 g of a mixture of **16** and hydroxy ketone) 0.063 g (7%) of hydroxy ketone, ir 1705, 3050 cm^{-1}, mass spectrum *m/e* 220 (M^+). Owing to the small amount of material, this was not further investigated.

Tetracyclo[7.3.1.1^{7,11}.0^{1,6}]tetradecane (**23**).—The Wolff–Kishner reduction of **16** (0.48 g) by the procedure of Whitlock and Siefken[36] gave 0.26 g (59% yield) of **23** (oil). For analysis it was purified by column chromatography on silica gel (25 g, elution with pentane). The nmr (complex pattern, δ 2.40–0.85), ir, and mass spectra[37] were identical with those of the disproportionation product from **24**.[26,37]

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.36; H, 11.64.

Oxidation of 11 (0.74 g, 4.25 mmol) conducted by procedure A as above gave 0.71 g of crude product. Column chromatography gave 0.085 g (11%) of unreacted **11**, eluted with pentane; then elution with ether gave 0.05 g (6%) of **17** [ir (CCl_4) 1705–1715 cm^{-1}] and 0.47 g (*ca.* 55% yield) of a product exhibiting in the ir spectrum a broad absorption at 1705–1725 cm^{-1} and the ν_{OH} centered at 3380 cm^{-1} (CCl_4). In the mass spectrum intense peaks were present both at *m/e* 206 (mol wt of hydroxy ketone) and at *m/e* 190 (mol wt of **17**). Therefore, this product was probably a mixture of **17** and hydroxy ketone.

Oxidation of 2-methyleneadamantane (**12**) (0.74 g, 5 mmol) was conducted by procedure A as above. When the pentane extract was concentrated, a small amount of diol **25** precipitated. The remaining solution was chromatographed on 25 g of silica gel. Elution with hexane gave the acetal **27** (after small amounts of unreacted **12**). Elution with hexane–benzene mixtures (with increasing benzene content) gave the carbinol **28**, the ketone **15**, and the aldehyde **26** (eluted in this sequence). An approximate analysis of the residue from the pentane extract was provided by integrating the nmr spectrum using the CH_2O signal for **25**, the CHO_2 signal for **27**, the CH_3 signal for **28**, and the CH=O signal for **26**; the amount of **15** was calculated by difference.

2-Hydroxymethyl-2-hydroxyadamantane (**25**).—The aqueous solution from oxidation of **12** (after extraction with pentane) was extracted four times with chloroform. After drying, evaporation of the solvent gave *ca.* 45–48% yield of **25** (combined with the diol recovered from the pentane extract, 50–55%). (The same product was obtained by shaking an ether solution of 2-epoxymethyleneadamantane[27a] with an aqueous acid solution.) **25** was obtained as white needles (from benzene): mp 211.9–213.0° (sealed tube); nmr ($CDCl_3$) δ 3.95 (s, 2 H, CH_2O), 2.05 (2 H, OH), 2.50–1.50 (14 H, complex).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.18; H, 9.65.

Acetal of 25 and 26 (**27**).—To 0.71 g (3.84 mmol) of diol **25**, a benzene solution of aldehyde **26** (prepared from 4.26 mmol of 2-epoxymethyleneadamantane[27a]) and 10–15 mg of *p*-toluenesulfonic acid were added. After dilution with benzene to 45 ml, the solution was refluxed for 18 hr, using a Dean–Stark trap to remove water. The flask was cooled in ice–water, 0.5 ml of concentrated ammonia and a few drops of water were added, and the resulting mixture was then stirred for 1 hr at room temperature. Anhydrous Na_2SO_4 was added and the stirring was continued for 30 min. The solid was filtered off and washed with benzene. The residue from evaporating the benzene solution was dissolved in pentane (no residue was left) and evaporated again to give an almost quantitative yield of **27** (based on **25**), mp 220–

(33) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967); H. L. Goering, C. Brown, and C. B. Schewene, *ibid.*, **90**, 6214 (1968).

(34) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(35) A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron Lett.*, 5281 (1970).

(36) H. W. Whitlock, Jr., and M. W. Siefken, *J. Amer. Chem. Soc.*, **90**, 4929 (1968).

(37) S. Hála, J. Novak and S. Landa, *Sb. Vys. Sk. Chem.-Tekhnol. Praze, Tekhnol. Paliv*, **D-19**, 31 (1969).

223° (slight decomposition). For analysis, a sample was sublimed at 140° (0.3 mm): nmr δ 5.12 (1 H, d, J = 7.5 Hz, CHO_2), 3.70 (2 H, AB pattern, CH_2O), 2.45–0.85 (29 H, complex); mass spectrum m/e 328 ($M\cdot^+$), 327, 326, 193.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.10; H, 9.82.

Acknowledgments.—We are indebted to J. Halpern for transmitting details of his work prior to publication, to E. C. Taylor for helpful suggestions, and to J. A. Berson, C. W. Jefford, and W. Kraus for supplying us with reference samples or spectra. This work was supported by grants from the National Science Foundation (GP 29078), the National Institutes of Health (GM-19134), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Hoffmann-La Roche Inc., Nutley, N. J.

Registry No.—**9**, 15760-35-7; **10**, 41171-88-4; **11**, 41171-89-5; **12**, 875-72-9; **16**, 41163-74-0; **17**, 41163-75-1; **20**, 41171-91-9; **21**, 27174-68-1; **22**, 41171-93-1; **23**, 41171-94-2; **25**, 41171-95-3; **26**, 39750-93-1; **27**, 41171-97-5.

The Chemistry of the *trans*-Trimethylenenorbornene Ring System. II. Thermal Rearrangement to the *cis,anti,cis*-Tricyclo[5.3.0.0^{2,6}]decane System[1a,b]

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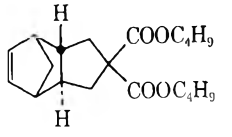
At temperatures near 200° 9-carbomethoxy-*trans*-5,6-trimethylene-2-norbornene undergoes a facile 1,3-sigmatropic rearrangement to give 9-carbomethoxy-*cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]dec-3-ene in essentially quantitative yield. Pyrolysis of 9,9-dicarbo-*tert*-butoxy-*trans*-5,6-trimethylene-2-norbornene under similar conditions affords 9-carboxy-*cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]dec-3-ene, whereas the corresponding saturated diester shows no rearrangement. The structures of these products are established by degradation to the parent hydrocarbon. The facility with which the rearrangement takes place is ascribed to the relief of internal strain. The specificity of the reaction and the marked stability of the reactants toward reverse Diels–Alder fragmentation are explained in terms of the orbital symmetry requirements of the system.

We recently reported the first successful synthesis[2] of the *trans*-5,6-trimethylene-2-norbornene ring system (**1**) and demonstrated that in structures of this type the rigid norbornene cage undergoes significant structural distortion in order to minimize the strain associated with the trans trimethylene bridge. As part of a general investigation of the chemistry of this new system, we herein describe its characteristic thermal behavior.

Results and Discussion

When a solution of the methyl ester **2a**[2] in decalin was heated at 220–230°, a facile stereospecific rearrangement occurred affording the isomeric ester **5** as the sole product. Saponification of this new ester then gave the carboxylic acid **7**, a product that could also be obtained in good yield by the pyrolysis of the di-*tert*-butyl ester **1**[2] under the same conditions. Similar treatment of the corresponding saturated diester **3**,[2] however, afforded only the unrearranged acid **4**.[2] The rearrangement of the methyl ester **2a** was shown to be irreversible by heating a 1.0 M solution of the ester **5** in Nujol at 225°. After 2 hr under these conditions, no change in the nmr spectrum of the reaction mixture was detected.



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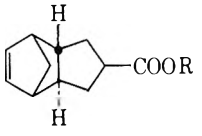
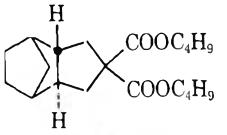


2a, R = CH_3
b, R = H



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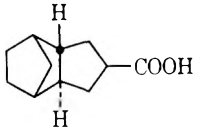

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The infrared spectrum of the rearranged ester (**5**) indicated a relatively unstrained olefinic linkage[3] ($\nu_{C=C}$ 1610 cm^{-1}) and a nonconjugated ester carbonyl group[4] ($\nu_{C=O}$ 1740 cm^{-1}). The structure of this compound was established by degradation to the parent hydrocarbon. The acid **7** readily absorbed 1 equiv of hydrogen to give the saturated acid **6**. Hunsdiecker decarboxylation[5] of **6** then afforded the bromide **8a**,[6] which on hydrogenolysis on palladium in the presence of potassium carbonate[7] yielded *cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]decane (**9**). The infrared spectrum and gas chromatographic retention times of this product were identical with those of an authentic sample of **9** obtained by the Wolff–Kishner reduction of the diketone **10**.[8,9]

The thermal isomerization of the *trans*-trimethylenenorbornenes to derivatives of the tricyclo[5.3.0.0^{2,6}]-decane system is unprecedented among the more familiar *endo,cis*- and *exo,cis*-trimethylenenorbornenes (dicyclopentadienes). The dicyclopentadienes have long

(1) (a) Grateful acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. (b) For part I of this series see ref 2. (c) W. B. King Visiting Professor, Department of Chemistry, Iowa State University, 1971–1972.

(2) G. B. Clemans, M. N. Essiet, and R. L. Tyson, *J. Org. Chem.*, **37**, 2312 (1972).

(3) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **80**, 1700 (1958).

(4) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, Chapter 5.

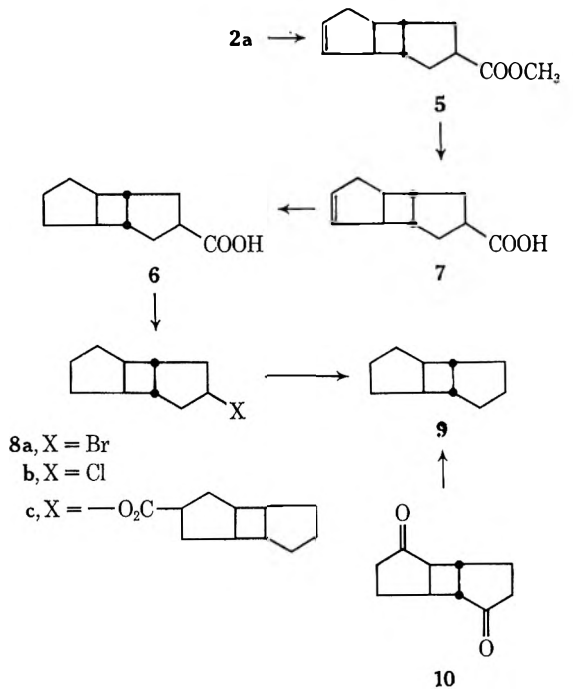
(5) J. Cason and D. M. Walba, *J. Org. Chem.*, **37**, 669 (1972).

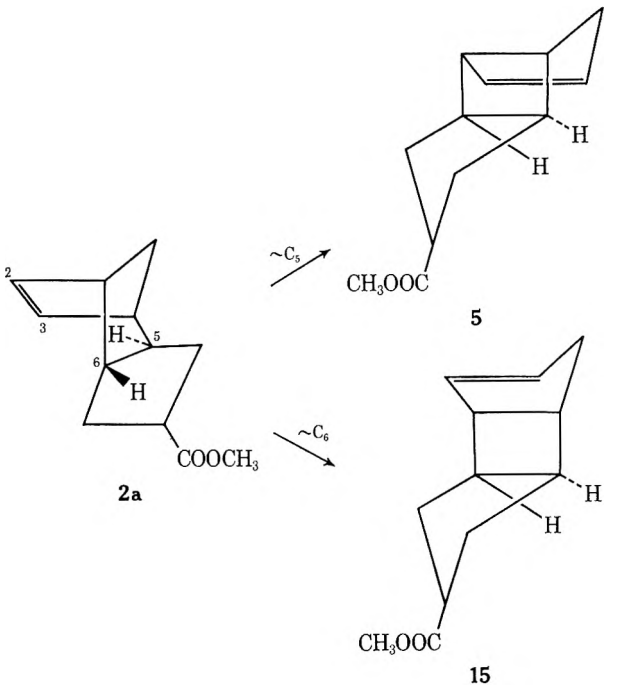
(6) The bromide **8a** was accompanied by lesser amounts of the corresponding chloride **8b** and the ester **8c**. Analogous products have been observed in the decarboxylation of other carboxylic acids; see, for instance, F. W. Baker, H. D. Holz, and L. M. Stock, *J. Org. Chem.*, **28**, 514 (1963).

(7) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley, New York, N. Y., 1971, Chapter 20.

(8) P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962).

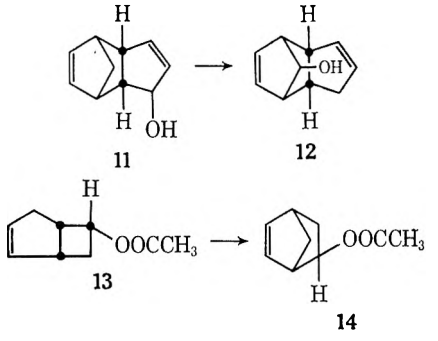
(9) A sample of the diketone **10** was kindly supplied by Dr. P. E. Eaton. This material had mp 125–126° (lit.[8] 125–126.5°), ir (KBr) 1706 cm^{-1}.





been known[10] to undergo thermal fragmentation by a reverse Diels–Alder process. Woodward and Katz observed that the dicyclopentadienol **11** thermally rearranged to the isomeric alcohol **12**,[11] and other workers have reported[12] similar rearrangements of related dicyclopentadienes.

The isomerization of **2a** is essentially the reverse of the 1,3-sigmatropic rearrangement of the bicycloheptene **13** to the norbornene **14** reported by Berson.[13] In



contrast to this latter transformation, however, the rearrangement of **2a** is considerably faster and is unaccompanied by side reactions.[14] Examination of the structure of **2a** reveals that both C_5 and C_6 are correctly positioned to undergo 1,3-sigmatropic migration (to give **5** and **15**, respectively) and that both processes are constrained to a suprafacial geometry[15,16] by the cage system. In either case the symmetry-required[15] inversion of the migrating center would relieve the strain imparted by the trans ring junction by yielding either the cis,anti,cis (**5**) or cis,syn,cis (**15**) product. Nonetheless, the observation that **5** is the sole product of the reaction clearly shows that the rearrangement is specific for migration of C_5.

In traversing the reaction coordinate leading to **5**, clockwise rotation about the 5,6 bond not only permits the required[15] bonding interaction between the back lobe of the orbital of the migrating atom (C_5) and the orbital of the migration terminus (C_2), but also results in a continuous release of the strain of the trans trimethylene bridge as the inversion of C_5 progresses. In the alternative migration of C_6 to C_3, however, a counterclockwise rotation is forced by the trimethylene bridge which requires either a symmetry-forbidden rearrangement with retention or a severe uncoupling of the interacting orbitals to allow inversion of configuration of C_6. As a result, neither process can compete effectively with the concerted migration of C_5 to afford the product **5**.[17]

The stability of the *trans*-trimethylenenorbornenes toward reverse Diels–Alder fragmentation is quite striking since such a process, common among both the dicyclopentadienes and norbornenes, would appear potentially to be very effective in relieving strain. In fact, however, the symmetry-allowed pathway ($-[{}_4\pi_s + {}_2\pi_s]$)[15] for the fragmentation of **2a** leads to the highly strained *trans*-cyclopentene **17**, and thus this route is rendered energetically inaccessible to the system.

The unique thermal properties of the compounds reported here compared to those of the dicyclopentadienes are thus seen to be a direct result of the trans

(10) (a) For an excellent review of early studies of the dicyclopentadienes see G. T. Youngblood, Ph.D. Dissertation, Duke University, Durham, N. C., 1957; (b) M. Rosenblum, *J. Amer. Chem. Soc.*, **79**, 3179 (1957).

(11) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(12) D. L. Allara, Ph.D. Dissertation, University of California, Los Angeles, Calif., 1964, and references cited therein.

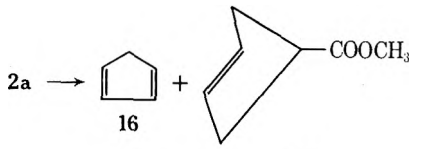
(13) J. A. Berson, *Accounts Chem. Res.*, **5**, 406 (1972), and references cited therein.

(14) The rate of isomerization of **2a** was estimated by carrying out the reaction in an nmr sample tube and noting the changes in the nmr spectrum of the reaction mixture with time at 225°. In this way the half-life of **2a** (1.0 *M* in decalin) was found to be about 20 min under these conditions. Only a 5% conversion was observed for **13** (0.6 *M* in decalin) after 1 hr at 300°. The isomerization of **13** was complicated by Diels–Alder fragmentation–recombination of the product (**14**) under the reaction conditions: J. A. Berson and J. W. Patton, *J. Amer. Chem. Soc.*, **84**, 3406 (1962).

(15) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1971.

(16) J. A. Berson and G. L. Nelson, *J. Amer. Chem. Soc.*, **89**, 5503 (1967).

(17) The possibility that the migration of C_6 occurs by way of a radical process rather than the sigmatropic pathway proposed here is rendered extremely unlikely by the previously noted specificity of the reaction. Further, the intermediate diradical in such a pathway would be expected[16] to close preferentially to the *endo,cis*-dicyclopentadiene isomeric with **2a** rather than to **5**.



16 17

geometry of the trimethylene bridge. Other aspects of the chemistry of the *trans*-trimethylenenorbornene ring system will be reported in the future.

Experimental Section

General.—Infrared spectra were obtained using a Perkin-Elmer Model 337 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Chemical shifts (δ) are reported downfield relative to tetramethylsilane as internal reference in the indicated solvents, and coupling constants (J) are reported in hertz. Mass spectra were obtained with a Varian MAT CH-4 spectrometer. Gas chromatographic analyses were carried out using either a Hewlett-Packard Model 700 or a Gow-Mac Model 69-500 gas chromatrograph. In both cases a 6-ft column of 5% Carbowax on Chromosorb P was used at the indicated temperatures. All melting points and boiling points are uncorrected. Microanalyses are by M-H-W Laboratories, Garden City, Mich.

Thermal Rearrangements.—All pyrolyses were carried out by the same general procedure of which the following is representative. A solution of 338 mg (1.0 mmol) of the di-*tert*-butyl ester **1** in 5 ml of diphenyl ether (Nujol and decalin were used as solvents in some runs) was heated at 210–230° under an atmosphere of dry nitrogen for 6.0 hr. The solution was then cooled, taken up in ether, and extracted with two 5-ml portions of 10% sodium hydroxide and with 5 ml of water. The combined aqueous extracts were washed once with ether and were acidified with 4 ml of concentrated hydrochloric acid. The precipitate was taken up with three 30-ml portions of ether, and the combined ether layers were washed once with saturated brine, dried ($MgSO_4$), and concentrated to yield the acid **7** in essentially quantitative crude yield as a pale yellow oil that crystallized on cooling. Recrystallization of this material from light petroleum followed by sublimation at reduced pressure afforded the pure product as white needles: mp[18] 83–86°; ir (KBr) 3300–2800 (OH), 3044 (vinyl H), 1690 (C=O), 1609 cm^{-1} (C=C); nmr ($CDCl_3$) δ 11.4 (s, 1, COOH), 5.77 (m, 2, vinyl H); mass spectrum (16 eV) *m/e* (rel intensity), 178 (18), 133 (2), 132 (2), 113 (2), 112 (5), 66 (100).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.31; H, 7.87.

Treatment of the saturated di-*tert*-butyl ester **3** under similar conditions gave the unrearranged acid **4** in 92% yield as a white solid, mp 46–48°. The infrared spectrum of this material was identical with that of the same compound reported earlier[2] and showed no depression of melting point on admixture with an authentic sample.

The isomerization of the methyl ester **2a** was carried out similarly except that decalin was used as solvent. The product was not isolated as such, but was saponified in aqueous sodium hydroxide yielding the acid **7**, identical in melting point and mass spectrum with the same product obtained above.

9-Carbomethoxy-*cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]dec-3-ene (5).—The carboxylic acid **7** was esterified by the same procedure reported earlier[2] for the esterification of the acid **2b**. The product (**5**) was obtained after distillation at reduced pressure as a colorless oil: ir (neat) 3038 (vinyl H), 1734 (C=O), and 1609 cm^{-1} (C=C); nmr (CCl_4) δ 5.73 (m, vinyl H), 3.67, 3.65 (s, methoxyl H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.27; H, 8.61.

***cis,anti,cis*-Tricyclo[5.3.0.0^{2,6}]decane-4-carboxylic Acid (6).**—A solution of 415 mg (2.33 mmol) of rearranged acid **7** in 20 ml of ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 30% palladium-on-carbon catalyst. A total of 56 ml of hydrogen was absorbed (theoretical = 52 ml). The catalyst was removed by filtration through Celite, and the solvent was evaporated to afford the crude acid **6** in essentially quantitative yield. This material was recrystallized from light petroleum to give the pure product as white needles: mp[18] 93–110°; ir (KBr) 3300–2500 (OH), 1690 cm^{-1} (C=O); nmr (CCl_4) δ 13.4 (s, 1, COOH), 3.0 (m, 1, α-H); mass spectrum (70 eV) *m/e* (rel intensity) 180 (25), 135 (47), 134 (100), 68 (25), 67 (73).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.46; H, 8.77.

4-Bromo-*cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]decane (8a).—This compound was prepared by an adaptation of the procedure of Cason and Wilba.[5] A stirred mixture of 362 mg (2.0 mmol) of the saturated acid **6**, 284 mg (1.31 mmol) of red mecuric oxide, and 20 ml of carbon tetrachloride was heated until 10 ml of solvent had distilled. Distillation was continued, and a solution of 136 μl (2.5 mmol) of bromine in 10 ml of carbon tetrachloride was added over a period of 1.2 hr. When addition was complete, an additional 5 ml of solvent was distilled, and the final volume of the reaction mixture had been reduced to about 5 ml. This mixture was diluted with 50 ml of ether and was filtered through Celite. The filtrate was washed with two 5-ml portions of 5% aqueous sodium hydroxide and with 5 ml of water. The resulting ether solution was dried ($MgSO_4$) and concentrated to afford the crude product as a pale yellow oil.

Preliminary separation of the product mixture was achieved by chromatography on a dry 1.5 × 10 cm column of alumina. A mixture of the bromide **8a** and the chloride **8b**[6] (198 mg) was eluted with 100 ml of pentane, and the ester **8c**[6] (187 mg) was subsequently eluted with 100 ml of ether. The halide mixture was further fractionated by preparative gas chromatography at 185°. The chloride **8b** was eluted first and was collected as a colorless oil: ir (CCl_4) 2930, 2845, 1265 cm^{-1}; positive Beilstein test for halogen.[19] The bromide **8a** was eluted later and was likewise collected as a colorless oil: ir (CCl_4) 2920, 2845, 1230, 1180 cm^{-1}; positive Beilstein test for halogen.[19]

The ester **8c**[6] was similarly purified and was obtained as a colorless oil: ir (CCl_4) 1730 cm^{-1}.

***cis,anti,cis*-Tricyclo[5.3.0.0^{2,6}]decane (9).**[7]—A 51-mg sample of the halide mixture (**8a** and **8b**) obtained above was dissolved in 20 ml of methanol, and 66 mg of potassium carbonate and 38 mg of 30% palladium on carbon were added. The mixture was then subjected to hydrogen at atmospheric pressure and room temperature for 24 hr. The reaction mixture was filtered through Celite and concentrated. The residue was taken up in pentane, filtered, and concentrated to yield a pale yellow oil. Gas chromatographic analysis of this product at 140° indicated that the bromide **8a** had reacted completely, but that some of the chloride (**8b**) remained. The hydrocarbon **9** appeared at considerably shorter retention time than either **8a** or **8b** and was collected as a colorless oil: ir (CCl_4) 2920, 2830, 1465, 1450 cm^{-1}. The infrared spectrum of this product was identical with that of the same compound obtained below by the reduction of the diketone **10**. Further, the two samples had identical retention times on two different columns on gas chromatographic analysis.

Wolff–Kishner Reduction of the Ketone 10.—The diketone **10** was converted into the hydrocarbon **9** by the procedure of Eaton.[8] The product was purified by gas chromatography at 140° and was obtained as a colorless oil.

Acknowledgment.—The author is indebted to the Department of Chemistry of Iowa State University for partial support of this work.

Registry No.—**1**, 41163-81-9; **2a**, 41265-37-6; **3**, 41163-82-0; **4**, 40252-86-6; **5** epimer a, 41163-83-1; **5** epimer b, 41163-84-2; **6** epimer a, 41163-85-3; **6** epimer b, 41163-86-4; **7** epimer a, 41163-87-5; **7** epimer b, 41163-88-6; **8a** epimer a, 41163-89-7; **8a** epimer b, 41163-90-0; **8b** epimer a, 41163-91-1; **8b** epimer b, 41163-92-2; **8c**, 41172-07-0; **9**, 36444-30-1; **10**, 2065-43-2.

(18) Since the compounds in this series are obtained as mixtures of epimers, sharp melting points are often not observed.

(19) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., 1958, p 177.

ห้องสมุด กรมวิทยาศาสตร์

Diazotization of *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-one and *endo*-3-Aminomethylbicyclo[3.3.1]nonane[1]

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Diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (1) under various conditions was investigated. In a protic medium (acetic acid), 3-methylbicyclo[3.3.1]non-2-en-7-one (3) was the only major product. With an aprotic system (benzene), 4-protoadamantanone (4) was the principal product, accompanied by 3. *endo*-3-Aminomethylbicyclo[3.3.1]nonane (2) was diazotized under the same sets of conditions yielding (a) elimination products, 3-methylbicyclo[3.3.1]non-2-ene (5) and 3-methylenebicyclo[3.3.1]nonane (6); and (b) substitution products, 3-acetoxymethylbicyclo[3.3.1]nonane (7) and 3-hydroxymethylbicyclo[3.3.1]nonane (8). Catalytic hydrogenation of 3 resulted in reductive cyclization to 1-adamantanol in excellent yield. Sodium borohydride reduction of 3 furnished 3-methyl-7-hydroxybicyclo[3.3.1]non-2-ene (9), which was converted to 1-methyl-2-oxaadamantane (10) on exposure to a Lewis acid catalyst or hydrogen and palladium. The stereochemical and mechanistic aspects of the various transformations are treated.

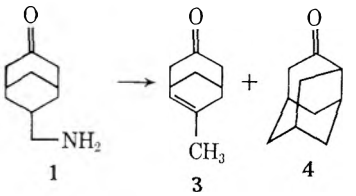
In prior work from this laboratory, rearrangement of 1-*N*,*N*-dichloroaminoadamantane with aluminum chloride, followed by exposure to hydrochloric acid, yielded *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (1).[3] Wolff–Kishner reduction of 1 gave high yields of *endo*-3-aminomethylbicyclo[3.3.1]nonane (2).[4] The objective of the present study was to investigate the response of these amines to diazotization conditions, and to elucidate the mechanistic features. In addition, the chemical behavior of some of the novel products was examined.

Important advances in the chemistry of aliphatic deamination *via* diazotization have been made in recent years. The aspects of synthetic utility and mechanism have been reviewed.[5-9]

Results and Discussion

Synthetic Aspects.—Amines 1 and 2 were deaminated by two procedures. Procedure I entailed aprotic diazotization in benzene with an equivalent amount of acetic acid and a slight excess of isoamyl nitrile.[10] Procedure II involved reaction with isoamyl nitrite in acetic acid.

Under aprotic conditions, 1 gave principally 4-protoadamantanone (4) (67% yield), together with 3-methylbicyclo[3.3.1]non-2-en-7-one (3) (20% yield) and two minor products (unidentified ketones), eq 1



1 3 4 (1)

(Table I). Compound 4 was identified by comparison of ir and nmr spectra with those of the authentic material,[11-13] formation of the 2,4-dinitrophenylhydrazone derivative,[11,12] and Wolff-Kishner reduction to 4-protoadamantane.[14] Compound 3, a colorless liquid, was characterized by the presence of a carbonyl band in the ir spectrum and an endocyclic double bond (δ 5.5, 1 H, indistinct doublet split by the bridgehead proton) and an allylic methyl (δ 1.6, 3 H, singlet) group in the nmr spectrum. Microanalyses were consistent with the proposed structure. Chemical identification was carried out by Wolff–Kishner reduction to 3-methylbicyclo[3.3.1]non-2-ene (5), which was also synthesized by an alternate route.[4] Under protic conditions, 1 gave 3 as the only major product (48% yield) with traces of 4 and unidentified ketones.

TABLE I

DIAZOTIZATION OF 1[a]

Solvent	Products, % yield 4	3
C_6H_6	67	20
CH_3CO_2H	Trace	48
CH_3OH	*b, c*	*b, c*
n-C_6H_{14}[d]	65	15
o-$C_6H_4Cl_2$[e]	72	16
m-$C_6H_4(OCH_3)_2$	70	15
HCO_2H[f]	*b, g*	*b, g*
p-$ClC_6H_4CO_2H$[h]	69	9

[a] Amine, 0.01 mol; isoamyl nitrite, 0.011 mol; acetic acid, 0.01 mol; solvent, 20 ml; 80°; 1 hr; unless otherwise indicated. [b] Tar and a small quantity of viscous liquid containing traces of 3 and 4. [c] Recovered amine, 60%. [d] Slow reaction; acetate salt of 1 is quite insoluble. [e] Gas evolution began at room temperature; fast reaction. [f] Acetic acid omitted. [g] Recovered amine, 54%. [h] Benzene solvent, acetic acid omitted.

Diazotization of amine 2 under either protic or aprotic conditions gave 3-methylbicyclo[3.3.1]non-2-ene (5), 3-methylenebicyclo[3.3.1]nonane (6), 3-acetoxymethylbicyclo[3.3.1]nonane (7), and 3-hydroxymethylbicyclo[3.3.1]nonane (8), eq 2 (Table II). Compounds 5 and 6 were identified by comparison with authentic samples.[4] Structural assignment for 7 was based on the ir spectrum (ester absorption) and

(1) Chemistry of Adamantanes and Related Compounds. VII; for the preceding publication in the series see ref 4; preliminary communication, J.-H. Liu and P. Kovacic, *Chem. Commun.*, 564 (1972).
(2) From the Ph.D. Thesis of J.-H. L., 1973.
(3) P. Kovacic, J.-H. Liu, E. M. Levi, and P. D. Roskos, *J. Amer. Chem. Soc.*, **93**, 5801 (1971).
(4) J.-H. Liu, G. A. Gauger, and P. Kovacic, *J. Org. Chem.*, **38**, 543 (1973).
(5) J. H. Ridd, *Quart. Rev., Chem. Soc.*, **15**, 418 (1961).
(6) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961.
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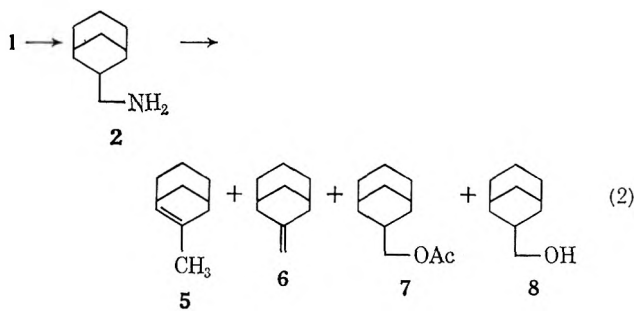
(10) L. Friedman and J. H. Bayless, *J. Amer. Chem. Soc.*, **91**, 1790 (1969).
(11) J. R. Alford and M. A. McKervey, *Chem. Commun.*, 615 (1970).
(12) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970).
(13) R. M. Black and G. B. Gill, *Chem. Commun.*, 972 (1970).
(14) H. W. Whitlock, Jr., and M. W. Siefken, *J. Amer. Chem. Soc.*, **90**, 4929 (1968).



(2)

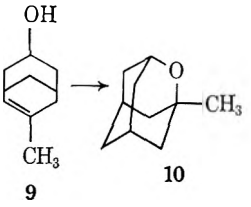
TABLE II
DIAZOTIZATION OF 2[a]

Solvent	Products, % yield 5	6	7	8
C_6H_6	21	15	35	4
CH_3CO_2H	29	6	28	5
CH_3OH[b]	No reaction			
CH_3CO_2H[b]	No reaction			
H_2O[c]	No reaction			

[a] Amine, 0.01 mol; isoamyl nitrite, 0.011 mol; acetic acid, 0.01 mol; solvent, 20 ml; 80°; 1 hr; unless otherwise indicated. [b] HCl salt of 2 was used. [c] H_2SO_4 (0.03 mol) in place of CH_3CO_2H; isomayl nitrite was replaced by 0.01 mol of sodium nitrite.

nmr spectrum (acetyl group at δ 2.1 and methylene doublet, J = 4 Hz, at δ 3.9). However, there were extraneous bands at δ 1.5–1.6, apparently arising from an impurity (about 10%), probably an isomeric material which did not separate during glpc. Rearrangement followed by combination with a nucleophile is a frequent occurrence in such reactions.[5,8] Information concerning the nature of **8** was obtained from the ir spectrum and comparison with the alcohol derived from hydrolysis of **7**. The nmr spectrum of **8** from diazotization exhibited extraneous bands, similar to those found for **7**, indicating the presence of a minor impurity (not separable in glpc). Independent syntheses of **7** and **8** were devised. Compound **6**, obtained by Hofmann degradation of **2**,[4] was converted to **8** *via* hydroboration and subsequent oxidation with hydrogen peroxide.[15] This alcohol displayed the same ir spectrum and glpc retention time as did that from diazotization. The nmr spectra were essentially identical except for absorption bands from the impurity in the diazotization product. Microanalysis provided data in agreement with theory. Esterification of **8** (from hydroboration) yielded acetate **7**. Glpc retention time and the ir spectrum corresponded to those of **7** from hydrolysis of **8** from diazotization. Nmr and microanalytical data were also used in identification.

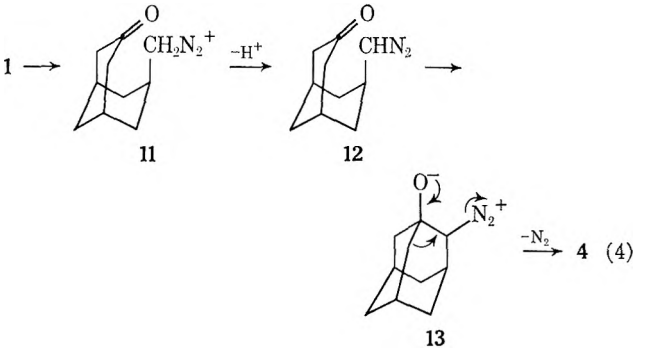
Hydrogenation of **3** in absolute ethanol with palladium on charcoal gave 1-adamantanol (91% yield). In contrast, sodium borohydride reduction generated 3-methyl-7-hydroxybicyclo[3.3.1]non-2-ene (**9**) in good yield. In addition to the ir spectrum for **9**, nmr data were particularly informative, showing an endocyclic olefinic proton (δ 5.85, 1 H, indistinct doublet), a proton adjacent to the hydroxyl group (δ 3.95), an allylic methyl group (δ 1.65), and an exchangeable proton (δ 2.9, singlet). Compound **9** was converted to 1-methyl-2-oxaadamantane (**10**) by exposure to formic acid at reflux, by hydrogenation with palladium on charcoal, or by treatment with acetic anhydride and zinc chloride, eq 3. Characterization of **10**, prepared by an alternate route, is described elsewhere.[4]



(3)

Stereochemistry.—The parent hydrocarbon, bicyclo[3.3.1]nonane, is known to exist in the chair–chair conformation,[16,17] despite some steric interaction of the hydrogens at C-3 and C-7. Monosubstitution at the C-3 or C-7 position may change the stereochemistry. Thus, an exo substituent maintains the original conformation, whereas an endo one results in conversion to the chair–boat form.[16,18–20] However, these two conformers are in rapid equilibrium at room temperature.[20] The aminomethyl groups in **1** and **2** are present in the endo configuration,[4] as well as hydroxymethyl and acetoxymethyl in **8** and **7**, respectively. Since **6** would be expected to prefer a chair–chair conformation, hydroboration should result in addition from the less hindered site,[21] also giving rise to the endo forms of **7** and **8**. We gave the endo assignment to the hydroxyl in **9** based on nmr splitting patterns, making use of pertinent literature data.[19,20,22,23] Further support was provided by analogy to hydride reduction of related ketones in the bicyclo[3.3.1]nonane series.[22]

Reaction Mechanisms.—Several pathways appear reasonable for conversion of **1** to **4**. One possibility is outlined in eq 4.



(4)

Formation of diazoalkanes from primary diazonium ions has been described.[5–8,24,25] **12** to **4** has analogy in the well-known intermolecular reaction of ketones

(15) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

(16) G. L. Buchanan, "Topics in Carbocyclic Chemistry," Vol. I, D. Lloyd, Ed., Plenum Press, New York, N. Y., 1969, p 199.

(17) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

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(21) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, Chapter 8.

(22) S. J. Padegimas and P. Kovacic, *J. Org. Chem.*, **37**, 2672 (1972).

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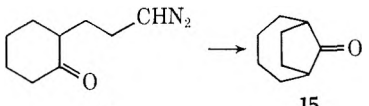
(24) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

(25) (a) G. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970); (b) *ibid.*, **24**, 159 (1970).

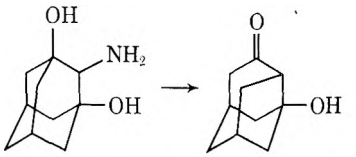
with diazoalkanes,[26] and particularly in the intramolecular example[27] depicted in eq 5. Our mechanistic



14 15 (5)

scheme is in accord with that proposed by Gutsche[27] and coworkers for **14** to **15**.

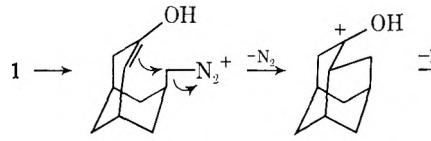
The intermediacy of **13** derives support from the observation that diazotization[11] of **16** gives **17**, eq 6.



16 17 (6)

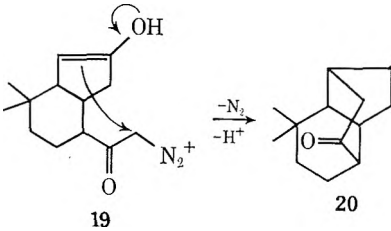
Other skeletal rearrangements of adamantanes to protoadamantanes have been noted by various investigators.[11,28-30]

An alternative mechanistic possibility is shown in eq 7. A structure (**19**), strikingly similar to **18**, was



18 (7)

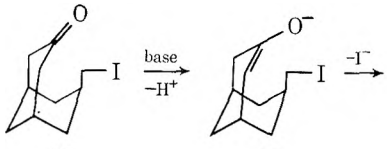
invoked[31] by Miyano and Dorn to account for an analogous interaction, eq 8. However, we feel that



19 20 (8)

this pathway is much less likely since enol content in monoketones is extremely low.[32,33]

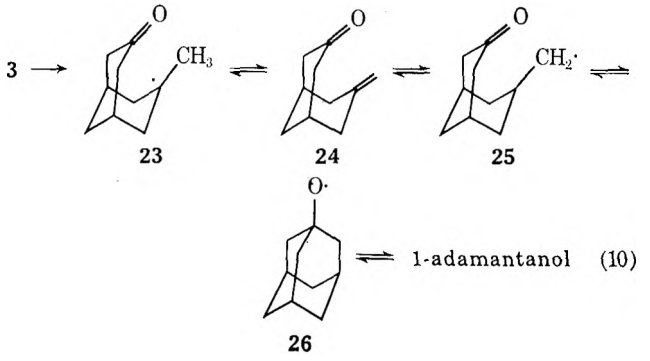
Mention should also be made of another route reported for the synthesis of **4**, involving exposure of the iodo ketone **21** to base.[12,13] The reaction may entail SN2 displacement of halide by enolate anion **22**, eq 9. If so, the process bears resemblance to that described in eq 7.



21 22 (9)

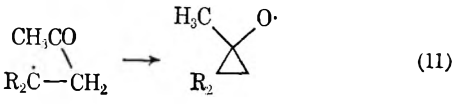
Compound **3** would result from hydride shift followed by proton elimination. The rearrangement–elimination pathway appears to be favored under protic conditions.[8]

Attention will now be devoted to the ring closures observed for **3** and **9**. Transannular reactions in cyclic systems represent an interesting area of stereochemistry.[34] In relation to the present work, a number of examples are recorded in which a bicyclo[3.3.1]nonane is converted to an adamantane derivative.[16,35-37] Equation 10 furnishes a mechanistic rationale for



23 24 25 26 1-adamantanol (10)

reductive cyclization of **3** to 1-adamantanol on hydrogenation with palladium on charcoal. Since alkene isomerization[38,39] can occur under these conditions, it is reasonable to postulate the existence of intermediates such as **23**, **24**, and **25**. In fact, 7-methylenebicyclo[3.3.1]nonan-3-one (**24**) was converted to 1-adamantanol almost quantitatively on exposure to the same reducing environment. Species **23** and **25** may be present as adsorbed forms on the catalyst. Alternatively, hydrogen atom attack on carbonyl oxygen may be involved at some stage. Generally, an olefinic bond is more susceptible to hydrogenation than the carbonyl group.[40a] The situation is complicated by the fact that the rate of reduction of the alkene linkage decreases with increasing substitution (three alkyl groups in the present case).[40b] Starting material **3** was recovered when hydrogen was omitted, indicating that catalyst alone is incapable of effecting isomerization. A transformation analogous to eq 10 is set forth in eq 11.[41] Conversion of **25**



(11)

to **26**, as well as eq 11, represents the reverse of β fission of alkoxy radicals.

Another case of ring closure was observed in the conversion of **9** to **10** under Lewis acid conditions or on contact with H_2/Pd, eq 3. The cation **27** is a reasonable intermediate when acid catalysis is employed.

(26) W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).
(27) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *J. Org. Chem.*, **28**, 610 (1963).
(28) M. L. Sinnott, H. J. Storesund, and M. C. Witing, *Chem. Commun.*, 1000 (1969).
(29) Z. Majerski, P. v. R. Schleyer, and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 5731 (1970).
(30) Z. Majerski, S. H. Liggero, and P. v. R. Schleyer, *Chem. Commun.*, 1596 (1970); R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, **18**, 1 (1971).
(31) M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).
(32) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 376.
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(34) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **20**, 119 (1966).
(35) H. Stetter, J. Gärtner, and P. Tacke, *Chem. Ber.*, **98**, 3888 (1965).
(36) H. Stetter, J. Gärtner, and P. Tacke, *Angew. Chem., Int. Ed. Engl.*, **4**, 153 (1965).
(37) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).
(38) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6087 (1960).
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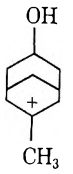
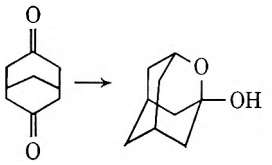
(40) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley, New York, N. Y., 1971: (a) p 152; (b) p 128.
(41) C. L. Karl, and E. J. Maas, and W. Reusch, *J. Org. Chem.*, **37**, 2834 (1972).



27

The radical counterpart of **27** may play a similar role during catalytic hydrogenation. A related overall result was obtained during hydrogenation of **28** in the presence of Raney nickel,[42] eq 12.



(12)

28

Transannular ring closures of alcohols to tricyclic ethers have also been effected by lead tetraacetate[20,43a] or irradiation in the presence of mercuric oxide–iodine.[20] For example, bicyclo[3.3.1]nonan-3-ol served as precursor to oxaadamantane.[20]

Reaction conditions, mostly solvent, were altered in attempts to throw additional light on the course of reaction. In the diazotization of **1** (Table I), polarity of solvent was varied widely (acetic acid, benzene, and hexane). It has been pointed out that the extent of diazoalkane formation should increase in an aprotic medium.[8,25b] Changing the solvent from polar acetic acid to nonpolar benzene greatly increased the yield of **4**, in accord with the postulate set forth in eq 4. We are unable to predict which form, keto or enol, of **1** would be favored by a decrease in solvent polarity, and hence cannot judge the result in relation to eq 7. Whether the solvent was benzene or hexane made little difference in composition of the product mixture. Reaction rate (based on gas evolution) in hexane was considerably slower than in benzene, presumably a reflection of solubility or solvation factors.

Among other variables, the effect of alteration in the Lewis base character of the aromatic solvent (*o*-dichlorobenzene, benzene, and *m*-dimethoxybenzene) was explored. There was no significant change in the ratio of **3**:**4**. Rough approximations based on gas evolution gave the indicated influence on reaction rate, o-$C_6H_4Cl_2$ > C_6H_6 ~ m-$C_6H_4(OCH_3)_2$. The consequences of variation in acidity of the medium were also determined. When *p*-chlorobenzoic acid, a stronger acid, was substituted for acetic acid, the yield of **4** remained constant, whereas the amount of **3** decreased somewhat. With an additional increase in acidity (formic acid), little product was formed and most of the starting material was recovered, presumably owing to essentially complete protonation of the amine.

Table II summarizes data from additional scrutiny of diazotization involving **2**. Only elimination (**5** and **6**) and substitution (**7** and **8**) products were found. In benzene or acetic acid, the ratio of the two pathways was essentially the same, 36:39 and 35:33, respectively. The increase in yield of **5** in acetic acid appears to reflect the favorable effect of a polar solvent on ionic rearrangements.[8] However, some olefinic product may be derived from thermolysis involving *tert*-acetate impurity present in **7**.[43b] In both systems, acetate product (**7**) predominated over alcohol (**8**). This may be a consequence of the existence of tight ion pairs[9] (acetate anion) in the diazotization medium, in addition to the order of nucleophilicity,[44] AcO^- > H_2O.

Experimental Section

Materials and Analytical Procedures.—Benzene (thiophene-free, Mallinckrodt), isoamyl nitrite (Aldrich), 1-adamantanol (Aldrich), and glacial acetic acid (Du Pont, 99.7%) were used as received. Amino ketone **1**[3] and amine **2**[4] were synthesized according to literature procedures. Ir spectra were obtained with a Beckman IR-8 spectrophotometer (calibrated with the 1601.8-cm^{-1} band of polystyrene). Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million (δ) (in $CDCl_3$ unless otherwise indicated) relative to tetramethylsilane as internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Micro-Tech Laboratories, Skokie, Ill. Glpc was conducted on a Varian Aerograph 1800 instrument with a 10 ft × 0.25 in. column, 15% Carbowax 20M on Chromosorb W (45/60 mesh). The yields were calculated by determining the weights of the glpc peak areas, and by weighing the individual collected products (total loss of 5–10% compared to injected weight). Melting points and boiling points are uncorrected.

Diazotization of 1. Procedure I.[10]—A mixture of **1** (1.67 g, 0.01 mol), benzene (20 ml), acetic acid (0.8 g, 0.01 mol), and isoamyl nitrite (1.4 g, 0.011 mol) was placed in a flask equipped with a condenser and drying tube. The mixture was heated at 80° for 1 hr. Gas evolution immediately occurred and gradually subsided. The homogeneous solution was cooled and washed in succession with water, 5% sodium carbonate, and water, then dried and freed of benzene. Glpc analysis of the light yellow oil (2 g) (isothermal at 180°, 100 ml/min) revealed the presence of 4-protoadamantanone (**4**) (67% yield) and **3** (20% yield).

Compound **4**, mp 206.5–207.5° (sealed tube), lit. mp 205–208°,[11] 210–212°,[12] 212–214°,[13] was identified by comparison of ir and nmr spectra with those of the authentic material. The 2,4-dinitrophenylhydrazone (bright orange, mp 194–195°, lit. mp 193–194.5°,[11] 195–196°[12]) was obtained after three crystallizations from ethanol–chloroform. Wolff–Kishner reduction of **4** gave protoadamantane in 65% yield, mp 210–212° (sealed tube) (lit.[14] mp 210.5–212°).

Procedure II.—A mixture of **1** (5.8 g, 34.5 mmol), acetic acid (60 ml), and isoamyl nitrite (9.7 g, 83 mmol) was heated at 80° for 1 hr. Gas was rapidly evolved at room temperature. Water (200 ml) was added to the cooled solution, followed by extraction with Skelly F. The organic layer was washed in succession with water, dilute base, and water, dried, and freed of solvent. The crude product (5.5 g) on distillation provided **3**, colorless liquid (2.5 g, 48% yield): bp 138–140° (17 mm); ir (neat) 2970, 2850, 1710, 1420, 1380, 1370, 1350, 1300, 1230, 1170, 1100, 1055, 910, and 835 cm^{-1}; nmr δ 5.5 (indefinite d, 1 H), 2.9–1.9 (m, 10 H), 1.6 (s, 3 H).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.87; H, 9.53.

Chemical confirmation of the structure of **3** was obtained by Wolff–Kishner reduction to **5**, which was identical to authentic material.[4]

Hydrogenation of 3 to 1-Adamantanol.—Compound **3** (0.6 g, 4 mmol) was hydrogenated overnight at room temperature in 50 ml of absolute ethanol with 10% palladium on charcoal (0.3 g) in a Parr apparatus. After filtration, removal of solvent afforded 1-adamantanol (0.55 g, 91% yield) as a white solid, identified by comparison with commercial material. In a control experiment, in which hydrogen was replaced by nitrogen, glpc after work-up indicated that starting material was recovered unchanged.

(42) H. Stetter, P. Tacke, and J. Gärtner, *Chem. Ber.*, **97**, 3480 (1964).

(43) (a) P. Brun, M. Pally, and B. Waegell, *Tetrahedron Lett.*, 331 (1970). (b) We are grateful to a referee for mentioning this possibility.

(44) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structures," McGraw-Hill, New York, N. Y., 1968, p 289.

Hydrogenation of 24 to 1-Adamantanol.—7-Methylenebicyclo[3.3.1]nonan-3-one[45] (0.5 g, 3.3 mmol) was hydrogenated, and the product was isolated as described for **3**. 1-Adamantanol (0.5 g, 98% yield) was obtained.

endo-**3-Methyl-7-hydroxybicyclo[3.3.1]non-2-ene (9).**—A mixture of **3** (0.75 g, 5 mmol), absolute ethanol (150 ml), and sodium borohydride (0.76 g, 20 mmol) was stirred at room temperature overnight. Water was added, and the product was extracted with chloroform. Evaporation of solvent from the dried solution provided **9** (0.4 g, 50% yield by glpc analysis): mp 32.5–33°; ir (CCl_4) 3580, 2950, 1430, 1380, 1350, 1300, 1200, 1110, 1070, 1060, 760, and 930 cm^{-1}; nmr δ 5.85 (indefinite d, 1 H), 3.95 (m, 1 H),[19,20,22,23] 2.9 (s, 1 H, exchangeable with D_2O), 2.5–1.5 (m, 13 H, sharp s at 1.65).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.04; H, 10.47.

1-Methyl-2-oxaadamantane (10). Procedure A.—A product mixture containing **9** (principal component, 0.15 g, 1 mmol) was heated at 100° in formic acid (3 ml) for 8 hr. After the mixture was cooled, ether (20 ml) and water (20 ml) were added. The organic layer was washed with 5% sodium carbonate and then water, dried, and freed of solvent. Glpc analysis indicated that the main product was **10** (0.13 g, 88% yield) whose spectral data were identical with previously reported values.[4]

Procedure B.—Compound **9** (0.288 g, 1.88 mmol) was hydrogenated as described for the hydrogenation of **3**. An 82% yield (0.23 g) of **10** was obtained.

Procedure C.—In an attempt to synthesize the acetyl derivative,[46] a mixture of **9** (2 g), acetic anhydride (25 ml), and zinc chloride (2 g) was heated at 95–105° for 1 hr. The cooled solution was quenched with ice water and extracted with ether. The ether layer, after being stirred overnight with 10% sodium bicarbonate, was separated, washed with water, dried, and freed of solvent. A dark brown liquid (1 g) was obtained which contained **10** as the major component (glpc).

Diazotization of 2.—Diazotization of **2** under various conditions was performed as described in the case of **1**, yielding **5**, **6**, **7**, and **8**. Compounds **5** and **6** were identified by comparison with authentic samples.[4] Compound **7** was identified by comparison with authentic material (*vide infra*). The ir spectra and glpc retention times were essentially identical. However, the nmr spectrum of the diazotization product indicated the presence of an impurity (about 10%, nmr absorption at δ 1.5–1.6). Compound **8** was identified by comparison with authentic material (*vide infra*). The ir spectra and glpc retention times were essentially identical (more thorough investigation was not carried out because of the paucity of material).

3-Hydroxymethylbicyclo[3.3.1]nonane (8) from 6.—Hydroboration[15] of **6** (1.3 g, 9.6 mmol) gave 1.1 g of liquid product. Glpc analysis indicated that **8** (0.91 g, 62% yield) was the principal component: ir (neat) 3420–3350, 2900, 2860, 1460, 1110, 1080, 1040, 1020, and 990 cm^{-1}; nmr δ 3.5 (d, 2 H, J = 4 Hz), 2.3–1.8 (m, 16 H, one exchangeable with D_2O).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.58; H, 12.01.

8 from 7.—Acetate **7**, obtained from diazotization of **2**, was hydrolyzed with 20% sodium hydroxide. The ir spectrum and glpc retention time of the product were essentially identical with those of the alcohol obtained from hydroboration of **6**. However, the nmr spectrum showed the presence of an impurity (about 10%, absorption at δ 1.5–1.6.

3-Acetoxymethylbicyclo[3.3.1]nonane (7) from 8.—A mixture of **8** (0.83 g, 5.4 mmol, obtained from **6**), zinc chloride (1 g, 7.3 mmol), and acetic anhydride (12.5 g) was stirred at 105° for 1 hr, then cooled, quenched with ice water, and extracted with ether.[46] The ether solution was stirred with 5% sodium carbonate for 5 hr at room temperature. After the ether layer was separated, washed with water, dried, and freed of solvent, crude **7** was obtained (1.1 g). Glpc analysis indicated 90% purity (92% yield). Product from glpc collection showed ir (neat) 2950, 2880, 1760, 1470, 1360, 1220, 1110, 1080, 1030, 980, and 885 cm^{-1}; nmr δ 3.9 (d, 2 H, J = 4 Hz), 2.1 (s, 3 H), 2.1–0.9 (m, 15 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.44; H, 10.26. Found: C, 73.67; H, 10.43.

Acknowledgment.—We are grateful to the National Science Foundation and the Graduate School of the University of Wisconsin—Milwaukee for support of this work. We thank Drs. G. B. Gill and W. H. W. Lunn for spectral data on 4-protoadamantanone.

Registry No.—**1**, 34650-78-7; **2**, 37445-20-8; **3**, 38339-46-7; **6**, 19437-17-3; **7**, 41189-05-3; **8**, 19490-36-9; **9**, 41189-07-5; **10**, 6508-22-1; isoamyl nitrite, 110-46-3.

(45) We are grateful to Drs. A. R. Gagneux and K. Scheibli for a sample of this material.

(46) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1962, p 380.

Thermal and Photochemical Reactions of Some Bicyclic Aziridine Enol Ethers[1a]

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Received May 8, 1973

Acid–base-catalyzed, thermal, and photochemical rearrangements of some bicyclic aziridine enol ethers are described. For example, 6-phenyl-2,4-bis(benzhydrylidene)-3,5-dioxa-1-azabicyclo[4.1.0]heptane (**3a**), an azirine–ketene adduct, rearranges on alumina to give dioxazepine **4**, which undergoes a further transformation to yield lactone **6**. The latter is converted to the isomeric 1,3 diketone **8** on treatment with alcoholic base. On the other hand, thermolysis of **3a** at 140–150° gives the seven-membered ring diether **15a**, an isomer of **4**, and lactone **16a**, an isomer of **6**. Dioxazepine **15a** rearranges to **16a** on further heating while **15c** leads to the five-membered lactone **19c**. Photolysis of **3a** at 310 nm results in the formation of a mixture of compounds from which **15a** and **16a** are isolated. Further photolysis of **15a** affords **16a**. These results are discussed. The mechanistic pathway for both pyrolysis and photolysis involves R–O cleavage of a cyclic enol ether C=C—O—R followed by O–C or C–C ring closure with rearrangement of R.

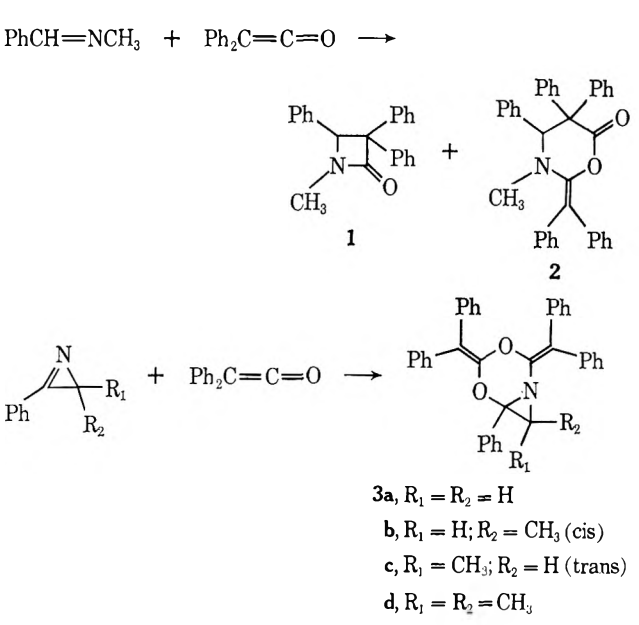
Imines have been shown to react with ketenes to yield 1:1 and/or 1:2 adducts of structures of type **1** and **2**, respectively.[2] In contrast, we have found that a number of 1-azirines react with diphenylketene to give 1:2 cycloadducts that possess the dioxa-1-azabicycloheptane structure **3**.[3]

One interesting feature of this novel heterocyclic system is that it contains a variety of functional groups. Of special interest would be the comparison of the thermal and photolytic behavior of this fused three-

(1) (a) Cycloaddition Reactions. XIV. For paper XIII in this series see A. Hassner and D. J. Anderson, *J. Org. Chem.*, **38**, 2565 (1973). (b) On sabbatical leave from the American University of Beirut, Beirut, Lebanon.

(2) (a) R. Huisgen, B. A. Davis, and M. Morikam, *Angew. Chem., Int. Ed. Engl.*, **1**, 826 (1968); (b) F. Duran and L. Ghosez, *Tetrahedron Lett.*, 245 (1970); (c) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971); H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1968), and other papers in the series.

(3) A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).



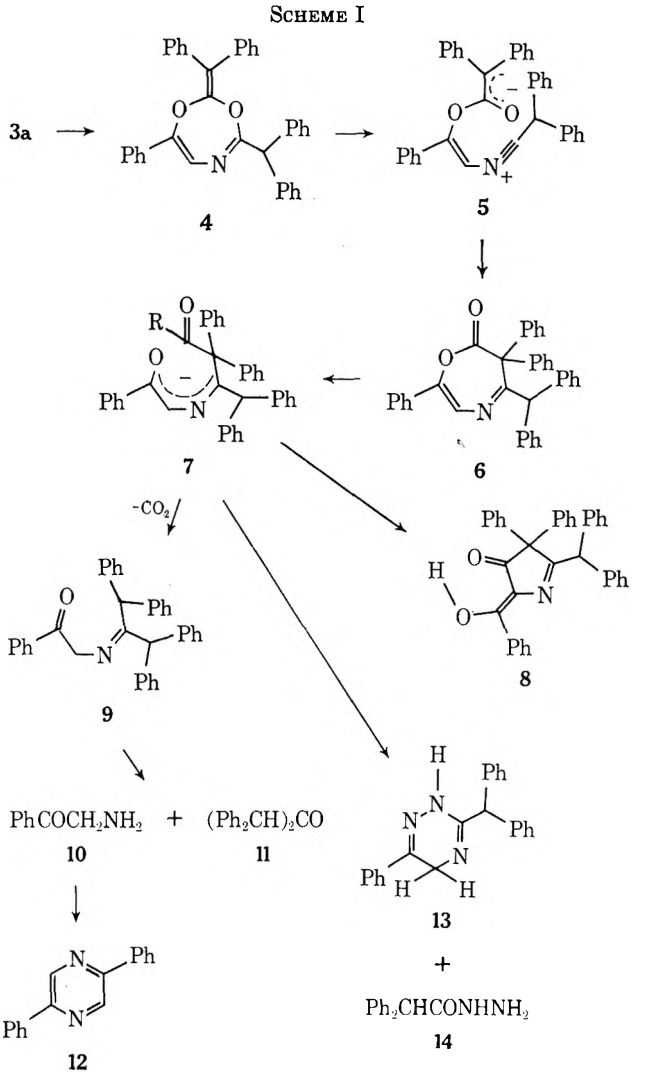
membered ring system with that of simpler aziridines that were studied recently.[4]

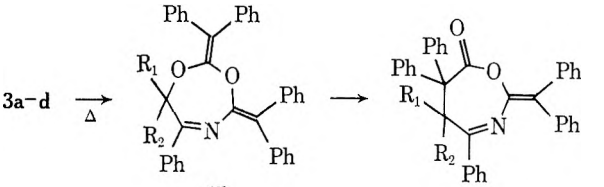
Results

Acid–Base Reactions.—Chromatography of dioxazabicycloheptane **3a** on a neutral alumina column or on silica gel resulted in a rearrangement to dioxazepine **4**, the structural proof of which has already been reported.[3] Furthermore, it was found that the fate of aziridine **3a** depended on the duration of contact with alumina. If a concentrated benzene solution of **3a** was left on the chromatography column for 30 min prior to elution, the isolated product was lactone **6** and not dioxazepine **4**. The latter was also converted to lactone **6** on treatment of a benzene solution of **4** with alumina (Scheme I). Lactone **6** showed an infrared carbonyl absorption at 1750 cm^{-1} and a vinyl ester function at 1130 cm^{-1}; its nmr spectrum exhibited a singlet at τ 4.75 (1 H) in addition to the aromatic protons; the mass spectrum gave a strong parent peak at m/e 505. Treatment of lactone **6** with methanolic potassium hydroxide transformed it into 1,3 diketone **8** as the major product; 1,1,3,3-tetraphenyl-2-propanone (**11**)[5] and traces of 2,5-diphenylpyrazine (**12**), identified by comparison with an authentic sample, were also isolated. 1,3 diketone **8** gave a blue-green complex with ferric ions, and showed broad infrared carbonyl bands typical of 1,3 diketones (1660–1575 cm^{-1}). Analogous ring contraction reactions are discussed below. The reaction of lactone **6** with hydrazine proceeded to furnish dihydrotriazine **13** and diphenylacethydrazide **14** in good yield. The structure of **13** was established by spectroscopic data, and that of **14** by comparison with an authentic sample.

Thermolysis.—The dioxazabicycloheptanes **3a–d** were found to be thermally labile. When a diglyme solution of **3a** was heated at 140–150° for 3 min, a mixture composed of starting material, dioxazepine **15a**, and oxazepinone **16a** was obtained. The identity of each component was evident from its infrared spectrum. Separation of this mixture was effected by thick layer chromatography, whereby the starting material was isolated as the rearranged dioxazepine **4**. Attempts to effect the rearrangement of **3a** into **15a**, as the only product,

Scheme I





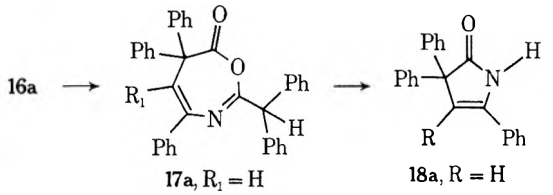
revealed that the reaction did not proceed to a reasonable extent at temperatures below 130°. Furthermore, it was found that **15a** rearranged into **16a** when heated above its melting point (128°). This fact made the isolation of **15a** from **3a** without the formation of **16a** rather difficult. However, the heating of a triglyme solution of **3a** at 180–190[4] yielded oxazepinone **16a**, in 45% yield, as the only isolable product. The structure of dioxazepine **15a** was established by its mass spectrum parent peak at m/e 505, infrared absorptions at 1738 (m), 1668 (s), and 1598 cm^{-1} (w) (see Discussion), and nmr singlets at τ 5.1 (1 H),

(4) (a) R. Huisgen and H. Maeder, *J. Amer. Chem. Soc.*, **93**, 1777 (1971); (b) A. Padwa, J. Smolanoff, and S. I. Wetmore, Jr., *Chem. Commun.*, 410 (1972), and references cited therein.

(5) D. C. Dean, W. B. Dickinson, O. R. Quayle, and C. T. Lester, *J. Amer. Chem. Soc.*, **72**, 1740 (1950).

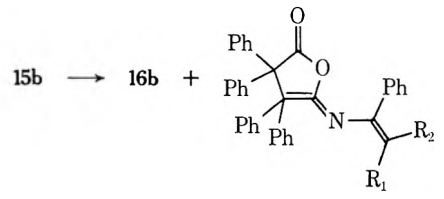
4.75 (1 H), and 2.25–2.82 (m, 25 H). Coupling of the methylene protons in **15a** was not detected on the A-60A nmr instrument.

Oxazepinone **16a** showed a parent peak at *m/e* 505 and $M^+ - CO_2$ at *m/e* 477, vinyl lactone absorptions at 1752 and 1150 cm^{-1} in the infrared, and an nmr singlet at τ 5.9 (broad s, 2 H) in addition to the aromatic protons. Treatment of oxazepinone **16a** with acid effected a 1,5-prototropic shift and gave isomer **17a**, the structure of which was established by spectroscopic data. The reaction of **16a** or **17a** with alcoholic potassium hydroxide afforded enaminoamide **18a**[6] in a quantitative yield and diphenylacetic acid,



both of which were identified by comparison with authentic samples.

The behavior of **3b,c** on heating at 140-150° was analogous to that of **3a**. Dioxazepine **15b** and oxazepinone **16b** were isolated, although in this case **15b** was the major product (15% yield) and **16b** formed only in traces. The heating of dioxazepine **15b** in triglyme at 180–190° for 3 min afforded **16b** as the major product, and a mixture of cis (**19a**) (R_1 = H; R_2 = CH_3) and trans (**19b**) (R_1 = CH_3; R_2 = H)



isomers in a 2:5 ratio (nmr). The structure of **19a,b** was based on a parent peak at *m/e* 519 in the mass spectrum, infrared bands at 1812, 1710, and 690 cm^{-1}, and nmr doublets at τ 8.62 (J = 7 Hz) and 8.3 (J = 7 Hz), a quartet at 4.5, and the aromatic protons at 2.5–2.9 (25 H) (see Discussion). Treatment of **16b** with methanolic base gave enaminoamide **18b** and diphenylacetic acid. Similarly, dioxazabicycloheptane **3d** yielded dioxazepine **15c** on heating at 140–150°. The spectroscopic properties of **15c** were consistent with the assigned structure. Further heating of dioxazepine **15c** at 180–190° gave imino lactone **19c** as the only isolable product in 50% yield. The spectroscopic properties of **19c** were analogous to those of **19b**.

Photolysis.—Irradiation of a benzene solution of bicyclic aziridine **3a–d** with a Rayonet 310-nm lamp gave a mixture of products in each case. Separation by column or thick layer chromatography on neutral alumina or silica gel afforded **15a**, **15b**, **15c**, and oxazepinones **16a** and **16b** from the corresponding bicyclic aziridines. Dioxazepines **15a**, **15b**, and **15c** were the major products of photolysis. Preparatively, photolysis of **3a** constituted a better route to **15a** than the thermal reaction mentioned above. These dioxazepines (**15a** and **15b**) were found to be converted to oxazepinones **16a** and **16b** on further photolysis. Whereas **3d** was rearranged to **15c**, the latter was recovered unchanged. Prolonged photolysis of **15c** (24 hr) resulted in the formation of polymeric material. Unlike thermolysis, photolysis of **3d** or **15c** for 4 hr did not yield any detectable amount (by tlc) of **19c**.

Discussion

Although the bicyclic aziridine systems **3a–d** contain a number of functional groups, it is reasonable to assume that the above rearrangements are initiated at the labile aminal function. This would be especially true in ionic reactions because of the availability of an unshared pair of electrons on either nitrogen or oxygen. For example, the rearrangement of **3a** into dioxazepine **4** is probably initiated by the interaction of alumina with the basic nitrogen in **3a**. Such a reaction pathway is supported by the fact that the rearrangement was reported[7] to proceed in a dry hydrogen chloride–benzene solution, and by the findings that bicyclic aziridines **3b–d** are stable on an alumina chromatography column. Such stability is maintained owing to the steric interaction imposed by the R substituents in **3b–d** toward an incoming electrophile.

The formation of lactone **6** can be postulated to arise from a reverse Ritter-type reaction to yield intermediate **5** (Scheme I), which undergoes a carbon–carbon ring closure to give the thermodynamically stable lactone **6** as compared to **4**. The possibility that lactone **6** is derived from **4** gains support from the fact that dioxazepine **4** on alumina was found to rearrange to **6**.

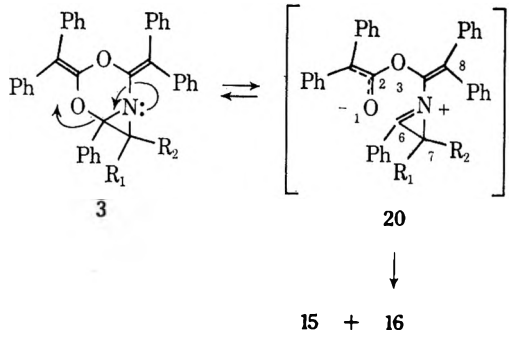
The ring contraction of lactone **6** into 1,3 diketone **8** is envisaged to occur by a methoxide attack on the carbonyl group followed by an intramolecular displacement of the methoxide ion by the enolate carbon [**6** → **7** (R = OCH_3) → **8**]. A possible route to side products **11** and **12** (namely hydrolysis of intermediate **9**) is shown in Scheme I. Furthermore, dihydrotriazine **13** most likely arises through intermediate **7** (R = $NHNH_2$) and subsequent reaction of the protonated **7** with another mole of hydrazine.

It should be noted that the formation of **4** as well as of **6** is the result of that C—N bond cleavage in **3** which marks the original C=N in the azirine. On the other hand, the thermal products **15** and **16** arise from cleavage of what was the original C—N bond in the azirine precursor.

The pyrolysis products **15a**, **15b**, **15c**, **16a**, and **16b** can best be explained to be formed from **3** *via* the common intermediate **20**. An intramolecular attack by enolate anion *via* oxygen upon C_7 gives dioxazepines **15**, while a similar attack of the same anion through carbon leads to oxazepinone **16**. It is interesting to note that **20** is also the postulated intermediate in the formation of **3a–d** from 1-azirines and diphenylketene.[3]

(6) F. R. Japp and F. Klingeman, *J. Chem. Soc.*, **57**, 662 (1890).

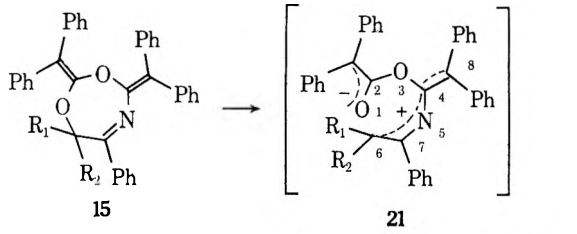
(7) A. S. Miller, Ph.D. Thesis, The University of Colorado, Boulder, Colorado, 1971.



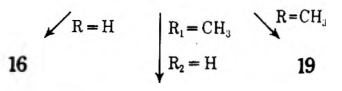
3 20

15 + 16

Moreover, the thermal isomerization of **15** to lactones **16a**, **16b**, and **19a–c** above 140° can be postulated to



15 21



16 19

16 + 19

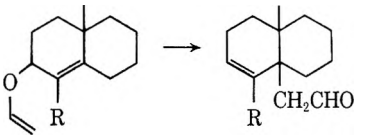
occur through the common intermediate **21**, whereby oxazepinone **16** is the result of an attack of the carbon of the enolate anion on C_7, and product **19** is produced *via* the same attack on C_8.

It is imperative to stipulate at this point that the thermolysis of **3a–d** most likely proceeds *via* diradical intermediates analogous to **20** and **21** and the ionic forms **20** and **21** are merely used here for easier illustration. A free-radical mechanism would be analogous to that involved in the thermal rearrangement of α-alkoxystyrenes into alkyl phenyl ketones,[8] for which Wiberg and coworkers[9] have presented evidence in support of a chain radical process. The thermal isomerizations of **4** to **6** and **15** to **16** further illustrate the preference for C—C *vs* C—O bond formation for the system C—O—C=C → O=C—C—C.

As mentioned above, dioxazepines **15a,b** are rearranged, on heating, into oxazepinones **16a,b**. Whether **15a,b** also are intermediates in the thermal transformation of **3a–c** at 180–190° into **16a,b** cannot be discerned from the above results. However, it seems likely that dioxazepines **15b,c** are intermediates in the formation of imino lactone **19**. Whereast he five-membered ring lactone **19** was found to be the predominant product from either **3d** or **15c** ($R_1 = R_2 = CH_3$), it was only the minor product (**19a,b**) from the monomethyl derivative **15b**, and was not detected at all in the thermolysis of the demethyl system **3a** or **15a**. These facts indicate that so long as the steric bulk at C_7 is not great as in the case of $R_1 = R_2 = H$ or $R = CH_3$ and $R_2 = H$ in intermediate **21**, carbon–carbon bond formation at that site is preferred. However, if two CH_3 substituents are present, positions 6 and 8 become sterically equivalent and ring closure occurs at the site of the most stable radical or carbonium ion, namely C_8, and hence product **19** results.

Much of the evidence in support of the structural assignments of dioxazepines **15a–c** and imino lactones **19a–c** rests on spectroscopic data and mass spectra. The infrared spectra of **15a–c** showed three equally spaced bands at 1735, 1668, and 1600 cm^{-1} which were medium, strong, and weak in intensity, respectively. Although the band at 1735 cm^{-1} is unusually high for an enol ether, cyclic ketene acetals have been recently reported to show intense bands near 1730 cm^{-1},[10] and a similar pattern probably due to coupling or Fermi resonance[10] is found in the ir spectrum of **3** with medium, strong, and weak bands at 1665, 1630, and 1595 cm^{-1}, respectively. The mass spectrum of **19c** showed a host of peaks at *m/e* 333, 332, 331, 330, 329, and 256, 255, 253, 252, and 179, 178, 177. Such peaks can be explained to be due to the ions of the fragment Ph_2CCPh_2, which undergoes two consecutive losses of phenyl groups.

Moreover, the recent report by Dauben and Dietsche[11] on the thermolysis of vinyl ethers of type **22** to yield **23** bears a close analogy to the rearrangement of **15** to **19**.



22 23

The present photochemical investigation was initiated when it was observed that the colorless bicyclic aziridines **3a–c** developed a yellow color on standing in daylight for some weeks. Since these compounds exhibit strong maxima in the ultraviolet in the regions of 310 and 260 nm, we chose to irradiate **3a–d** at the former wavelength. We observed the formation of the same products which were isolated from the thermal reactions of these bicyclic aziridines. These results can be rationalized through biradical or ionic intermediates of type **20** and **21**. It is obvious that such a system (**3a–d**) is rich with photolabile functions, and hence no conclusive mechanistic evidence can be drawn from this preliminary study. Yet, based on the careful work of Baldwin and Walker[12] on the mechanism of the photoreactions of phenylketene acetals (**24** → **25** and **26**), it is reasonable to postulate that a similar homolytic decomposition of the C_1—O bond in the photoexcited **3a–d** initiates the formation of a biradical intermediate (related to **20**) which recombines through a C—O or C—C bond formation to give **15** or **16**.

$$\underset{24}{PhCH{=}C(OEt)_2} \xrightarrow{h\nu} \underset{25}{PhCH_2CO_2Et} + \underset{26}{PhCHEtCO_2Et}$$

Moreover, the phototransformation of **15a,b** into **16a** and **16b**, respectively, can be traced to the homo-

(8) (a) L. Claisen, *Chem. Ber.*, **29**, 2931 (1896); (b) L. Claisen and E. Haase, *ibid.*, **33**, 3778 (1900); (c) F. H. MacDougall, W. M. Lauer, and M. A. Spielman, *J. Amer. Chem. Soc.*, **55**, 4089 (1933).

(9) (a) K. W. Wiberg and K. I. Rowland, *ibid.*, **77**, 1159 (1955); K. W. Wiberg, T. M. Shryne, and R. R. Kintner, *ibid.*, **79**, 3160 (1957); (c) K. W. Wiberg, R. R. Kintner, and M. L. Motell, *ibid.*, **85**, 450 (1963).

(10) W. G. Bentrude, W. D. Johnson, and W. A. Kahn, *ibid.*, **94**, 3058 (1972); K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 19.

(11) W. G. Dauben and T. J. Dietsche, *J. Org. Chem.*, **37**, 1212 (1972). The chemistry of enol ethers has been reviewed by F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 295 (1969).

(12) J. E. Baldwin and L. E. Walker, *J. Amer. Chem. Soc.*, **88**, 3769, 4191 (1966).

lytic cleavage of the C—O bisallylic bond in **15** to give diradical (or ion) **21**.

The photochemical behavior of bicyclic aziridines **3a–d** under varied wavelength and solvent conditions should await further investigation. Finally, it is interesting to note that compounds **3a**, **4**, **6**, **8**, **15a**, **16a**, and **17a** are all structural isomers.

Experimental Section[13]

2-Benzhydrylidene-4-diphenylmethyl-7-phenyl-1,3,5-dioxazepine (4).—6-Phenyl-2,4-bis(benzhydrylidene)-3,5-dioxa-1-azabicyclo[4.1.0]heptane[1a] (**3a**) (1 g) was dissolved in benzene (5 ml) and poured onto a neutral alumina column (30 g). Elution with Skellysolve F–benzene (1:1) yielded 2-benzhydrylidene-4-diphenylmethyl-7-phenyl-1,3,5-dioxazepine (**4**), 0.3 g (33% yield), mp 178–180°. The analytical sample (benzene–methanol) melted at 180–181°. The yield of **4** varies with the rate of elution; the longer the starting material is left on the column the lower the yield of **4** and the higher that of product **6** (see below). Further elution with benzene–chloroform gave *N*-phenacyldiphenylacetamide, the identity of which was established by comparison with an authentic sample. **4**: ir 1670, 1600 (w), 1498, 1210, 1150, 1120, 1010, 770, 730, and 705 cm^{-1}; nmr τ 3.35 (s, 1 H), 2.62–3.22 (m, 25 H); mass spectrum M^+ 311, 310, 206, 195, 194, 179, 178, 167, 166, 165, 152, 105, 78, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.38; H, 5.35; N, 2.81.

Rearrangement of 3a or 4 into 2,6,6-Triphenyl-5-diphenylmethyl-7*H*-1,4-oxazepin-7-one (6).—1,3,5-Dioxazepine **4** (0.3 g) was dissolved in hot benzene (40 ml). Neutral alumina (20 g) was added and the hot solution was stirred for 1 hr at room temperature. The solution was filtered, and the alumina was washed with dichloromethane (100 ml). The filtrate was evaporated, and the residue was recrystallized from methanol: rocky crystals; 80 mg (27% yield); mp 214–215°; ir 1750, 1670 (w), 1500, 1130, 1030, 910, 770, 750, and 710 cm^{-1}; nmr τ 2.75 (s, 1 H), 2.8 (m, 26 H); mass spectrum M^+ 505, 477, 400, 384, 372, 310, 294, 282, 267, 252, 206, 195, 194, 179, 167, 166, 165, 152, 105, 91, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.55; H, 5.50; N, 2.62.

Oxazepinone **6** was directly obtained from **3a** by placing a warm benzene solution of the latter (2.5 g in 40 ml) on a neutral alumina column (60 g) that was prepared in Skellysolve F–benzene (1:1). After the column was left to stand at room temperature for 2 hr, elution with benzene (400 ml) followed by dichloromethane (500 ml) and evaporation of the fractions yielded 0.7 g of oxazepinone **6**.

Rearrangement of Oxazepinone 6 into 2-Benzoyl-4-diphenylmethyl-5,5-diphenyl-3-aza-3-cyclopentenone (8).—Oxazepinone **6** (0.25 g) was placed in 5% methanolic potassium hydroxide (20 ml). The slurry was heated on the steam bath for 15 min, during which the starting material dissolved and the solution turned bright yellow. Dilution with water resulted in the precipitation of a gummy yellow residue which was collected by filtration and treated with hot methanol (10 ml). Acidification of the solution with acetic acid resulted in the formation of a cream-colored solid, which was collected by suction filtration and washed with cold methanol. Recrystallization of this solid from benzene–methanol gave prismatic yellow needles (0.15 g, 60% yield) of 1,3 diketone **8**: mp 212–213°; ir 1660, 1610, 1575, 1495, 1350, 1160, 1100, 820, 750, 730, and 700 cm^{-1}; nmr τ 4.82 (s, 1 H), 2.3–2.8 (m, 24 H), −0.6 (m, 2 H); mass spectrum M^+ 505, 477, 400, 338, 310, 268, 267, 265, 252, 208, 206, 194, 178, 167, 166, 165, 152, 105, 91, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.52; H, 5.16; N, 2.71.

Concentration of the mother liquor gave 1,1,3,3-tetraphenylpropanone (20 mg): mp 132° (lit. mp 132°);[5] ir 1710, 1500, 1180, 1160, 740, and 710 cm^{-1}; nmr τ 4.7 (s, 2 H), 2.7 (m, 20 H). Examination of the mother liquor on a thin layer plate showed the presence of 2,5-diphenylpyrazine, the identity of which was established by comparison with an authentic sample.

Reaction of Oxazepinone 6 with Hydrazine.—Oxazepinone **6** (50 mg) was dissolved in hot methanol. A solution of 95% hydrazine (2 ml) was added to the solution, which was heated on the steam bath for 5 min and diluted with water to the incipient point. 2-Diphenylmethyl-5-phenyl-1*H*,4*H*-1,3,6-triazine (**13**) (25 mg, 78% yield) was collected, mp 173–175°. The analytical sample (methanol) melted at 176–177: ir 3200, 1630, 1500, 1350, 1300, 1240, 1090, 1020, 990, 770, 730, and 700 cm^{-1}; nmr τ 5.68 (s, 2 H), 4.82 (s, 1 H), 2.55–2.8 (m, 13 H), 2.2–2.35 (m, 2 H). (the singlet at τ 4.82 was exchanged with D_2O in traces of sodium methoxide); mass spectrum M^+ 325, 324, 310, 234, 220, 194, 193, 166, 164, 152, 104, 103, 77.

Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.35; H, 5.92; N, 13.18.

Evaporation of the mother liquor of the above reaction gave a residue which was composed of triazine **13** and diphenylacethydrazide. The identity of the latter was confirmed by comparison with an authentic sample.

Thermal Conversion of Bicyclic Aziridine 3a into Oxazepinone 16a or 16a and 1,3,5-Dioxazepine 15a.—Dioxazabicycloheptane **3a** (2 g) was dissolved in triglyme, and the solution was heated at 180–190° for 3 min. The cold, bright yellow solution was diluted with water, and the resulting yellow gum was isolated by decantation of the solvent followed by treatment with hot methanol. The yellow product was collected and recrystallized from benzene–methanol to afford 0.9 g of oxazepinone **16a**, mp 221–222°. The product was identical with that obtained by the photolysis of **3a**.

The above reaction was performed on 0.5 g of **3a** in diglyme at 140–150°, and the resulting yellowish gum was found, by infrared, to be a mixture of the starting material **3a**, 2,4-bis(benzhydrylidene)-6-phenyl-7*H*-1,3,5-dioxazepin (**15a**), and 2-benzhydrylidene-4,6,6-triphenyl-5*H*,7*H*-1,3-oxazepin-7-one (**16a**). Repeated thin layer chromatography of the above mixture on silica gel gave 1,3,5-dioxazepine **4** (rearrangement product from **3a**), 1,3,5-dioxazepine **15a**, and 1,3-oxazepin-7-one **16a** in very low yields. **15a**, which was prepared in a better yield from the photolysis of **3a**, was rearranged completely into **16a** on heating (in diglyme) at 140–150°.

Rearrangement of Oxazepinone 16a into 2-Diphenylmethyl-4,6,6-triphenyl-7*H*-1,3-oxazepin-7-one (17a).—Oxazepinone **16a** (0.7 g) was dissolved in hot benzene (50 ml) to which acetic acid was added (5 ml). The solution was refluxed on the steam bath for 3 hr. Evaporation of benzene left a yellowish syrup which was washed with water. The gummy product was treated with hot methanol, and the resulting white solid was collected, washed with methanol, and recrystallized from benzene–methanol as rocky white crystals: 0.5 g; mp 176–177°; ir 1768, 1665, 1600 (w), 1495, 1380, 1090, 1080, 770, 740, and 710 cm^{-1}; nmr τ 5.35 (s, 1 H), 3.66 (s, 1 H), 2.5–3.1 (m, 23 H), 2.2–2.45 (m, 2 H); mass spectrum M^+ 505, 477, 461, 384, 358, 311, 310, 295, 294, 283, 282, 269, 268, 267, 265, 253, 252, 207, 194, 191, 179, 178, 169, 168, 167, 165, 152, 132, 105, 91, 78, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.31; H, 5.50; N, 2.79.

Conversion of Oxazepinone 16a or Oxazepinone 17a into 2,4,4-Triphenyl-2-pyrrolin-5-one (18a) and Diphenylacetic Acid.—Oxazepinone **16a** (70 mg) was dissolved in 3% methanolic potassium hydroxide (30 ml). The solution was refluxed on the steam bath until it became colorless (20 min). Concentration of the solvent (5 ml) and dilution with water to the incipient point of precipitation gave a white solid (**18a**) which was collected by suction filtration, washed with water, and dried (42 mg), mp 226–228°. The product was identical with an authentic sample of 2,4,4-triphenyl-2-pyrrolin-5-one.[6] Acidification of the mother liquor, extraction with chloroform, and evaporation of the latter gave diphenylacetic acid (18 mg), identified by comparison with a known sample.

Similarly, oxazepinone **17a** (50 mg) was treated with 3% methanolic potassium hydroxide and product **18a** and diphenylacetic acid were isolated.

The same procedure was used in the conversion of oxazepinone **16b** (0.24 g) into 2,4,4-triphenyl-3-methyl-2-pyrrolin-5-one (**18b**, 0.12 g). The product was recrystallized from benzene–acetone: 120 mg; mp 238–240°; ir 3190, 1695, 1500, 1315, 1190, 780, 765, and 705 cm^{-1}; nmr τ 8.18 (5, 3 H), 2.5–2.8 (m, 15 H); mass spectrum M^+ 325, 310, 296, 282, 267, 265, 248, 223, 222, 220, 205, 204, 203, 202, 191, 189, 179, 178, 165, 115, 104, 91, 77.

(13) All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were measured in Nujol on a Perkin-Elmer 451 grating spectrometer. Nmr spectra were taken in deuterated chloroform with TMS as an internal reference using a Varian A-60A spectrometer. Mass spectra were determined on a Varian M.A.T. CH-5 instrument. Elemental analyses were performed at the Galbraith Laboratories, Inc.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.03; H, 5.92; N, 4.15.

Thermal Rearrangement of 3b,c into 2,4-Bis(benzhydrylidene)-6-phenyl-7-methyl-7*H*-1,3-dioxazepine (15b) or 2-Benzhydrylidene-5-methyl-4,6,6-triphenyl-5*H*,7*H*-1,3-oxazepin-7-one (16b).—Dioxazabicycloheptane **3b,c** (1 g of cis–trans 2:1 mixture) was dissolved in diglyme (6 ml) and the solution was refluxed at 140–150° for 2 min. Water was added to the cold solution and the supernatant liquid was decanted. The yellow gum was dissolved in benzene (5 ml) and chromatographed on a column of neutral alumina (20 g) that was prepared in Skellysolve F–benzene (1:1). Elution with the latter solvent mixture and evaporation of the fractions gave dioxazepine **15b** (150 mg). The product was recrystallized from methanol: mp 154°; ir 1735 (m), 1668 (s), 1600 (w), 1495, 1250, 1215, 1155, 1045, 1020, 775, and 700 cm^{-1}; nmr τ 8.3 (d, 3 H, J = 8 Hz), 4.5 (q, 1 H, J = 8 Hz), 2.2–3 (m, 25 H); mass spectrum M^+ 519, 491, 475, 337, 332, 325, 311, 310, 297, 296, 282, 269, 266, 253, 252, 232, 220, 219, 195, 194, 193, 178, 177, 167, 166, 165, 164, 152, 133, 118, 117, 116, 115, 105, 91, 77.

Anal. Calcd for $C_{37}H_{29}O_2N$: C, 85.52; H, 5.63; N, 2.70. Found: C, 85.56; H, 5.72; N, 2.70.

When the above reaction was conducted in triglyme at 180–190° the isolated product was 1,3-oxazepin-7-one **16b**, 46% yield, as yellow, hard needles from benzene–methanol: mp 223–225°; ir 1765, 1600 (w), 1495, 1172, 1165, 1128, 780, 755, 710, and 698 cm^{-1}; nmr τ 8.3 (d, 3 H, J = 8 Hz), 5.3 (q, 1 H, J = 8 Hz), 3.4–3.7 (m, 2 H), 2.5–3.0 (m, 23 H), 2.0–2.28 (m, 2 H); mass spectrum M^+ 519, 491, 475, 327, 325, 309, 297, 296, 283, 282, 281, 280, 268, 267, 266, 265, 221, 195, 194, 193, 178, 168, 167, 165, 117, 105, 91, 77.

Anal. Calcd for $C_{37}H_{29}O_2N$: C, 85.52; H, 5.63; N, 2.70. Found: C, 85.81; H, 5.56; N, 2.79.

Thermal Rearrangement of Dioxazepine 15b into Oxazepinone 16b and Tetraphenyl-*N*-(1-phenylpropene)iminosuccinic Anhydride (19a,b).—Dioxazepine **15b** (150 mg) was heated in triglyme (2 ml) at reflux temperature for 1 min. The solution turned bright yellow, and the cold solution was diluted with water. The resulting curdy yellow solid was collected by filtration. Thin layer chromatography on silica gel, with benzene as the eluent, indicated the formation of two products only, one yellow and the other colorless. The crude product was treated with Skellysolve F and the insoluble yellow solid was found to be oxazepinone **16b** (110 mg, 73% yield). Evaporation of Skellysolve left a whitish residue which upon rubbing with methanol gave a solid that melted at 178–185°, an indication of a mixture. Nmr showed two doublets for the methyl group suggestive of a cis–trans mixture of **19a,b** in a ratio of 2:5: ir 1812 (m), 1710 (s), 1640 (w), 1600 (w), 1495, 1200, 1100, 1080, 970 (s), 960 (s), 760, 720, 712, 710, and 700 cm^{-1}; mass spectrum M^+ 519, 491 (w), 332, 309, 256, 255, 254, 194, 193, 180, 179, 178, 177, 166, 165, 117, 105, 91, 77.

Thermal Rearrangement of 3d into 2,4-Bis(benzhydrylidene)-6-phenyl-7,7-dimethyl-7*H*-1,3,5-dioxazepine (15c) or into 19c.—Dioxazabicycloheptane **3d** (0.5 g) was dissolved in diglyme (3 ml) and the solution was heated at 140–150° for 5 min. The cold solution was diluted with water (5 ml) and the resulting solid was filtered, washed with methanol, and dried, 0.3 g (60% yield) of **15c**. Recrystallization from methanol gave needles that melted at 145°: ir 1738 (m), 1665 (s), 1595 (w), 1490, 1255, 1220, 1210, 1155, 1045, 1021, 960, 920, 770, 750, and 705 cm^{-1}; nmr τ 8.33 (s, 6 H), 2.3–3.1 (m, 25 H); mass spectrum M^+ 533, 351, 339, 324, 323, 195, 194, 166, 165, 131, 129, 116, 105, 91, 77.

Anal. Calcd for $C_{38}H_{31}O_2N$: C, 85.52; H, 5.86; N, 2.62. Found: C, 85.42; H, 5.81; N, 2.51.

Thin layer chromatography of the residue from the mother liquor did not yield any detectable oxazepinone 16c.

Similarly, the heating of a triglyme solution of 6-phenyl-2,4-bis(benzhydrylidene)-7,7-dimethyl-3,5-dioxa-1-azabicyclo[4.1 0]-heptane (**3d**, 100 mg) at 180–190° gave tetraphenyl-*N*-(1-phenyl-2-methylpropylene)iminosuccinic anhydride (**19c**, 60 mg). Recrystallization of the product from benzene–methanol gave 60 mg of white, hard prisms of **19c**, mp 211–213°. Thin layer chromatography of the residue from the mother liquor did not yield any traceable products other than **19c**: ir 1810 (m), 1705 (s), 1600 (w), 1495, 1225, 1140, 1120, 1110, 1070, 990, 770, and 710 cm^{-1}; nmr τ 8.6 (s, 3 H), 8.33 (s, 3 H), 2.65–3.9 (m, which included three sharp singlets, 25 H); mass spectrum M^+ 533, 505 (w), 489 (w), 350, 339, 333, 332, 331, 330, 329, 324, 323, 311, 256, 255, 254, 253, 252, 240, 239, 238, 234, 195, 194, 181, 180, 179, 178, 177, 166, 165, 152, 131, 119, 116, 115, 105, 104, 103, 91, 77.

Anal. Calcd for $C_{38}H_{31}O_2N$: C, 85.52; H, 5.86; N, 2.62. Found: C, 85.70; H, 6.01; N, 2.50.

Conversion of Dioxazepine 15c into 19c.—Heating of dioxazepine **15c** (40 mg) in triglyme (0.5 ml) at 180–190° for 5 min produced 20 mg of **19c** after crystallization from methanol–acetone.

Thin layer chromatography on silica gel or alumina did not furnish evidence for the formation of oxazepinone **16c**.

Photolysis of **15c** at 310 nm in benzene for 4.5 hr at 15° gave mainly starting material. Further photolysis for 24 hr yielded polymeric material and traces of the starting material.

Photolysis of Dioxazabicycloheptanes 3a–d.—Dioxazabicycloheptane **3a** (1 g) was dissolved in benzene (600 ml) and the solution was irradiated with a 310-nm light for 7 hr at 15°. The resulting bright yellow solution was concentrated to 4 ml and poured onto a neutral alumina (30 g) column that was preprepared in Skellysolve F. Elution with Skellysolve F–benzene (1:1) gave 2,4-bis(benzhydrylidene)-6-phenyl-7*H*-1,3,5-dioxazepine (**15a**). Recrystallization of the product from methanol yielded needles (65 mg) that melted at 127–128°. Further elution with benzene–dichloromethane (2:1, 1:1) gave 2-benzhydrylidene-4,6,6-triphenyl-5*H*,7*H*-1,3-oxazepin-7-one (**16a**), which after recrystallization from benzene–methanol was collected as yellow, short needles (95 mg), mp 221–222°. In some cases, traces of product **16a** were isolated.

Product **15a** had ir 1738 (m), 1668 (s), 1615 (w), 1598 (w), 1495, 1240, 1215, 1160, 1040, 1020, 870, and 710 cm^{-1}; nmr τ 5.1 (s, 1 H), 4.75 (s, 1 H), 2.25–2.82 (m, 25 H); mass spectrum M^+ 505, 477, 461, 311, 310, 296, 295, 294, 284, 283, 268, 267, 266, 254, 253, 252, 224, 208, 207, 206, 195, 194, 193, 192, 181, 180, 179, 167, 166, 165, 103, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.48; H, 5.28; N, 2.58.

Product **16a** had ir 1752, 1630 (w), 1600 (w), 1495, 1170, 1150, 770, and 710 cm^{-1}; nmr τ 5.9 (s, 2 H), 3.4–3.52 (m, 2 H), 2.55–3 (m, 21 H), 2.1–2.3 (m, 2 H); mass spectrum M^+ 505, 477, 461, 311, 310, 294, 283, 282, 268, 267, 265, 253, 252, 232, 207, 204, 195, 194, 192, 180, 179, 178, 167, 166, 165, 152, 132, 105, 91, 77.

Anal. Calcd for $C_{36}H_{27}O_2N$: C, 85.52; H, 5.38; N, 2.77. Found: C, 85.70; H, 5.51; N, 2.92.

The above procedure was followed in the photolysis of 6-phenyl-2,4-bis(benzhydrylidene)-7-methyl-3,5-dioxa-1-azabicyclo[4.1.0]heptane (**3b,c**, 0.8 g) which yielded 2,4-bis(benzhydrylidene)-6-phenyl-7-methyl-7*H*-1,3,5-dioxazepine (**15b**, mp 152–154°, 120 mg, 15% yield) and 2-benzhydrylidine-4-phenyl-5-methyl-6,6-diphenyl-5*H*,7*H*-1,3-oxazepin-7-one (**16b**, 10 mg, 1% yield). Both products **15b** and **16b** were identical with those obtained from the thermolysis of **3b,c**.

Similarly, the photolysis of 6-phenyl-2,4-bis(benzhydrylidene)-7,7-dimethyl-3,5-dioxa-1-azabicyclo[4.1.0]heptane (**3d**, 1 g) in benzene gave **15c** (0.25 g, 25% yield). The product was identical with that obtained from the thermolysis of **3d** at 180–190°.

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Registry No.—**3a**, 33893-01-5; **3b**, 37005-08-6; **3c**, 37005-09-7; **3d**, 37005-10-0; **4**, 37005-11-1; **6**, 40711-53-3; **8**, 40711-54-4; **13**, 40711-55-5; **15a**, 40711-56-6; **15b**, 40711-57-7; **15c**, 40711-58-8; **16a**, 40711-59-9; **16b**, 40711-60-2; **17a**, 40711-61-3; **18a**, 28172-27-2; **18b**, 40711-63-5; **19a**, 40742-87-8; **19b**, 40711-13-5; **19c**, 40711-64-6; hydrazine, 302-01-2.

Influence of Solvent and Brominating Agent on the Steric Course of the Bromine Addition to 1-Phenylcyclohexene and 2-Phenyl-3-bromocyclohexene

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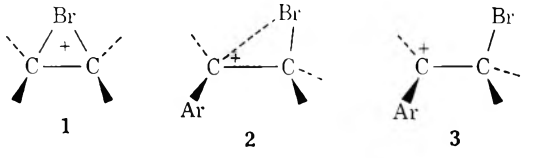
The addition of bromine to 1-phenylcyclohexene yields complex mixtures of up to five products, identified as the unsaturated bromide **8**, the *trans*- and *cis*-dibromides **5** and **6**, and the *meso*- and *dl*-tribromides **9** and **10**, in ratios which depend largely on the reaction conditions. While the addition of free bromine in $CHCl_3$ or benzene affords larger amounts of **6**, **9**, and **10**, the use of pyridine perbromide as the brominating agent remarkably reduces their formation in favor of the *anti*-dibromo adduct **5**. It is shown that **9** and **10** arise from bromine addition to **8**, formed in part from **4** through cationic intermediate **15** and in part through bromine-catalyzed elimination of HBr from the primary product **5**. The marked decrease in the formation of *syn*-dibromo adduct **6** and of unsaturated bromide **8** with pyridine perbromide is ascribed to the intervention of a more concerted addition mechanism and to nucleophilic solvation by base in the transition state for the addition. The bromination of **8** with free bromine in $CHCl_3$ leads to an excess of the *dl*-tribromide **10**, whereas the use of ethyl ether as the solvent or pyridine perbromide or pyridinium hydrobromide perbromide as the brominating agent strongly favors the formation of the meso isomer **9**, arising through anti addition.

The mechanism of the electrophilic addition of bromine to alkenes has been widely investigated both from the kinetic and the stereochemical point of view.[1,2] Apart from the relative importance of the various kinetically significant processes involved, it is now known[3-9] that the nature of the intermediates of the addition depends on the structure of the substrate and on the reaction medium, ranging from strongly bridged bromonium ions of the type originally postulated by Roberts and Kimball[10] (**1**) to weakly bridged species of the type **2**, or open ions like **3**.



1 2 3

While intermediates of type **1** are involved in the bromination of nonconjugated olefins, which give only anti adducts irrespective of the reaction medium,[4] in the case of aryl-substituted compounds the unsymmetrically bridged **2** or open species **3** must be involved to rationalize the nonstereospecific course of the addition, which leads to syn as well as to anti adducts and depends on the reaction medium.[4,6-8]

The solvent polarity has been considered as the main factor affecting the extent of bridging in the intermediate, and consequently the stereochemical results of the bromination of a conjugated substrate.[7,8] However, also the ability of the solvent to coordinate with the attacking electrophile and to solvate cationic intermediates must be taken into account.[4] Our previous work[11] on the addition of bromine to nonconjugated substituted cyclohexenes revealed a marked influence of the coordination of bromine by a basic solvent or by added tertiary amines on the ratio between diaxial and diequatorial adducts. As an extension of our research, we therefore chose 1-phenylcyclohexene as a substrate suitable for a study of the influence of the solvent and the brominating agent on the ratio of syn to anti addition. Only very inadequate reports are found in the literature[12-15] concerning bromine addition to this olefin, the complexity of the reaction having prevented the isolation of the products. Previous systematic studies on the steric course of the bromination of aryl-substituted olefins were confined to acyclic derivatives, in which the possibility of rotation about the carbon–carbon single bond in the intermediates **2** or **3** makes the understanding of the mechanism of the syn addition ambiguous. Such uncertainty is obviously eliminated by using a cyclic compound like **4**; this is a further reason for our interest in this substrate.

Results

The addition of bromine to 1-phenylcyclohexene was accompanied by the evolution of hydrogen bromide and yielded complex mixtures of up to five products, containing from one to three bromine atoms, in ratios which depended largely on the reaction conditions. Although it was usually not possible to separate the single components of these mixtures, we succeeded in identifying all of them as compounds **5**, **6**, **8**, **9**, and **10**, and in analyzing the mixtures through pmr methods.

The *trans*-dibromide **5** was isolated by low-temperature crystallization of the bromination mixture obtained by treatment of **4** with pyridine perbromide in carbon tetrachloride; its configuration was assigned on the

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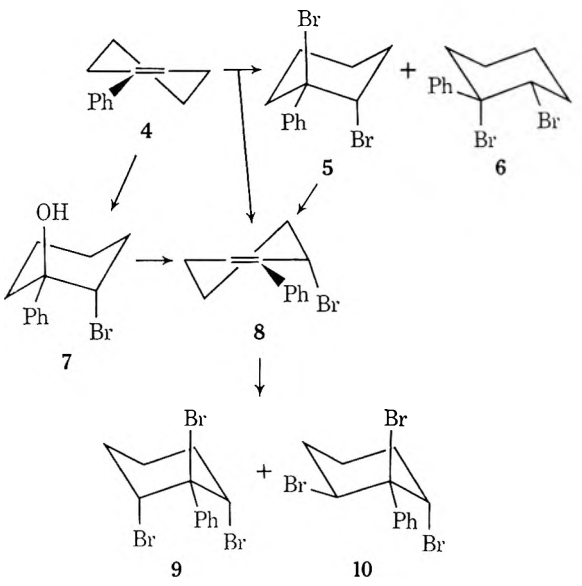
(13) M. Mousseron and F. Winternitz, *Bull. Soc. Chim. Fr.*, **12**, 70 (1945).
(14) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1246 (1954).
(15) **J. Heublein and I. Koch**, *Z. Chem.*, **9**, 28 (1969).

basis of the half band width (6 Hz)[16] of the pmr signal at δ 5.10 ppm, due to the proton α to Br.[17]

The tribromides **9** and **10** were prepared as shown in Scheme I. Treatment of **4** with NBS in DMSO–water

SCHEME I



gave the bromohydrin **7**, whose structure was defined by its resistance to oxidation with Jones reagent and its transformation in 1-phenyl-1,2-epoxycyclohexane by treatment with alkali. Dehydration of **7** with sulfuric acid in acetic acid afforded 2-phenyl-3-bromocyclohexene (**8**), which, by treatment with bromine in chloroform, gave a mixture of the tribromides **9** and **10**. The main component **10** was separated by crystallization. The diastereoisomer **9** was similarly isolated from the bromination mixture obtained from the reaction of **8** with pyridine perbromide in carbon tetrachloride. Its meso configuration and its conformation with axial bromine atoms were deduced from the pmr spectrum, which showed a narrow signal at δ 5.34 ppm (half band width 6 Hz) due to the two magnetically equivalent equatorial hydrogens α to bromine.[18] On the other hand, the spectrum of the less symmetric isomer **10** displayed a more complicated pattern of signals, owing to overlap of the resonances of the two protons α to bromine; their nonequivalence was, however, deduced by the comparison of spectra obtained in different solvents, like carbon tetrachloride and benzene-d_6, which affect in a different way their chemical shifts (Figure 1). Unfortunately, no bromination procedure of **4** led to formation of the *cis*-dibromo derivative **6** in sufficient amount to permit its isolation, which was also made difficult by an extensive decomposition during attempts at chromatographic separation. However, its formation in small amount under all examined conditions was inferred from the presence of the typical doublet of doublets[16] (X part of an ABX system, $J_{AX} + J_{BX} = 15$ Hz) in the pmr spectra of all the bromination mixtures from **4**. Furthermore, the same signal was observed, though with very low intensity, besides that of **5** in the spectrum of the reaction product obtained by treatment of **7** with hydrogen bromide in chloroform. Although this substitution reaction prevalently gives the *trans*-dibromide **5**, as expected on the basis of an SNi type mechanism,[19] favored by anchimeric assistance by the vicinal bromine atom, the formation of a small amount of the inverted substitution product **6** is also conceivable owing to the tendency of the phenyl substituent to stabilize an open ion intermediate of type **3**, which may lead to **6** in addition to **5**.

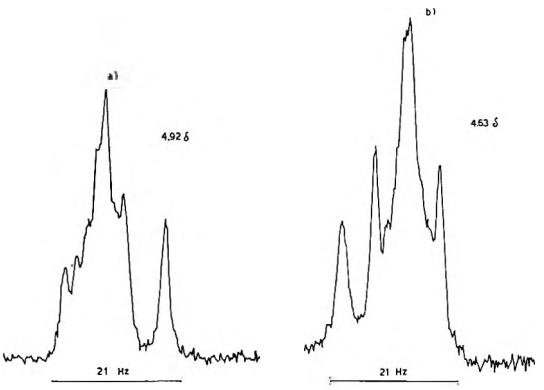


Figure 1.—The medium field part of the pmr spectrum of dibromide **10** in CCl_4 (a) and in C_6D_6 (b).

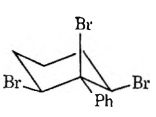
Preliminary experiments of bromination of 1-phenylcyclohexene were carried out by slowly adding a 1 *M* solution of bromine in chloroform to solutions of the olefin. Development of hydrogen bromide was observed and the pmr analysis of the crude reaction mixtures showed that the product composition considerably changed according to the amount of added bromine and to reaction time. In order to reduce the amount of unreacted olefin in the reaction products, and to obtain comparable results in the quantitative experiments in different solvents, the additions were carried out with an excess of the brominating agents for fixed times. The product distributions were determined by pmr analysis, the signals of the protons α to bromine being sufficiently separated to allow for an acceptable integration (Figure 2). The results are summarized in Table I.

The fact that the tribromides **9** and **10** were obtained also when the addition of bromine in chloroform was performed in the dark and, although in slightly smaller amounts, at −70°, speaks against their formation through a free-radical process. The use as the brominating agent of pyridine perbromide, either preformed or produced *in situ*, remarkably reduced

(16) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 286.

(17) Since *trans*-1,2-dibromocyclohexane has a preferred conformation with axial bromine atoms [P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 3, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1967, p 231, and H. Booth, in Vol. 5, 1969, p 149; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967)] and a phenyl group prefers the equatorial position, conformations other than those shown for **5** and **6** in Scheme I can practically be excluded.

(18) The more stable conformation of the alternative meso form would have two axial equivalent hydrogens α to bromine (**11**), which should give a



11

broad multiplet. Furthermore, structure **11** would hardly account for the easy isomerization of the *meso*- into the *dl*-tribromide (see Discussion).

(19) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **22**, 189 (1966).

TABLE I

PRODUCT COMPOSITION IN THE BROMINATION OF 1-PHENYLCYCLOHEXENE

Solvent	Brominating agent (% excess)	Reaction time, min	Products, mol % 5	6	8	9	10
$CHCl_3$	Br_2 (50)	15	52	11		12	25
$CHCl_3$	Br_2 (100)	195	22	11		16	51
$CHCl_3$ + Py	Br_2 (50)	30	76	6	12	6	
$CHCl_3$ + Py	Br_2 (100)	120	62	6		26	6
CCl_4	$C_5H_5NBr_2$ (50)	30	86	4	10		
CCl_4	$C_5H_5NBr_2$ (100)	120	82	4		14	
C_6H_6	Br_2 (50)	15	50	13		22	15
C_6H_6	Br_2 (100)	120	43	13		21	23
Et_2O	Br_2 (50)	30	62	8	10	16	4
Et_2O	Br_2 (100)	120	52	8		32	8

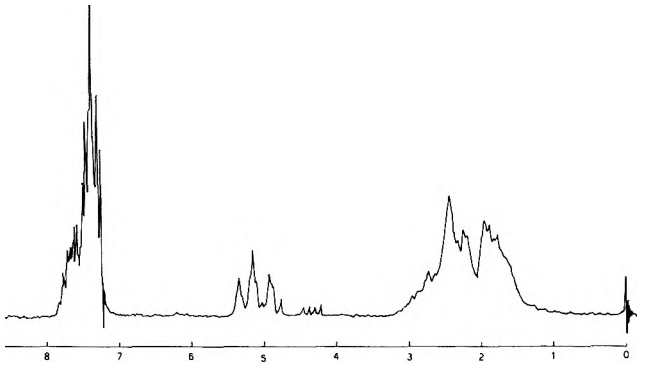


Figure 2.—Pmr spectrum in CCl_4 of a typical mixture obtained by bromination of 4 with an excess of Br_2 in $CHCl_3$.

the formation of the *cis*-dibromide and of the tribromides. A similar, although less marked effect, was found when the addition of bromine was carried out in a basic solvent like ethyl ether. In these cases, however, the reaction mixtures contained appreciable amounts of the unsaturated bromo derivative **8**, in spite of the excess of brominating agent employed. On the other hand, the addition of free bromine in chloroform or benzene led to formation of larger amounts of **6**, **9**, and **10**, while only traces of unsaturated compounds were found. Larger excesses of bromine and longer reaction times resulted in a decrease of the *trans*-dibromide and an increase of the tribromo derivatives, this effect being more pronounced in the addition performed with free bromine. In contrast, the amount of *cis*-dibromide was completely unaffected. Furthermore, the ratio between the relative amounts of tribromides changed according to the reaction conditions. All these observations suggested that concomitant transformation of **5** into **9** and **10** and of **9** into **10** could occur in the reaction medium, **6** being stable. Consistent with this was the fact that when solutions of the *trans*-dibromide **5** in various solvents were exposed to bromine, hydrogen bromide was evolved and the tribromides **9** and **10**, but not the *cis*-dibromide **6**, were slowly formed. On the other hand, **5** was completely stable when exposed to hydrogen bromide. The extent of transformation of **5** into **9** and **10**, as a function of the amount of added bromine, of reaction time, and of solvent is reported in Table II.

Several points of interest emerge from these results. Firstly, the rate of conversion of **5** into **9** and **10** appears to depend on the bromine concentration and on the solvent employed, the rate order being chloroform > benzene > ethyl ether. However, in all solvents the transformations were too slow to account for the whole amounts of tribromides formed in the bromine addition to **4**. Therefore it can be concluded that most of **9** and **10**, formed from **4** after short reaction times, arises through a pathway which does not involve the formation of **5** as the primary product. Moreover, while in ethyl ether the *meso*-tribromide **9** was the main product irrespective of the extent of conversion, in chloroform and in benzene the product composition markedly changed in favor of the *dl* isomer **10** with increasing degree of conversion, showing that in the presence of bromine **9**, which is formed under kinetic control, isomerizes to the more stable isomer **10**. This point was confirmed by experiments carried out with pure **9** and **10**: whereas **10** was unaffected by prolonged exposition to bromine in chloroform, **9** under the same conditions was slowly transformed into **10**. On the other hand, the bromine-catalyzed isomerization was slower in ethyl ether as the solvent, and hydrogen bromide alone had no effect.

TABLE II

CONVERSION OF DIBROMIDE 5 INTO TRIBROMIDES 9 AND 10 IN THE PRESENCE OF BROMINE

Solvent	Molar ratio of 5:Br_2	Reaction time, min	Products, mol % 5	9	10
$CHCl_3$	2:1	15	85	5	10
$CHCl_3$	1:0.75	15	81	6	13
$CHCl_3$	1:1	15	78	7	15
$CHCl_3$	1:1	1440	10	14	76
C_6H_6	2:1	15	95	3	2
C_6H_6	1:1	1440	16	12	72
Et_2O	2:1	30	97	3	
Et_2O	1:1	160	78	18	4
Et_2O	1:1	1440	44	40	16

The formation of tribromides in the bromination of **4** can be visualized (Scheme I) as arising from bromine addition to the unsaturated bromo derivative **8**, formed in part directly from **4** and in part through bromine-catalyzed elimination of hydrogen bromide from the primary product **5**. In order to verify this scheme, the product composition from the bromination of **8** under several conditions was examined. Since the rate of addition to **8** appeared to be slower than that to **4**, longer reaction times (2 hr) and smaller excesses of brominating agents (20%) were employed. Under these conditions the isomerization of the adduct **9** to **10** was minimized. The results, obtained by pmr analysis, are reported in Table III.

As observed for **4**, the product distribution was strongly influenced by the reaction conditions: while

TABLE III

PRODUCT COMPOSITION IN THE BROMINATION OF 2-PHENYL-3-BROMOCYCLOHEXENE

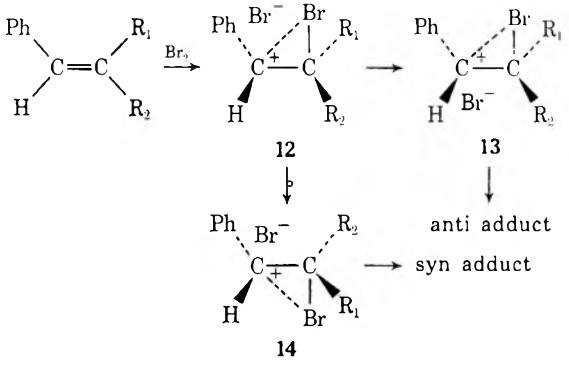
Solvent	Brominating agent	Reaction time, min	Products, mol % 9	10
$CHCl_3$	Br_2	120	25	75
CCl_4	$C_5H_5NBr_2$	120	90	10
Et_2O	Br_2	120	80	20
CH_3COOH	$C_5H_5NHBr_3$	120	90	10

pyridine perbromide as the brominating agent and ethyl ether as the solvent strongly favored the formation of the unstable isomer **9**, bromine in chloroform afforded an excess of **10**. It is emphasized that the **9** to **10** ratios are in fairly good agreement with those obtained in the brominations of **4** under similar conditions (see Table I), thus confirming the formation of the tribromides **9** and **10** from **4–8**.

Discussion

According to recent views, the electrophilic step in the bromine addition to styrene derivatives in nonpolar solvents leads to the initial formation of an intimate ion pair, whose positive moiety should be an unsymmetrically bridged ion of type **2**, resembling a benzylic cation more than a bromonium ion.[4,6,9,20,21] Nucleophilic attack by bromide counterion can occur through two different pathways, affording either *anti*- or *syn*-dibromo adducts (Scheme II). Owing to steric

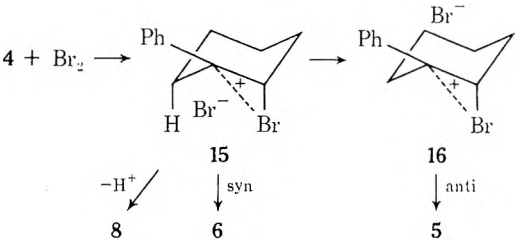
SCHEME II



and ion–dipole repulsion between the first bonded bromine and the attacking bromide ion in the ion pair **12**, a reorientation of **12** to **13** can occur before the attack, leading to anti adducts. However, since the neighboring bromine bridging in the intermediate should be very weak, internal rotation around the C_α–C_β bond has been postulated to give **14**, whose collapse would result in net syn addition. It should be pointed out that a direct collapse of **12** to syn adducts has been considered less probable owing to the bulk of the first bonded bromine atom.[4,6]

According to this picture, the first formed intermediate in the bromine addition to 1-phenylcyclohexene in chloroform or benzene could be represented as **15** (Scheme III); reorientation and rear-side attack by bromide ion can lead to the *anti*-dibromo adduct **5**, which is actually the main product of the primary reaction. On the other hand **15**, owing to the restric-

SCHEME III



tions imposed by the six-membered ring, cannot undergo internal rotation around the C_α–C_β bond and according to Scheme II should not give the syn adduct. In contrast, appreciable amounts of **6** are found in the bromination mixtures of **4**, showing that internal rotation followed by rear-side attack is not a necessary path for syn addition, which can also occur through direct collapse of an intimate ion pair intermediate. Our results also show that in a cyclohexene system syn additions to give products such as **6** are quite possible sterically; therefore the fact that cyclohexene itself gives exclusively trans product demonstrates clearly that in the parent system (without phenyl stabilization) anti addition is almost certainly due to strong cyclic bromonium ion formation, and not due to the steric effect of the first attached bromine atom in an open ion.

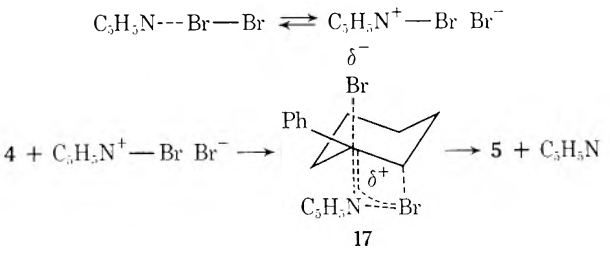
The benzylic cation character of the positive moiety of **15** is confirmed by the extensive occurrence of proton loss from C-6 to give the unsaturated bromo derivative **8**, which undergoes further bromine addition affording the tribromides **9** and **10**. Owing to the necessity for the bromide counterion of **15** to reorient to the less hindered side, presumably through a solvent-separated ion pair, the lifetime of the cation should be long enough to cause proton elimination. The extent of proton loss from **15** can be roughly estimated by subtracting from the total amounts of **8**, **9**, and **10**, reported in Table I, those of **9** and **10** arising from the bromine-catalyzed transformation of the firstly formed **5** under the reaction conditions (see Table II). Although accurate values cannot be obtained, since the reaction conditions and particularly the bromine concentrations cannot be exactly reproduced, these data permit the inference that about 20–30% of intermediate **15** loses a proton to yield **8**, the larger amount being formed in benzene. Values ranging from 30 to 40% of proton elimination have been reported[15] for the bromination of **4** in acetic acid and in its mixtures with carbon tetrachloride, nitromethane, and water. Such a marked tendency to elimination seems to be peculiar to the aryl-substituted cyclohexene system, since no formation of allylic bromides was reported in the bromination of side-chain methyl-substituted styrenes,[3,4,6] with the exception of *α,o,o,p*-tetramethylstyrene, which yields only substitution products owing to steric inhibition of the development of an sp^3 character at the benzylic carbon atom owing to the presence of the two *o*-methyl groups.[22]

The marked decrease in the formation of the *syn*-dibromo adduct **6** when using pyridine perbromide as the brominating agent parallels a considerable reduc-

(20) P. B. D. de la Mare, *Quart. Rev., Chem. Soc.*, **3**, 126 (1949).
(21) J. E. Dubois and W. V. Wright, *Tetrahedron Lett.*, 3101 (1967).
(22) E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 1243 (1968).

tion in the proton loss to give **8**. This suggests that a more concerted anti attack should be involved under these conditions. In a previous paper[11] we suggested that an ionization of the pyridine–bromine complex could simultaneously provide both the electrophile and the nucleophile. If this is true, a rapid rear-side attack by an external bromide ion on the α carbon could occur without the necessity of any reorientation of the intermediate; furthermore, the base, which conveys the electrophilic bromine to the reaction site, could solvate from the cis side the incipient benzylic cation, hindering a syn attack by bromide ion. The transition state for the addition could therefore be represented as **17** (Scheme IV), which is similar

SCHEME IV



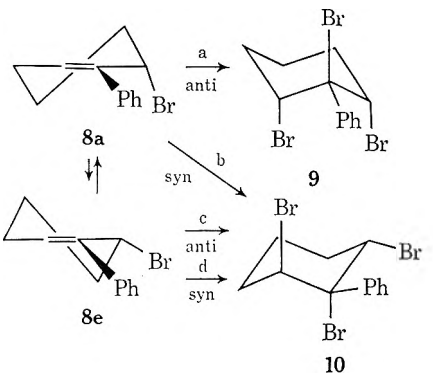
17

to that proposed[23] for the E2Hal elimination of bromine from *trans*-1,2-dibromocyclohexane with thiophenoxide as base.

The fact that the use of ethyl ether instead of chloroform or benzene as the solvent for the addition of bromine to **4** tends to decrease, although less markedly, the amount of syn adduct may conceivably be attributed to coordination of the halogen, since it is known that ethers form addition compounds with bromine.[24] However in this case, the ether being present in a large excess, solvation can be provided for the incipient benzylic carbocation both from the cis side by the molecule of ether carrying the electrophile and from the trans side by external molecules of solvent. The lack of a specific syn solvation could account for the smaller degree of suppression of the syn addition than expected on the basis of the coordination of the halogen. Solvation of the β-bromo-α-phenylcarbonium ion by an ether solvent such as dioxane to give an unstable oxonium ion intermediate has been postulated[4] to rationalize the stereochemical results of the bromination of *cis*- and *trans*-β-methylstyrenes.

The effect of the coordination of bromine by bases on the steric course of the addition to 2-phenyl-3-bromocyclohexene is also striking. However, in this case the interpretation is complicated by the presence of the bromine atom in **8**, which prevents establishing the mode of formation of the *dl*-tribromo derivative **10**. Indeed, whereas the *meso*-tribromide **9** can only be formed through anti addition, the isomer **10**, having one bromine in a trans and one in a cis relationship to the central halogen atom, could be formed either through anti diaxial addition or through syn addition from the side opposite to the allylic bromine of **8**. It is therefore impossible to infer with certainty, from the present data, the occurrence of syn addition of bromine to **8**, since the stereochemical results could also be explained on the basis of an exclusive anti diaxial addition on the two possible conformers with pseudoaxial (**8a**) or pseudoequatorial bromine (**8e**) (Scheme V, paths a and c; anti diequatorial additions,

SCHEME V



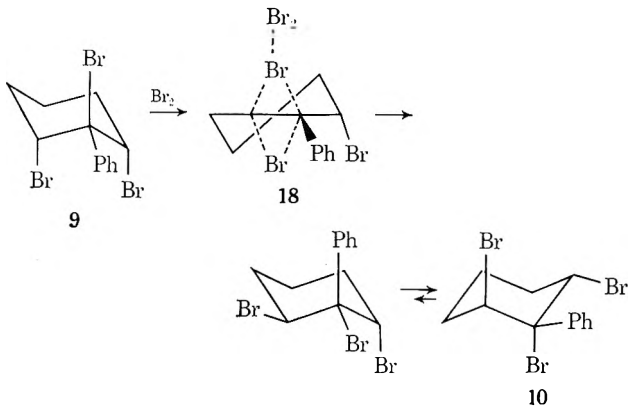
which could also give **9** from **8e** and **10** from **8a**, are not considered in the scheme since they would involve less favorable preboat transition states).

Although the half band width of the proton α to bromine (6 Hz) in the pmr spectrum of **8** indicates that conformation **8a** is strongly preferred over **8e**, in agreement with reports on similarly substituted cyclohexene derivatives,[25] it cannot be excluded that part of the addition may occur through the less stable conformer **8e**. However, since pyridine perbromide has been shown to suppress the syn addition to **4**, this suggests that a decrease of importance of paths b and d, rather than a diversion from path c to path a, could be responsible for the strong increase in the **9** to **10** ratio in the bromination of **8** with this reagent. Consistent with this is the fact that identical results are obtained by performing the bromination in acetic acid with pyridinium hydrobromide perbromide, a reagent which is known[26] to suppress the syn addition to phenyl-substituted olefins. A similar trend is found in the addition of bromine in ethyl ether, which, like pyridine, can coordinate bromine.

The *meso*-tribromide **9** is slowly transformed into **10** on treatment with bromine at room temperature. Since a single inversion of configuration on C-2 seems to be very unlikely, this isomerization can be visualized as the result of a 1,2 interchange on two vicinal centers bearing trans-oriented bromine atoms, resembling the thermal interconversions between diaxial and diequatorial dibromocyclohexanes and steroid derivatives.[27-29] In this case the driving force for the easy isomerization clearly is due to strong syn-diaxial interaction between the 1,3 bromine atoms. Thus, the role of molecular bromine should be that of increasing the extent to which bond breaking occurs in the transition state (**18**) by causing a lowering of electron density in the benzylic carbon–bromine bond (Scheme VI). Similar catalytic effects by carboxylic acids and phenols[30] and by mercuric bromide[31] have

(23) E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968).
(24) O. Hassel and C. Romming, *Quart. Rev., Chem. Soc.*, **16**, 1 (1962).
(25) E. W. Garbisch, *J. Org. Chem.*, **27**, 4249 (1962).
(26) L. F. Fieser, *J. Chem. Educ.*, **31**, 291 (1954).
(27) P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *J. Chem. Soc., Perkin Trans. 2*, 58 (1972).
(28) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).
(29) J. F. King and R. G. Pews, *Can. J. Chem.*, **43**, 847 (1965).
(30) H. Kwart and L. B. Weisfeld, *J. Amer. Chem. Soc.*, **78**, 635 (1956).
(31) V. Hach, *J. Org. Chem.*, **36**, 2568 (1971).

SCHEME VI



been reported for the thermal rearrangement of steroidal dibromides. In an analogous way, molecular bromine can cause the elimination of hydrogen bromide from dibromide **5** to give **8**.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Pmr spectra were registered with a Jeol C-60 HL spectrometer from CCl_4 solutions with TMS as internal standard. $MgSO_4$ was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator) at 30°. Petroleum ether refers to the fraction of boiling range 40–60°.

Starting Materials.—1-Phenylcyclohexene was prepared according to Garbisch.[32] Bromine was purified by refluxing with $CaBr_2$ and distillation.[33] Preformed pyridine perbromide was prepared immediately before use from bromine and pyridine in CCl_4.[34] Pyridine hydrobromide perbromide was prepared by the Fieser method.[35] CCl_4 was Rudi Pont spectranalyzed reagent grade. $CHCl_3$ was purified by washing with 2 *N* NaOH, concentrated H_2SO_4, and water, drying with K_2CO_3, and distillation, and was immediately used. Et_2O was freed from peroxides by washing with a solution of $FeSO_4$. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled.

***r*-1,*t*-2-Dibromo-1-phenylcyclohexane (5).**—Preformed pyridine perbromide (1.8 g, 7.5 mmol) was added to a solution of **4** (1.0 g, 6.3 mmol) in CCl_4 (25 ml) at 0°. The reaction mixture was stirred for 15 min, then poured into saturated aqueous Na_2SO_3; the organic layer was washed with water, 2 *N* HCl, and water, dried, and evaporated. Crystallization of the residue from pentane at −20° gave **5** (0.8 g): needles; mp 66–67.5°; pmr δ 5.10 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{14}Br_2$: C, 45.31; H, 4.44; Br, 50.25. Found: C, 45.50; H, 4.47; Br, 49.98.

***t*-2-Bromo-1-phenyl-*r*-1-cyclohexanol (7).**—NBS (13.4 g, 75.3 mmol) was added portionwise to a solution of **4** (6.0 g, 37.9 mmol) in a mixture of DMSO (80 ml) and water (4 ml) at 0° under an atmosphere of nitrogen. After standing for 1 hr at room temperature, the reaction mixture was poured into water and extracted with Et_2O. Evaporation of the organic layer after washing with water and drying gave an oily residue (9.6 g) which crystallized as prisms from petroleum ether at −20° (6.0 g). After recrystallization the solid had mp 48–49°; pmr δ 4.24 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.48; H, 5.92; Br, 31.32. Found: C, 56.58; H, 5.87; Br, 31.60.

A sample of this product was recovered unchanged after treatment with Jones reagent.[36] A solution of **7** (91.1 mg, 0.36 mmol) in MeOH (5 ml) was titrated with 0.1 *N* aqueous NaOH with phenolphthalein as the indicator. The consumption of base amounted to 3.6 ml. Dilution with water, extraction with $CHCl_3$, and evaporation of the dried organic layer gave pure 1-phenyl-1,2-epoxycyclohexane (52 mg).

2-Phenyl-3-bromocyclohexene (8).—The bromohydrin **7** (1.5 g) was treated with freshly prepared 20% (v/v) H_2SO_4–AcOH (4 ml) and the resulting mixture was swirled for 2.5 min and poured into petroleum ether–water. Evaporation of the organic layer, after washing with water, saturated aqueous $NaHCO_3$, and water and drying, afforded **8** (1.3 g), which crystallized as needles from petroleum ether: mp 50–52°; pmr δ 6.07 (–CH=, m, $W_{1/2}$ = 8 Hz, 1 H), 5.18 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{13}Br$: C, 60.77; H, 5.52; Br, 33.70. Found: C, 60.65; H, 5.44; Br, 33.55.

***r*-1,*t*-2,*c*-3-Tribromo-2-phenylcyclohexane (9).**—Preformed pyridine perbromide (0.77 g, 3.2 mmol) was added to a solution of **8** (0.60 g, 2.53 mmol) in CCl_4 (10 ml); after stirring at room temperature for 2 hr the reaction mixture was poured into saturated aqueous Na_2SO_3, and the organic layer was separated, washed with 2 *N* aqueous HCl, water, and saturated aqueous $NaHCO_3$, dried, and evaporated. The solid residue (0.89 g), dissolved in petroleum ether at room temperature, crystallized on cooling at −20° to give pure **9** (0.50 g): prisms; mp 95.5–97.5°; pmr δ 5.34 (–CHBr–, m, $W_{1/2}$ = 6 Hz, 2 H).

Anal. Calcd for $C_{12}H_{13}Br_3$: C, 36.30; H, 3.30; Br, 60.39. Found: C, 36.35; H, 3.18; Br, 60.70.

***r*-1,*c*-2,*t*-3-Tribromo-2-phenylcyclohexane (10).**—A 1 *M* solution of Br_2 in $CHCl_3$ (2.5 ml) was added dropwise at 0° to a solution of **8** (0.50 g, 2.1 mmol) in the same solvent (10 ml). The consumption of Br_2 was slow. After standing overnight, the solution was poured into saturated aqueous Na_2SO_3, washed with water, dried, and evaporated. Crystallization of the solid residue (0.77 g) from petroleum ether, carried out as described for **9**, gave pure **10** (0.35 g): needles; mp 134–135.5°; pmr δ 4.92 (–CHBr–, 2 overlapping m, 2 not equivalent H).

Anal. Calcd for $C_{12}H_{13}Br_3$: C, 36.30; H, 3.30; Br, 60.39. Found: C, 36.44; H, 3.35; Br, 60.70.

Brominations of 4 and 8 under Different Conditions. A. With Br_2.—A 1 *M* solution of Br_2 in $CHCl_3$ was added dropwise within 2 min to a stirred solution of 1.5 mmol of the unsaturated compound in 5 ml of the appropriate solvent. The additions were carried out at 0°, by using a 50 or 100% excess of Br_2 in the case of **4** and a 20% excess in the case of **8**. After the additions were complete, the reaction mixtures were stirred at room temperature for the times reported in Tables I and III, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The residues were directly analyzed by pmr.

B. With Br_2 in the Presence of Pyridine.—A 50 or 100% excess of a 1 *M* solution of Br_2 in $CHCl_3$ was added at 0° to a stirred $CHCl_3$ solution (5 ml) containing an equimolar amount of pyridine and 1.5 mmol of **4**. After stirring at room temperature for the times reported in Table I, the solution was washed with saturated aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated.

C. With $C_5H_5NBr_2$.—The solid brominating agent (50 or 100% excess in the case of **4**, 20% excess in that of **8**) was added to a solution of 1.5 mmol of the olefin in 5 ml of CCl_4. The mixture was stirred at room temperature for the times reported in Tables I and III, then treated as described in B.

D. With $C_5H_5NHBr_3$.—A 20% excess of the brominating agent was added to a solution of **8** (1.5 mmol) in dry AcOH (7 ml). After stirring for 2 hr at room temperature, the mixture was diluted with water and extracted with Et_2O; the organic layer was washed with water, saturated aqueous $NaHCO_3$, and water, dried, and evaporated.

The bromination mixtures arising from **4** were analyzed through their pmr spectra by integration of the signals at δ 4.32 (**6**, 1 H), 4.92 (**10**, 2 H), 5.10 (**5**, 1 H), 5.34 (**9**, 2 H), and 6.07 (**8**, 1 H); when appreciable amounts of **8** were present, the area of the signal of **5** was corrected for the presence of the overlapping signal of **8** at δ 5.18, by assuming that its area was equal to that of the vinylic proton signal at δ 6.07. The mixtures arising from the brominations of **8** were similarly analyzed on the basis of the signals at δ 4.92 and 5.34. The results are reported in Tables I and III.

Treatment of 5 with Br_2.—The required amount of a 1 *M* solution of Br_2 in $CHCl_3$ was added to solutions of 0.38 mmol of **5** in 1.5 ml of the appropriate solvent. The solutions were stored at room temperature in the dark for the times reported in Table II, then poured into saturated aqueous $NaHSO_3$. The organic layers were washed with water, dried, and evaporated.

(32) E. W. Garbisch, *J. Org. Chem.*, **26**, 4165 (1961).
(33) P. Pascal, "Nouveau Traité de Chimie Minérale," Vol. 16, Masson et Cie, Paris, 1960, p 340.
(34) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).
(35) L. F. Fieser and M. Fieser "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 967.
(36) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

The residues were analyzed by pmr. The results are reported in Table II.

Isomerization of 9 and 10. A.—A solution of 9 (0.40 g, 1.0 mmol) in $CHCl_3$ (3 ml) was treated with a 1 *M* solution of Br_2 in $CHCl_3$ (1 ml). After standing at room temperature in the dark for 100 hr, the solution was poured into saturated aqueous $NaHSO_3$; the organic layer was washed with water, dried, and evaporated. The pmr spectrum of the crude product showed the signals of 9 and 10 in the ratio 55:45; a third signal at δ 4.3 (doublet of doublets, W = 18 Hz) was also present (<5%). In contrast 10 was recovered unchanged after identical treatment with Br_2.

B.—A solution of 9 (0.40 g, 1.0 mmol) in Et_2O (3 ml) was treated with a 1 *M* solution of Br_2 in $CHCl_3$ (1 ml), left at room temperature in the dark for 100 hr, and worked up as described under A. The pmr spectrum of the crude reaction mixture indicated the presence of 9 and 10 in the ratio 73:27.

C.—A solution of 9 (0.40 g) in $CHCl_3$ (4 ml) was saturated with dry HBr and left at room temperature for 100 hr. After washing with water and saturated aqueous $NaHCO_3$, drying, and evaporation, unchanged 9 (ir and pmr) was recovered.

Treatment of 7 with HBr.—A solution of 7 (0.13 g) in $CHCl_3$ (5 ml) was saturated with dry HBr and left at room temperature for 3 hr. After washing with water, saturated aqueous $NaHCO_3$, and water, drying, and evaporation, a solid residue (0.14 g) was obtained, consisting of 5 accompanied by a small amount (~3%) of the isomer 6 (pmr). The dibromide 5 was recovered unchanged after standing for 15 hr in a $CHCl_3$ solution saturated with dry HBr.

Acknowledgments.—We wish to thank Professor G. Berti for helpful discussion. This work was supported in part by a grant from Consiglio Nazionale delle Ricerche.

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Stereochemistry of the Acid-Catalyzed Cyclization of 2-(3-Butenyl)-1-phenylcyclohexanols

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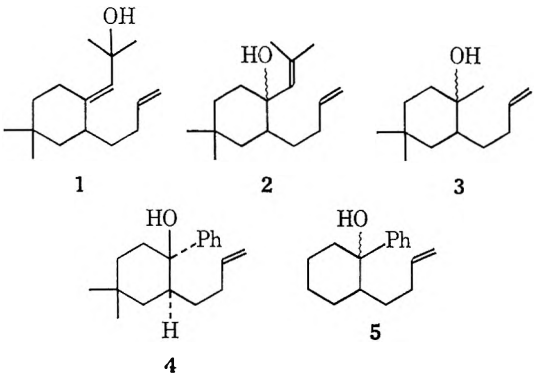
Acid-catalyzed cyclization of the phenyl-substituted alcohols 4 and 5 was shown to give cis-fused bicyclic formates with no detectable amount of trans-fused products. Since cyclization in deuterioformic acid led to no incorporation of deuterium into the cyclic product, intervention of cyclohexenyl intermediates cannot be involved in the reaction. This divergence from results obtained with other substituted cyclohexanols is considered to be a direct consequence of steric interactions involving the bulky and geometrically anisotropic phenyl group. The results show that the substituent at the cationic carbon in acid-catalyzed olefin cyclizations may significantly alter the mechanism and stereochemistry of acid-catalyzed olefin cyclizations.

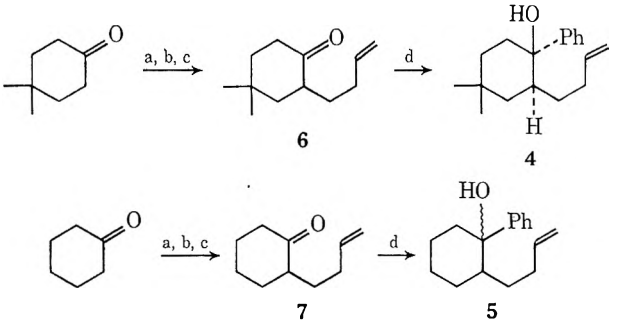
Olefinic cyclizations have recently become established as a key method for the construction of complex polycyclic compounds. In the course of a model study[1] on the stereochemistry and mechanisms of biogenetic-like olefin cyclizations, we have prepared and studied the acid-catalyzed cyclization of several 2-alkenylcyclohexane systems such as **1**, **2**, and **3**. We have now examined the cyclization of the related benzylic alcohols **4** and **5**. Although not directly relevant to biogenetic systems,[2] these cyclizations are of particular interest since the results are directly divergent from those obtained with previously studied systems.



The synthesis of the cyclization substrates is outlined in Chart I. Spectral and chromatographic data gave evidence for the presence of only one isomer in the product obtained from reaction of phenylmagnesium bromide with ketone **6**. By analogy with the reaction of 2-alkylcyclohexanones with Grignard reagents,[3] this

CHART I

SYNTHESIS OF CYCLIZATION ALCOHOLS[a]



[a] a, cyclohexylamine, $-H_2O$; b, EtMgBr; c, $CH_2{=}CH{-}CH_2CH_2X$; d, C_6H_5MgBr.

(1) Other papers in this series follow: (a) K. E. Harding, R. C. Ligon, T.-C. Wu, and L. Rode, *J. Amer. Chem. Soc.*, **94**, 6245 (1972); (b) K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973).

(2) Cyclization of alcohol 4 was considered of interest in relation to other biogenetic-like olefin cyclizations because the phenyl group might be expected to stabilize the intermediate cyclohexyl cation and thus reduce elimination–reprotonation reactions known to complicate many early attempts to examine cyclizations of cyclohexyl cations.[1b] However, it was recognized from the beginning that this alcohol was less satisfactory than alcohol 1 as a model compound because of the increased steric factors present with a phenyl substituent.

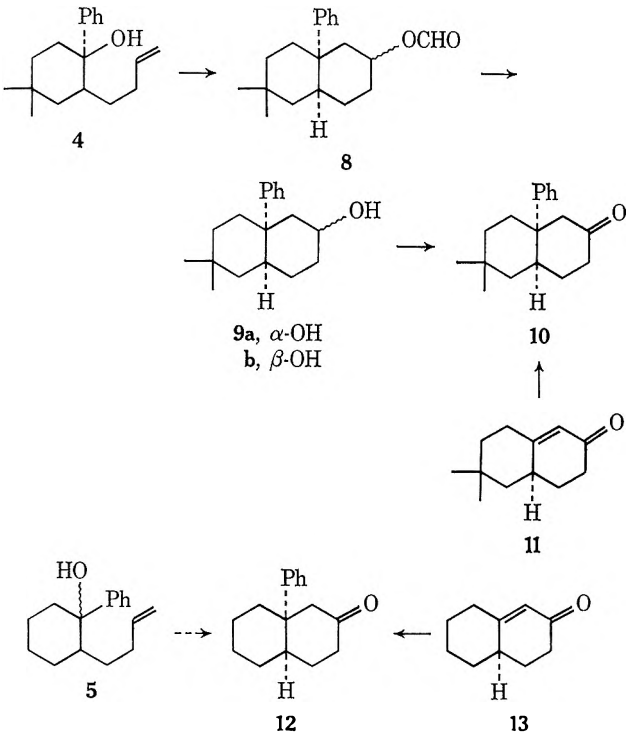
(3) J. R. Luderer, J. E. Woodall, and J. L. Pyle, *J. Org. Chem.*, **36**, 2909 (1971); J. Ficini and A. Maujean, *C. R. Acad. Sci., Ser. C*, **266**, 227 (1968).

alcohol has been assigned the trans structure 4.[4] Since alcohols 4 and 5 were tertiary benzylic alcohols, the crude alcohols were used directly in the cyclization studies.

Treatment of alcohol 4 with either 97% or anhydrous formic acid[7] at room temperature for 1 hr gave bicyclic formates (8) in high yield (Chart II). By thin

CHART II

CYCLIZATION REACTIONS AND COMPARISON COMPOUNDS



layer chromatography, the crude product was separated into a hydrocarbon fraction (15% yield) and a formate fraction (80% yield). The hydrocarbon fraction did not lead to additional formates upon retreatment with formic acid and was not investigated further. The nmr spectrum of the formate fraction indicated that it was a mixture. Three singlet absorptions for methyl groups were observed (δ 1.01, 1.00, and 0.96 ppm). Cleavage of the formate ester group with lithium aluminum hydride gave the corresponding alcohols (9) in quantitative yield. The product mixture was separated by preparative layer chromatography on silica gel into equal amounts of two isomeric alcohols. The nmr spectrum of the alcohol with lower R_f showed a single absorption at δ 0.99 ppm for the geminal dimethyl group and a multiplet at δ 3.24 ppm with a $W_{1/2}$ of 18 Hz. The spectrum of the other alcohol showed absorption at δ 0.93 and 0.98 ppm for the two methyl groups and a multiplet at δ 3.90 ppm with a $W_{1/2}$ of 10 Hz. Proof that these alcohols were isomeric only at the carbon bearing the hydroxyl group was obtained by Jones oxidation of the individual alcohols and of the mixture to give a single ketonic product (10).

Oxidation of the mixture of alcohols gave ketone 10 in a crude yield of 85%. Analysis by gc on two columns showed only one long retention time peak. No evidence for an isomeric ketone was obtained. Recrystallization from hexane gave pure ketone 10, mp 84–85°.

The structure and stereochemistry of this ketone were proven by comparison with material synthesized by an independent route. Addition of methyl vinyl ketone to the pyrrolidine enamine of 4,4-dimethylcyclohexanone gave the dimethyloctalone 11. Addition of phenylmagnesium bromide to octalone 11 in the presence of 1 mol % of cuprous bromide gave decalone 10, identical (melting point, ir, gc) with the ketone obtained from the cyclization reaction. The cis stereochemistry of phenyldecalone products obtained by conjugate addition to $\Delta^{1,9}$-2-octalone has been previously established.[8]

The mechanism of this cyclization of alcohol 4 was investigated by conducting the cyclization in deuterioformic acid.[9] A 50-mg sample of alcohol 4 was treated with 1 ml of deuterioformic acid at room temperature for 2 hr. The product was isolated and converted to crystalline ketone 10 in the normal manner. Mass spectral analysis of the ketone isolated from this cyclization showed no measurable incorporation of deuterium. This result proves that product formation is not occurring by deprotonation to a cyclohexenyl intermediate followed by reprotonation and cyclization.

Results from cyclization of alcohol 5 were consistent with those obtained with alcohol 4. Alcohol 5 consisted of both epimeric alcohols as evidenced by thin layer chromatography. This mixture was converted into bicyclic formates in high yield upon treatment with formic acid at room temperature. Hydrolysis and oxidation gave the phenyldecalone 12. No evidence was found for the isomeric trans product. Addition of phenylmagnesium bromide to $\Delta^{1,9}$-2-octalone gave authentic *cis*-9-phenyl-2-decalone (12), identical (gc, ir, melting point) with the decalone obtained from the cyclization reaction.

Discussion

The most notable features in the cyclizations of alcohols 4 and 5 are the essentially exclusive formation of cis-fused decalin products and the absence of cyclohexenes as intermediates in the reaction. Comparison of these results with results from cyclization of other 1-substituted cyclohexanols illustrates the influence of the phenyl substituent. Cyclizations of 1-methylcyclohexanols involve considerable elimination to cyclohexenyl intermediates.[10,11] For example, cyclization of alcohol 3 gives predominantly cis-fused products with predominant incorporation of one or more deuterium atoms.[12] In the cases of alcohols 1 and 2, where

(4) Spectral evidence consistent with this assignment has been obtained from nmr studies. The spectrum of alcohol 4 shows no methylene absorption below δ 2.0. An axial phenyl group on a cyclohexane has been shown to shift the C-2 and C-6 equatorial protons to significantly below δ 2.0 in several cases.[5,6] Use of lanthanide shift reagents did not simplify the spectrum sufficiently to allow unequivocal assignment of stereochemistry.

(5) P. J. Beeby and S. Sternhell, *Aust. J. Chem.*, **24**, 809 (1971).

(6) E. W. Garbisch, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).

(7) H. I. Schlesinger and A. W. Martin, *J. Amer. Chem. Soc.*, **36**, 1589 (1914).

(8) S. M. McElvain and D. C. Remy, *J. Amer. Chem. Soc.*, **82**, 3960 (1960).

(9) We thank Mr. David Bailey for conducting this experiment.

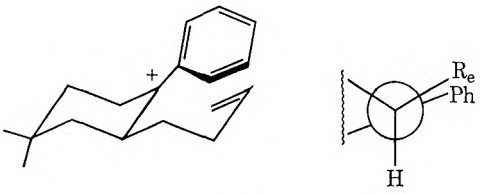
(10) P. T. Lansbury, *Accounts Chem. Res.*, **5**, 311 (1972), and references cited therein.

(11) D. C. Hibbit and R. P. Linstead, *J. Chem. Soc.*, 470 (1936); unpublished observations of W. S. Johnson and H. D. Doshan, see H. D. Doshan, Ph.D. Dissertation, Stanford University, 1968.

(12) K. Harding, R. C. Ligon, and W. D. Nash, unpublished observations.

elimination to cyclohexenyl intermediates is not observed, more than 90% of the cyclization product is trans fused.[1,12] This stereochemical divergence of the results obtained with alcohols **4** and **5** from results with other cyclohexanols eliminates their use as models for biogenetic-like olefin cyclizations.

Although the data available are insufficient to allow definitive rationalization for the stereochemistry of these cyclizations, the anomalous effect of the phenyl group may be considered to be a logical consequence of the steric requirements of the phenyl substituent. The normal conformation[13] for an intermediate cyclohexyl cation (**14**) would require either very large steric strain



14

of the $A^{1,3}$ type[11b] or rotation of the phenyl group resulting in loss of resonance stabilization of the catonic carbon. The unfavorable interactions present in structure **14** could be relieved in a number of ways. Conformational inversion to the alternate chair form,[14] conversion to a flexible conformation, flattening of the chair in cation **14** at C_2–C_1–C_6, or bending of the C_1–phenyl bond to give a nonplanar cationic carbon would result in such relief. Each of these conformations might be expected to lead to cis products preferentially.

In addition, the relative stabilities of the *cis*- and *trans*-9-phenyldecalin systems are not known, and the geometric anisotropy[15] of the phenyl group prevents use of *A* values to estimate stabilities in the manner used for methyldecalins. Thus the potential effect of the relative stabilities of the initially formed bicyclic cations upon the stereochemistry of the cyclization cannot be evaluated.

Experimental Section

Melting points were taken in open capillary tubes. Ir spectra were determined with a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were obtained with Varian Associates T-60 or HA-100 spectrometers operating at 60 or 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million downfield with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation.

4,4-Dimethylcyclohexanone.—This compound was prepared by hydrogenation of 4,4-dimethyl-2-cyclohexenone prepared according to the procedure of Dauben.[16] Thus, 30 g (0.242 mol) of 4,4-dimethyl-2-cyclohexenone, 3 g of 5% palladium-on-charcoal catalyst, and 600 ml of absolute ethanol were placed in a 1000-ml flask. The hydrogenation was conducted with a sloping-manifold atmospheric-pressure hydrogenator. After hydrogenation was complete, the hydrogenator was flushed with nitrogen and the catalyst was removed by filtration. About 25 ml of 10% hydrochloric acid was slowly added to the filtrate, followed by 1200 ml of water. The mixture was then extracted with ether. The combined ether extracts were washed several times with water, bicarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated to give 23.43 g (77% yield) of white crystals: mp 41–43° (reported mp 40–42°,[17] 38–41°[18]); ir (CCl_4) 1703 (carbonyl), 2950 ($-CH_3$), 1450 ($-CH_2-$), and the absence of 3020 and 800 cm^{-1} (–CH=CH–) peaks; nmr (CCl_4, 60 MHz) δ 1.1 (s, 6 H, geminal methyls), 1.5–1.85 (m, 4 H, methylenes), and 2.1–2.5 ppm (m, 4 H, α-methylenes).

2-(3-Butenyl)-4,4-dimethylcyclohexanone (6).—The procedure described by Stork and Dowd[19] for similar alkylations was slightly modified. Therefore, 1.8 g (8.7 mmol) of *N*-cyclohexyl-4,4-dimethylcyclohexylimine, prepared in the normal manner from 4,4-dimethylcyclohexanone, in 15 ml of tetrahydrofuran was added dropwise to a cold and stirred solution of 12 ml of 1 *M* ethylmagnesium bromide in tetrahydrofuran. The mixture was heated to reflux for 5 hr under nitrogen; then a solution of 1.9 g (9.1 mmol) of 3-butenyl tosylate,[20] prepared from 3-buten-1-ol,[21] in 15 ml of tetrahydrofuran was added dropwise. The reaction mixture was refluxed overnight and the imine salts were decomposed by dropwise addition of 9 ml of 10% hydrochloric acid solution and sufficient water to dissolve the precipitate. The aqueous solution was extracted with ether. The combined organic phases were washed (acid, bicarbonate, and brine), dried over anhydrous sodium sulfate, concentrated, and evaporatively distilled (0.18 mm, 86°) to give 1.2 g (77% yield) of ketone **6**: ir (film) 1703 (carbonyl), 1628, 986, and 910 cm^{-1} ($-CH=CH_2$); nmr (CCl_4, 60 MHz) δ 1.0 (s, 3 H, methyl), 1.2 (s, 3 H, methyl), 4.6–5.2 (m, 2 H, $-CH=CH_2$), and 5.4–6.0 ppm (m, 1 H, $-CH=CH_2$).

The ketone was about 95% pure with the presence of a small amount of unalkylated ketone shown by gc (Carbowax, 178°). The oxime was prepared and recrystallized twice as white microcrystals from ethanol–water solution, mp 83–83.5°.

Anal. Calcd for $C_{12}H_{21}ON$: C, 73.78; H, 10.84; N, 7.17. Found: C, 73.75; H, 10.78; N, 7.03.

1-Phenyl-2-(3-butenyl)-4,4-dimethylcyclohexanol (4).—A solution of 200 mg (1.11 mmol) of ketone **6** in 2 ml of anhydrous ether was added dropwise to 10 ml of a stirred 1 *M* solution of phenylmagnesium bromide in tetrahydrofuran. The solution was stirred under nitrogen for 11 hr, poured into water, and extracted with ether. The combined extracts were washed (water, bicarbonate, and brine), dried over magnesium sulfate, and concentrated to give 351 mg of a yellow oil. Chromatography over 12 g of silica gel to remove biphenyl gave 287 mg (100% crude yield) of alcohol **4**: ir (film) 3430 cm^{-1} (OH); nmr (CCl_4, 100 MHz) δ 0.99 and 1.01 (singlets, geminal methyls), 4.65–4.95 (m, 2 H, $-CH=CH_2$), 5.25–5.80 (m, 1 H, $-CH=CH_2$), and 7.28 ppm (m, 5 H, phenyl).

All spectral and chromatographic evidence for alcohol **4** indicated that it was a single isomer.

Cyclization of Alcohol 4.—A 200-mg sample (0.775 mmol) of alcohol **4** was dissolved in 30 ml of 97% formic acid and stirred at room temperature for 1 hr. The solution was poured into 150 ml of water and extracted three times with 50 ml of ether. The ether extracts were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated to yield 226 mg of a yellow oil. Preparative tlc gave 28 mg of hydrocarbons and 174 mg (79% yield) of formate esters. The nmr spectrum (CCl_4, 100 MHz) exhibited three distinct methyl signals as singlets at δ 0.87, 0.98, and 1.02 ppm.

A 100-mg sample of the hydrocarbon fractions obtained from several of the above cyclizations was retreated with 15 ml of 97% formic acid at room temperature for 24 hr. Analysis by tlc and nmr indicated that no significant conversion to nonhydrocarbon products occurred.

A 200-mg sample of the formate ester fraction was dissolved in anhydrous ether and added to an excess of a stirred solution of

(13) (a) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968); (b) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(14) This conformation is a very probable structure for the cationic intermediate in the cyclization of alcohol **5**. However, in the case of alcohol **4**, this conformation would contain a quite unfavorable 1,3-diaxial interaction between the butenyl side chain and the axial C-4 methyl.

(15) N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.*, 3259 (1971); S. Sicsic and Z. Welvart, *Chem. Commun.*, 499 (1966).

(16) W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).

(17) R. F. Miller and R. Adams, *J. Amer. Chem. Soc.*, **58**, 787 (1936).

(18) E. B. Reid and T. E. Gompf, *J. Org. Chem.*, **18**, 661 (1953).

(19) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(20) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 3773 (1964).

(21) R. B. Kinnel, B. B. Molloy, D. W. Graham, and K. E. Harding, *Org. Prep. Proced. Int.*, **4**, 27 (1972).

lithium aluminum hydride in ether. The solution was stirred at room temperature for 30 min. Isolation of product in the normal manner gave 180 mg (100% crude yield) of alcoholic product. Preparative tlc gave 68 mg of alcohol **9a**, nmr (CCl_4, 60 MHz) δ 0.87 (s, geminal methyl), 0.97 (s, geminal methyl), 3.79 (m, $W_{1/2}$ = 18 Hz, 1H, -CHO-), and 7.22 ppm (m, 5 H, phenyl), and 73 mg of alcohol **9b**, δ 0.98 (s, geminal methyls), 3.47 (m, $W_{1/2}$ = 18 Hz, 1 H, -CHO-), and 7.22 ppm (m, 5 H, phenyl).

A 100-mg sample of the crude alcohol mixture was dissolved in 5 ml of acetone and treated with an excess of Jones reagent.[22] The resulting product (85 mg) was subjected to evaporative distillation (0.07 mm, 130°) to give 80 mg (81% yield) of ketone **10**. Analysis by gc indicated the presence of only one ketonic component. Recrystallization from hexane gave pure ketone **10**: mp 85–86°; ir (KBr) 1690 cm^{-1} (carbonyl); nmr (CCl_4, 60 MHz) δ 1.05 and 1.15 (singlets, geminal methyls).

Anal. Calcd for $C_{18}H_{24}O$: C, 84.76; H, 9.02. Found: C, 84.76; H, 9.10.

Oxidation of alcohols **9a** and **9b** separately gave only ketone **10** in each case. The infrared spectrum of this ketone was essentially identical with the corresponding spectrum of authentic *cis*-6,6-dimethyl-9-phenyl-2-decalone, prepared as described below.

Cyclization of alcohol **4** in anhydrous formic acid[7] gave results indistinguishable from those described above using 97% formic acid.

Cyclization of Alcohol 4 in Deuterioformic Acid.—A 50-mg sample of alcohol **4** was treated with 1 ml of deuterioformic acid (98%, Merck Sharp and Dohme) for 2 hr at room temperature. Work-up as in the above cyclizations gave 50 mg of crude product. The product was treated with lithium aluminum hydride and then with Jones reagent to convert the product to ketone **10**. The mass spectrum of this ketone was essentially identical with that of authentic ketone **10**. In particular, the ratios of peaks at *m/e* 256 (P^+) and 257 ($P^+ + 1$) were indistinguishable.

2-(3-Butenyl)cyclohexanone (7).—The procedure described for the preparation of ketone **6** was used. Thus a solution of 5.37 g (0.03 mol) of *N*-cyclohexylcyclohexylimine, prepared in the normal manner from cyclohexanone, in 10 ml of tetrahydrofuran was added dropwise to a cold and stirred solution of 30 ml of 1.0 *M* ethylmagnesium bromide in tetrahydrofuran. The mixture was heated at reflux for 5 hr under nitrogen; then a solution of 4.05 g (0.03 mol) of 4-bromo-1-butene in 10 ml of tetrahydrofuran was added dropwise. The reaction mixture was refluxed overnight, and then the imine salts were decomposed by dropwise addition of 30 ml of 10% hydrochloric acid solution and sufficient water to dissolve the precipitate. The aqueous solution was extracted with ether. The combined organic phases were washed (acid, bicarbonate, and brine), dried over anhydrous sodium sulfate, concentrated, and distilled through a short-path apparatus to give 3.37 g (73% yield) of the desired ketone as a colorless liquid: bp 95–105° (0.3 mm) [lit.[11] bp 41–42° (0.007 mm)]; ir (film) 1703 (carbonyl group), 1628, 986, and 910 cm^{-1} (-CH=CH_2); nmr (CCl_4, 60 MHz) δ 0.7–2.58 (m, 13 H), 4.65–5.25 (m, 2 H, -CH=CH_2), and 5.3–6.3 ppm (m, 1 H, -CH=CH_2). The material was 98% pure by gc (Carbowax, 140°).

1-Phenyl-2-(3-butenyl)cyclohexanol (5).—A solution of 1.0 g (6.60 mmol) of 2-(3-butenyl)cyclohexanone in 10 ml of tetrahydrofuran was added dropwise into a stirred solution of 33 ml of 1 *M* phenylmagnesium bromide in tetrahydrofuran under nitrogen. After the mixture was stirred at room temperature for 6 hr, it was poured into ice-cold water and allowed to stand for 1.5 hr. The mixture was extracted with ether, and the ether extracts were washed (bicarbonate and brine), dried over magnesium sulfate, and concentrated. The biphenyl was removed by column chromatography to give 1.36 g (90% yield) of alcohol **5**: ir (film) 3400 (broad, -OH), 3030, 980, 910 (-CH=CH_2), 1580, 1490, 760, and 705 cm^{-1} (-C_6H_5); nmr (CCl_4, 60 MHz) δ 4.5–5.0 (m, 2 H, -CH=CH_2), 5.1–5.9 (m, 1 H, -CH=CH_2), and 7.30 ppm (m, 5 H, aromatic H).

Cyclization of Alcohol 5.—A 0.93-g (4.04 mmol) sample of alcohol **5** was treated at room temperature with 100 ml of 97% formic acid for 5 hr. The mixture was poured into water and extracted with ether. The combined ether extracts were washed (water, bicarbonate, and brine), dried over sodium sulfate, and concentrated to give 1.04 g (100% yield) of cyclic formates: ir (film) 1720 cm^{-1} (C=O).

The crude cyclic product was converted by formate ester cleavage and Jones oxidation into the corresponding ketone in the same manner as described for the cyclization of alcohol **4**. Analysis of the product by gc showed a single ketonic component identical in retention time with authentic *cis*-9-phenyl-2-decalone. Recrystallization of the ketone from hexane gave pure ketone **12**: mp 68–69°; ir (film) 1703 cm^{-1} (C=O). The infrared spectrum of this ketone was essentially identical with the spectrum of authentic *cis*-9-phenyl-2-decalone, prepared as described below.

6,6-Dimethyl-$\Delta^{1,9}$-2-octalone (11).—A solution of methyl vinyl ketone (1.42 g, 0.021 mol) in 20 ml of dry benzene was added to a solution of 2.62 g (0.0146 mol) of 1-pyrolidino-4,4-dimethylcyclohexene [bp 86–89° (1.4 mm)] prepared in the normal manner from pyrolidine and 4,4-dimethylcyclohexanone. The mixture was refluxed for 4 hr; 70 ml of water was added, and refluxing was continued for an additional 16 hr. The cooled reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed (3 *N* HCl, bicarbonate, and brine), dried over magnesium sulfate, concentrated, and evaporatively distilled (0.35 mm, 100°) to give 1.18 g (44% yield) of octalone **11**. Recrystallization gave pure octalone **11** as fine transparent needles: mp 72.5–73°; ir (CCl_4) 1670 (C=O) and 1620 cm^{-1} (C=C); nmr (CCl_4, 60 MHz) δ 0.96 and 1.06 (singlets, geminal methyls) and 5.72 ppm (s, vinyl H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.55; H, 10.05.

6,6-Dimethyl-9-phenyl-2-decalone (10).—A solution of 0.78 g (4.23 mmol) of 6,6-dimethyl-$\Delta^{1,9}$-2-octalone in 10 ml of anhydrous ether was added dropwise to 4.5 ml of an ice cold, stirred solution of 1 *M* phenylmagnesium bromide in ether containing 0.02 g of cuprous bromide. The reaction mixture was kept at 0° for 30 min, brought to room temperature, and stirred for an additional 1 hr. The reaction mixture was poured onto an ice–acetic acid mixture and extracted with ether. The combined ether extracts were washed (bicarbonate and brine), dried, concentrated, and distilled. Purification by thin layer chromatography and recrystallization gave pure decalone **10**: mp 85–86°; ir (CCl_4) 1705 cm^{-1} (C=O); nmr (CCl_4, 60 MHz) δ 1.05 and 1.15 (singlets, geminal methyls) and 7.15 ppm (m, 5 H, phenyl).

9-Phenyl-2-decalone (12).—The procedure of McElvain and Remy[8] was modified slightly. A solution of 0.5 g (3.3 mmol) of $\Delta^{1,9}$-2-octalone (**13**)[23,24] in 10 ml of anhydrous ether was added dropwise to 4 ml of an ice-cold, stirred 1 *M* solution of phenylmagnesium bromide in ether containing 0.02 g of cuprous bromide. The reaction mixture was kept at 0° for 30 min, brought to room temperature for 1 hr, poured onto an ice–acetic acid mixture, and extracted with ether. The combined ether extracts were washed (bicarbonate and brine), concentrated, and distilled. Purification by tlc and recrystallization gave pure decalone **12**: mp 68–68.5° (lit.[8] mp 68–69°); ir (film) 1703 cm^{-1} (C=O).

Acknowledgment.—We thank the Robert A. Welch Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Support by PHS Research Grant AM 15157 from the National Institute of Arthritis and Metabolic Diseases is also gratefully acknowledged. This research constitutes partial fulfillment of the M.S. degree requirements of C. Tseng.

Registry No.—**4**, 41163-76-2; **5**, 41171-98-6; **6**, 38481-13-9; **6** oxime, 38481-22-0; **7**, 16178-83-9; **9a**, 41163-77-3; **9b**, 41163-78-4; **10**, 41163-79-5; **11**, 4044-27-3; **12**, 41163-80-8; 4,4-dimethylcyclohexanone, 4255-62-3; methyl vinyl ketone, 78-94-4; 1-pyrrolidino-4,4-dimethyl-1-cyclohexene, 41172-02-5.

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(24) We thank Professor P. S. Mariano and Mr. E. Krochmal, Texas A & M University, for providing us with a sample of this octalone.

A General Route to 2,3-Diacyl-1,4-dihydro 1,4-Disubstituted 1,4-Epoxynaphthalenes[1] and 1,4-Disubstituted 2,3-Naphthalic Anhydrides[1]

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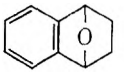
Received April 17, 1973

Treatment of 3,4-dicarbethoxy-2,5-dimethylfuran with benzyne generated from anthranilic acid afforded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3a**) in 77% yield. Hydrogenation yielded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**4**), which on treatment with concentrated sulfuric acid produced 1,4-dimethyl-2,3-naphthalic anhydride (**5**) in 82% yield. Similarly, 3,4-diacetyl-2,5-dimethylfuran yielded 3,4-diacetyl-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3b**) in 71% yield. On heating 3,6-dimethylphthalic anhydride with urea at 150°, 3,6-dimethylphthalimide was formed in 90% yield. Under similar conditions **5** was recovered unchanged. Heating **5** with urea in refluxing *N*-methylpyrrolidone for 4 hr afforded 1,4-dimethyl-2,3-naphthalimide (**7**) in 35% yield Treatment of 3,6-dimethylphthalimide with potassium hypochlorite yielded (87%) 2-amino-3,6-dimethylbenzoic acid but **7** was unchanged under similar conditions.

A number of naphthalene derivatives have been prepared by aromatization of derivatives of 1,4-epoxy-1,2,3,4-tetrahydro (**1**) and 1,4-epoxy-1,4-dihydronaphthalenes (**2**).[2-5] Derivatives of **1** are prepared either by



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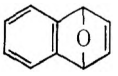
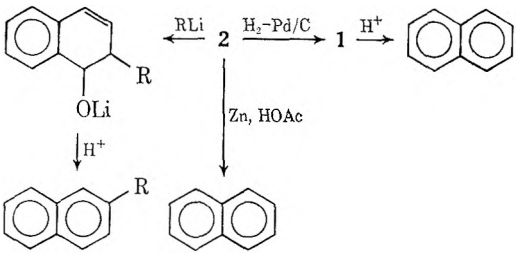


2

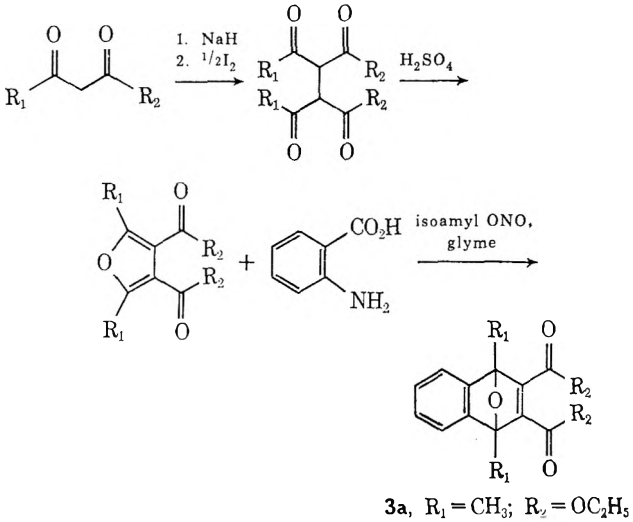
reaction of a dienophile with an isobenzofuran[2,6-8] or by reduction of derivatives of **2**. Aromatization is accomplished by acid-catalyzed dehydration of the adduct.[3] This method is of particular advantage for the preparation of 1,4-diarylnaphthalenes, since the required isobenzofurans are stable and readily accessible.[9] Unsubstituted and 1,4-dialkylisobenzofurans have only recently been isolated[10-12] and owing to their instability have not been used extensively as preparative intermediates.

Derivatives of **2** are generally prepared by trapping benzyne with furans.[3-6,13] Aromatization of these adducts is accomplished by catalytic reduction to derivatives of **1** followed by dehydration,[3] by direct deoxygenation with metals,[13-15] or by addition of an organometallic followed by dehydration.[4]



We have found an efficient and general route to 2,3-diacyl-1,4-dihydro 1,4-disubstituted 1,4-epoxynaphthalenes *via* addition of benzyne to 3,4-diacyl 2,5-disubstituted furans. The necessary furans can be prepared in good yield by dimerization of readily available 1,3 diketones or keto esters followed by dehydration.[16] Generation of benzyne by decomposition of anthranilic acid with isoamyl nitrite in refluxing 1,2-dimethoxyethane in the presence of the furans affords benzyne adducts in good yield (see Experimental Section). The general scheme is illustrated in Scheme I. Adducts **3a** and **3b** were prepared in 58 and 52% overall yields by this process starting with ethyl acetoacetate and acetylacetone. Reduction of **3a** in ethyl acetate with H_2–Pd/C afforded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**4**) in quantitative yield. Treatment of **4** with concentrated sulfuric acid

SCHEME I



3a, $R_1 = CH_3$; $R_2 = OC_2H_5$
b, $R_1 = R_2 = CH_3$

(1) This work formed part of the Ph.D. Thesis of James A. Cella, The Ohio State University, 1973.

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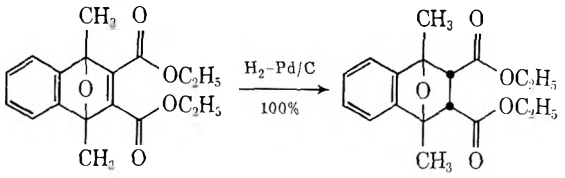

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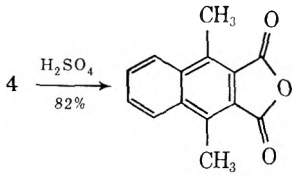
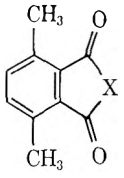
produced 1,4-dimethyl-2,3-naphthalic anhydride (**5**) in 82% yield.

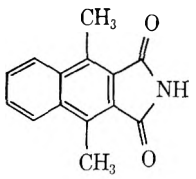


5

It is interesting to compare the stability of the ring system in **5** with that of 3,6-dimethylphthalic anhydride (**6a**). Anhydride **6a** reacted with 2 equiv of urea in 0.5 hr at 150° to produce imide **6b** in 90% yield. Under identical conditions **7** was recovered essentially



6a, X = O
b, X = NH



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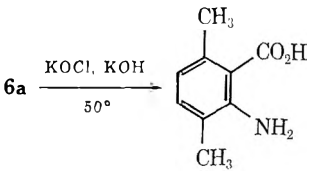
unchanged after 1 hr. Reaction of **5** with urea required prolonged treatment in refluxing *N*-methyl-2-pyrrolidone (bp 200°) and produced **7** in 35% yield. No effort was made to optimize this yield. Moreover, **6b** was readily converted in 87% yield to 2-amino-3,6-dimethylbenzoic acid (**8**), on treatment with aqueous



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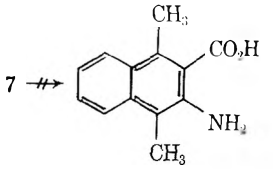
potassium hypochlorite and base at 50°, whereas **7** was recovered unchanged after similar treatment.

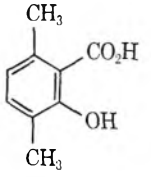


This lack of reactivity is undoubtedly due to an increased steric effect of the methyl groups caused by the buttressing effect of the peri hydrogens.[17]

Interestingly, attempted conversion of amino acid **8** to 2-iodo-3,6-dimethylbenzoic acid by diazotization followed by treatment with potassium iodide gave only 3,6-dimethylsalicyclic acid (**9**) in 94% yield.

(17) F. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 552.

The efficient production of **9** in this reaction is probably due to hydrolysis of the β-lactone **10**. Intermediates



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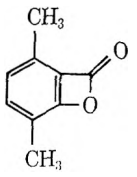

10

of this type have been postulated in similar systems.[18] Formation of **10** is facilitated in this system by the steric effect of the methyl group, which forces the carboxyl group into a good conformation for participation in the loss of nitrogen.

Experimental Section

General.—All melting points and boiling points are uncorrected. Microanalyses were performed by M. H. W. Laboratories, Garden City, Mich. Ir spectra were recorded on a Perkin-Elmer Infracord using sodium chloride disks or potassium bromide pellets. Nmr spectra were recorded on an A-60 instrument, Varian Associates, Palo Alto, Calif., and are reported as δ units relative to tetramethylsilane (TMS) as an internal standard. The terms "usual work-up" or "worked up as usual" mean that, after the organic solution was washed with 3 *N* HCl or 3 *N* K_2CO_3, water, and saturated salt solution, it was dried by passage through a cone of $MgSO_4$ and the solvents were removed on a rotary evaporator.

Materials.—1,2-Dimethoxyethane was distilled from calcium hydride and stored over molecular sieves. Isoamyl nitrite and anthranilic acid were obtained from the Aldrich Co. Acetylacetone was obtained from Chemical Samples. Sodium hydride was obtained as a 50% mineral oil dispersion from Ventron and was washed with pentane prior to use.

Diethyl α,β-Diacetylsuccinate.[19]—To a suspension of 21 g (0.5 mol) of sodium hydride in 250 ml of 1:1 dimethoxyethane–ether was added 65 g (0.5 mol) of ethyl acetoacetate. After 1 hr, a solution of 63.5 g (0.25 mol) of iodine in 150 ml of dimethoxyethane was added and the resulting mixture was stirred for 0.5 hr. The mixture was diluted with water and the phases were separated. Evaporation of the solvent afforded 58.0 g (90%) of diethyl α,β-diacetylsuccinate: ir (neat) 5.79 μ (1727 cm^{-1}) (C=O); nmr (CCl_4) δ 4.36 (s, 2, $COCHCO$), 4.20 (q, 4, OCH_2CH_3), 2.38 (s, 6, $COCH_3$), and 1.27 (t, 6, OCH_2CH_3). This material was used directly in the next step.

3,4-Dicarbethoxy-2,5-dimethylfuran.[20]—Diethyl α,β-diacetylsuccinate (9.7 g, 37.6 mmol) was dissolved in 100 ml of cold concentrated sulfuric acid. After 5 min, the solution was poured on ice and the resulting mixture was extracted three times with ether. Combined ether extracts were worked up in the usual way to yield 7.6 g (84%) of 2,5-dimethyl-3,4-dicarbethoxyfuran: bp 127–130° (1.0 mm); ir (neat) 5.80 μ (1724 cm^{-1}) (C=O); nmr (CCl_4) δ 4.28 (q, 4, OCH_2CH_3), 2.44 (s, 6, $ArCH_3$), and 1.32 (t, 6, OCH_2CH_3); mass spectrum *m/e* 240.

Tetraacetylethane.—To a suspension of 21.0 g (0.5 mol) of sodium hydride in 400 ml of ether was added 50 g (0.5 mol) of acetylacetone. After 1 hr, 65 g (0.25 mol) of iodine in 200 ml of ether was added and the mixture was stirred for 1 hr. After addition of water, the mixture was filtered to yield 39.5 g of tetraacetylethane. Concentration of the ether afforded an additional 2.3 g. The crude material (84.5%) was of sufficient purity to be carried on to the next step. Recrystallization from ethanol afforded pure tetraacetylethane, mp 191–194° (lit.[16] mp 191°).

3,4-Diacetyl-2,5-dimethylfuran.—Tetraacetylethane (25 g, 0.13 mol) was added slowly with stirring to 100 ml of cold concentrated sulfuric acid. When all of the solid dissolved, the mixture was poured into ice water and filtered to yield 19.4 g (85.5%) of 2,5-dimethyl-3,4-diacetylfuran as long, fluffy needles, mp 58.5–60° (lit.[16] mp 63°).

(18) See ref 13, p 76.
(19) J. A. Gardner and H. N. Rydon, *J. Chem. Soc.*, 45 (1938).
(20) L. Knorr, *Ber.*, **17**, 2866 (1884).

Addition of Benzyne to Furans.—Solutions of 38 g (277 mmol) of anthranilic acid and 38 ml (excess) of isoamyl nitrite each in 100 ml of glyme were added simultaneously in 1.5 hr to a refluxing solution of 155 mmol of the appropriate furan in 300 ml of glyme. After addition was complete, the mixture was refluxed for 0.5 hr and then allowed to cool. The cooled solution was diluted with 300 ml of ether and stirred with 3 *N* KOH. The phases were separated and the aqueous phase was extracted with ether. The combined ether extracts were worked up in the usual way to yield the appropriate dihydronaphthalenes: 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3a**), 77% yield, bp 140–145° (0.2 mm), mp 51–52°, ir (KBr) 5.81 (1721) (C=O) and 6.13 μ (1631 cm^{-1}) (C=O), nmr (CCl_4) δ 7.10 (m, 4, ArH), 4.11 (q, 4, OCH_2CH_3), 1.88 (s, 6, $ArCH_3$), and 1.19 (t, 6, OCH_2CH_3), mass spectrum *m/e* 316; and 3,4-diacetyl-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3b**), 71% yield, mp 101–102°, ir (KBr) 5.89 (1698) (C=O) and 6.03 μ (1658 cm^{-1}) (C=C), nmr ($CDCl_3$) δ 7.10 (m, 4, ArH), 2.12 (s, 6, $COCH_3$), and 1.86 (s, 6, $ArCH_3$), mass spectrum *m/e* 256.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.4; H, 6.3. Found: C, 68.2; H, 6.2.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3. Found: C, 75.3; H, 6.2.

2,3-Dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (4).—A mixture of 4.8 g (15 mmol) of **3a** and 0.3 g of 10% palladium on carbon (Engelhardt) in 125 ml of ethyl acetate was shaken in a Parr hydrogenation apparatus (55 psi). The theoretical amount of hydrogen was consumed in 5 min. The contents were filtered through Celite and the solvent was evaporated to yield 4.9 g (100%) of **4**: mp 67–68°; ir (KBr) 5.86 μ (1706 cm^{-1}) (C=O); nmr (CCl_4) δ 7.10 (s, 4, ArH), 3.78 (q, 4, OCH_2CH_3), 3.20 (s, 2, $CHCO_2C_2H_5$), 1.76 (s, 6, $ArCH_3$), and 1.00 (t, 6, OCH_2CH_3); mass spectrum *m/e* 318.

1,4-Dimethyl-2,3-naphthalic Anhydride (5).—Crude **4** (5.0 g, 15.7 mmol) was stirred with 100 ml of concentrated sulfuric acid chilled in an ice bath. The mixture was heated slightly until most of the solids dissolved and was then poured on crushed ice. The crude product was isolated by filtration and recrystallized from acetone. This process afforded in three crops 2.95 g (82%) of 1,4-dimethyl-2,3-naphthalic anhydride: mp 283–284°; ir (KBr) 5.50 and 5.68 μ (1818 and 1761 cm^{-1}) (C=O); mass spectrum *m/e* 226.

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.5; H, 4.4. Found: C, 74.7; H, 4.3.

3,6-Dimethylphthalimide (6b).[21]—An intimate mixture of 1.90 g of 3,6-dimethylphthalic anhydride and 1.4 g of urea was heated in an oil bath at 150° for 30 min. After a vigorous gas evolution, the mixture became solid. The solid was washed with water to yield 1.72 g (90%) of **6b**, mp 218–220°, mass spectrum *m/e* 175.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.6; H, 5.2. Found: C, 68.3; H, 5.3.

On similar treatment of 1.0 g of **5** with 0.55 g of urea for 60 min, no **7** was obtained.

(21) This experiment was performed by Mr. John Daniel.

1,4-Dimethyl-2,3-naphthalimide (7).—A mixture of 10.0 g (44 mmol) of 1,4-dimethyl-2,3-naphthalic anhydride and 5.0 g (excess) of urea was refluxed in 25 ml of *N*-methyl-2-pyrrolidone for 4 hr. The cooled mixture was poured on ice and filtered. The solids were recrystallized from *N*-methyl-2-pyrrolidone to yield 3.5 g (35%) of **7**: mp >325°; ir (KBr) 5.71 and 5.88 μ (1754 and 1701 cm^{-1}) (C=O); mass spectrum *m/e* 225.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.6; H, 4.9. Found: C, 74.9; H, 4.8.

2-Amino-3,6-dimethylbenzoic Acid.—A mixture of 1.3 g of calcium hypochlorite (Sentry, 65%), 0.9 g of potassium carbonate, and 0.25 g of potassium hydroxide in 50 ml of water was shaken for 5 min and then filtered. The filtrate contained *ca.* 12 mmol of potassium hypochlorite.[22] An additional 2.0 g (50 mmol) of potassium hydroxide was added and the resulting solution was stirred while 1.6 g (9.1 mmol) of 3,6-dimethylphthalimide was added. The phthalimide dissolved rapidly and the resulting solution was slowly heated to 50°. After 30 min, the mixture was acidified with a slight excess of acetic acid. The resulting solution was extracted with several portions of ether and combined extracts were worked up as usual to yield 1.3 g (87%) of 2-amino-3,6-dimethylbenzoic acid, mp 122–123°, mass spectrum *m/e* 165.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7. Found: C, 65.3; H, 6.5.

In a similar experiment **5** was recovered unchanged.[21]

Diazotization of 8.—A solution of 0.75 g (11 mmol) of sodium nitrite in 25 ml of water was added slowly to an ice-chilled mixture of 5 ml of concentrated hydrochloric acid and 1.65 g (10 mmol) of **8** in 25 ml of water. Addition was continued at 0–5° until a positive starch iodide test was obtained. To this mixture was added a solution of 1.8 g (11 mmol) of potassium iodide in 10 ml of water. Nitrogen evolved rapidly and the mixture was warmed slightly until no more gas evolution was observed. The mixture was transferred to a separatory funnel and extracted with five 100-ml portions of ether–benzene. The combined organic extracts produced after work-up 1.5 g (94%) of 3,6-dimethylsalicylic acid (**4**), mp 196–198° after recrystallization from benzene.[23]

Acknowledgment.—This work was supported by Grant 12554 of the National Science Foundation.

Registry No.—**3a**, 41174-77-0; **3b**, 41174-78-1; **4**, 41174-79-2; **5**, 40682-58-4; **6b**, 15540-88-2; **7**, 41174-82-7; **8**, 15540-91-7; diethyl α,β-diacetylsuccinate, 2049-86-7; 3,4-dicarbethoxy-2,5-dimethylfuran, 19434-69-6; tetraacetylethane, 5027-32-7; 3,4-diacetyl-2,5-dimethylfuran, 10599-72-1; anthranilic acid, 118-92-3; isoamyl nitrite, 110-46-3; 3,6-dimethylphthalic anhydride, 5463-50-3; urea, 57-13-6.

(22) M. S. Newman and H. L. Holmes, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 428.

(23) J. E. Joachim de Luna, French Patent 940,846 (Dec 24, 1948).

Mesoionic Compounds. XXIII. The *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide System[1]

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Reaction of 4,6-dimethyl-2-methylaminopyrimidine with carbon suboxide gave *anhydro*-2-hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide, a new fused-ring, heteroaromatic betaine containing a "masked" 1,4-dipolar system. With dimethyl acetylenedicarboxylate, dicyanoacetylene, and dibenzoylacetylene, 1,4-dipolar cycloaddition occurred with the formation of the appropriate 8,9-disubstituted pyrido[1,2-*a*]-pyrimidin-6-one system. Olefinic dipolarophiles such as *N*-phenylmaleimide, maleic anhydride, and tetracyanoethylene did not form cycloaddition products with the betaine.

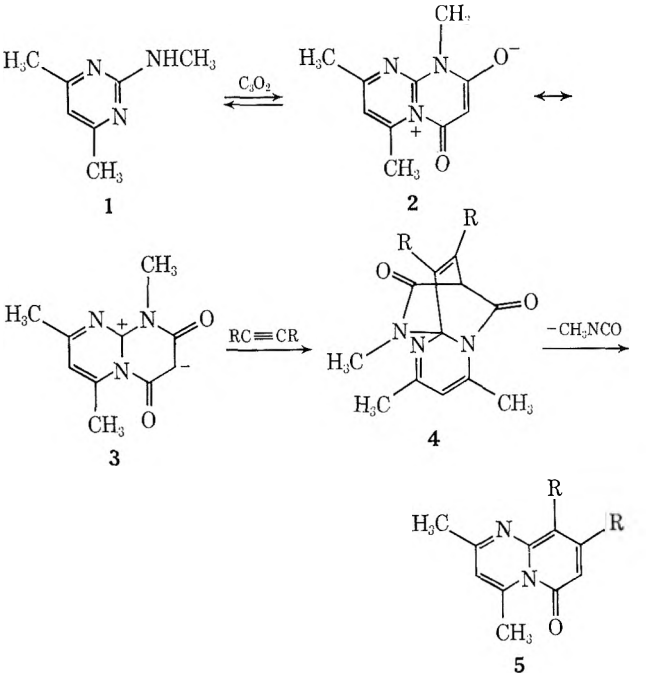
In recent publications it has been shown that N,N′-disubstituted amidines[2] and 2-methylaminopyridines[3] undergo ready reaction with carbon suboxide, forming in excellent yields heteroaromatic betaines such as *anhydro*-4-hydroxy-6-oxo 1,2,3-trisubstituted pyrimidinium hydroxide and *anhydro*-2-hydroxy-4-oxo-1-methylpyrido[1,2-*a*]pyrimidinium hydroxide, respectively. These betaines contain "masked" 1,4 dipoles and undergo cycloaddition with acetylenic dipolarophiles, the former giving substituted 2-pyridones and the latter substituted 4*H*-pyrido[1,2-*a*]pyrid-4-ones. In both cases methyl (or phenyl) isocyanate is eliminated from the initial 1:1 cycloadduct.

Carbon suboxide has also been found to undergo reaction with various N-substituted thioamides[4] with varying degrees of success. In these analogous anhydro 2,3-disubstituted 4-hydroxy-6-oxo-1,3-thiazinium hydroxides sulfur replaces one of the nitrogens of the above pyrimidinium betaines with an accompanying decrease in the stability of the ring system.

These amidines and the thioamides may be represented by a general structural formula RC(=X)ZH, and it is of particular interest to evaluate the scope and limitations of the possible variations of R, X, and Z. Such a series of reactions with carbon suboxide will provide several heteroaromatic betaines anticipated to have interesting chemical properties and, as part of this study, this communication describes the synthesis and characterization of a new fused-ring heteroaromatic betaine, *anhydro*-2-hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide (**2**).

4,6-Dimethyl-2-methylaminopyrimidine[5] (**1**), prepared from 4,6-dimethyl-2-pyrimidone[6] *via* the 2-chloro compound[7] and methylamine, underwent ready reaction with carbon suboxide in anhydrous ether, forming **2** in 88% yield. Analytical and mass spectral data showed that a 1:1 adduct had been formed and infrared data indicated the presence of two carbonyl groups (ν_{CO} 1740, 1670 cm^{-1}). The nmr spectrum showed that in addition to the three methyl groups there were only two singlet hydrogens to be considered. Their chemical shifts, τ 5.34 and 2.80, suggested that one was at a center of high electron density. These data are consistent with structure **2** for the adduct. Hydrolysis of **2** with water gave mainly 4,6-dimethyl-2-methylaminopyrimidine (**1**), the use of saturated sodium bicarbonate or 10% sodium hydroxide solution resulting in further degradation of the pyrimidine ring.

The betaine **2** is a resonance-stabilized, heteroaromatic system, structure **2a** representing a 1,4-dipolar contributor to the system. Acetylenic dipolarophiles such as dimethyl acetylenedicarboxylate, dicyanoacetylene, and dibenzoylacetylene underwent ready cycloaddition with **2** in boiling xylene, forming 8,9-disubstituted 2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones (**5**) in good yields. By analogy with



other such cycloadditions, **4** was most likely the intermediate in the reaction, methyl isocyanate being eliminated during the reaction process. The structures of the final products **5** were readily established by analytical and spectral data. Thus in 8,9-dicyano-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**5**, R = CN) a molecular ion at *m/e* 224 and analytical data indicated a molecular formula of $C_{12}H_8N_4O$ and infrared data showed the presence of the CN group (ν_{CO}

(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

(2) K. T. Potts and M. Sorm, *J. Org. Chem.*, **37**, 1422 (1972); T. Kappe and W. Lube, *Monatsh. Chem.*, **102**, 781 (1971); T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.*, **10**, 925 (1971).

(3) K. T. Potts and M. Sorm, *J. Org. Chem.*, **36**, 8 (1971).

(4) T. Kappe and W. Gosler, *Synthesis*, 312 (1972); K. T. Potts and M. Nichols, unpublished results.

(5) T. B. Johnson and K. G. Mackenzie, *J. Amer. Chem. Soc.*, **42**, 360 1909).

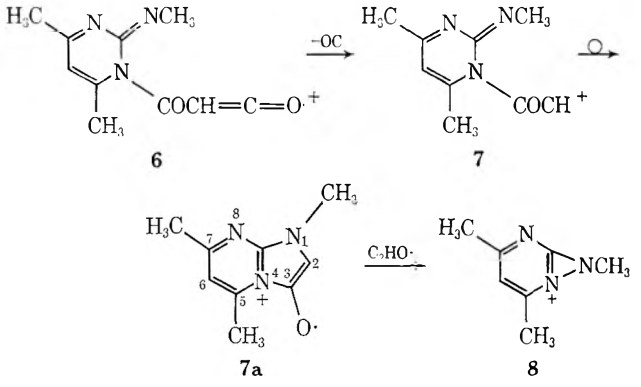
(6) T. Matsukawa and B. Ohta, *J. Pharm. Soc. Jap.*, **69**, 489 (1949); *Chem. Abstr.*, **44**, 3456 (1950).

(7) St. Angesterin, *Ber.*, **34**, 3956 (1901).

1690 cm^{-1}). The presence of two methyl groups was shown by the nmr spectrum (τ 7.50, 7.09), as well as two singlet protons (τ 3.50, 3.37), and the ultraviolet spectrum was consistent with that of 1,2-dicyano-4*H*-quinolizin-4-one.[3]

Ethyl phenylpropiolate, ethyl propiolate, diphenylacetylene, and phenylacetylene did not undergo cycloaddition with **2**, nor was it possible to obtain well-defined products from **2** and olefinic dipolarophiles. *N*-Phenylmaleimide, dimethyl maleate, fumaronitrile, *trans*-1,2-dibenzoylethylene, tetracyanoethylene, acrylonitrile, ethyl azodicarboxylate, and *tert*-butyl azodicarboxylate all failed to undergo reaction with **2**. Despite these shortcomings, this cycloaddition route offers a convenient synthesis of the 6*H*-pyrido[1,2-*a*]pyrimidin-6-one system which is not readily available by other methods, the most direct synthetic route from 2-aminopyridines leading to the isomeric 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[8]

In all the cycloaddition reactions of **2** with the acetylenic dipolarophiles, 4,6-dimethyl-2-methylaminopyridine was found in the reaction. With ethyl phenylpropiolate, phenylacetylene, and diphenylacetylene, the methylamino compound was the sole product obtained. This fragmentation of **2** is in direct contrast to the stability of the *anhydro*-2-hydroxy-4-oxo-1-methylpyrido[1,2-*a*]pyrimidinium hydroxide system[3] and is reflected in the mass spectrum of **2**. In addition to a moderately intense molecular ion at *m/e* 205 (18%), the most intense ion in the spectrum is the M − CO ion at *m/e* 177. Such a ready loss of CO can best be explained in terms of elimination from the valence bond isomer **6** of the molecular ion, a common feature encountered in mesoionic systems.[9] Subsequent rearrangement of **7** into **7a**, the ion anticipated from the unknown *anhydro*-3-hydroxy-1,5,7-trimethylimidazo[1,2-*a*]pyrimidinium hydroxide system, followed by loss of $HC_2O\cdot$, would give **8**, *m/e* 136, which



occurred in the spectrum of **2** to the extent of 20%. This is equivalent to the M − 1 ion observed in the spectrum of 4,6-dimethyl-2-methylaminopyrimidine (32%). It is not unexpected, then, that in the cycloaddition reactions of **2** a competing thermal fragmentation is occurring which becomes the predominant reaction pathway in the presence of moderately reactive acetylenic dipolarophiles. Accordingly it was found that, when **2** was heated in xylene for 14 hr, its precursor **1** was obtained in 25% yield.

(8) C. R. Hansen and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).

(9) K. T. Potts, R. Armbruster, E. Houghton, and J. Kane, *Org. Mass Spectrom.*, **7**, 203 (1973).

Experimental Section[10]

***anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide (2).**—4,6-Dimethyl-2-methylaminopyrimidine (**1**) (2.0 g, 1.35 mmol) in anhydrous ether (100 ml) and a catalytic amount of anhydrous aluminum chloride was added slowly to a stirred ethereal solution (100 ml) of a slight excess of carbon suboxide[11] (1.0 g, 1.48 mmol). After 12-hr reflux the yellow precipitate was collected and recrystallized from acetone, separating as cream prisms: 2.3 g (88%); mp 182° dec; ir (KBr) 3110, 3070 (CH), 1740, 1670 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 228 nm (log ϵ 3.91), 240 (3.95), 322 (3.20); nmr (DMSO-d_6) τ 7.46 (s, 3, C_8 CH_3), 6.72 (s, 3, C_6 CH_3), 6.48 (s, 3, NCH_3), 5.34 (s, 1, C_3 H), 2.80 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 205 (18, M·+), 177 (100, M − CO).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.41; H, 5.39; N, 20.41.

Cycloaddition Reactions with Acetylenic Dipolarophiles.—The following illustrates the general procedure used. *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide (**2**) (1.05 g, 3 mmol) and dimethyl acetylenedicarboxylate (0.64 g, 4.5 mmol) in dry xylene (200 ml) were heated under reflux for 3 hr. After evaporation of the solvent the crude residue was chromatographed on silica gel (Florisil F-100) using benzene–ethyl acetate (90:10) as eluent. Dimethyl 2,4-dimethyl-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-8,9-dicarboxylate (**5**, R = $COOCH_3$) crystallized from cyclohexane, and also from methanol, as cream prisms: 0.44 g (51%); mp 126.5–128°; ir (KBr) 3080, 3015, 2970, (CH), 1750, 1685, 1640 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 237 nm (log ϵ 4.16), 268 sh (4.08), 407 (3.82); nmr ($CDCl_3$) τ 7.56 (s, 3, C_2 CH_3), 7.04 (s, 3, C_4 CH_3), 6.20 (s, 3, C_8 $COOCH_3$), 6.12 (s, 3, C_9 $COOCH_3$), 3.40 (s, 1, C_3 H), 3.20 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 290 (67, M·+).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.80; H, 4.84; N, 9.68.

Similarly **8,9-dicyano-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one** (**5**, **R = CN**) crystallized from benzene–cyclohexane as yellow prisms: mp 220–221°; ir (KBr) 3070 (CH), 2230 (CN), 1690 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 239 nm (log ϵ 4.34), 274 (3.80), 399 (4.02), 418 (4.03); nmr ($CDCl_3$) τ 7.50 (s, 3, C_2 CH_3), 7.09 (s, 3, C_4 CH_3), 3.50 (s, 1, C_3 H), 3.37 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 224 (39, M·+).

Anal. Calcd for $C_{12}H_8N_4O$: C, 64.29; H, 3.60; N, 24.99. Found: C, 64.19; H, 3.60; N, 24.93.

8,9-Dibenzoyl-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**5**, **R = COPh**) crystallized from methanol as yellow prisms: 47%; mp 208–209°; ir (KBr) 3070, 2940 (CH), 1690, 1680, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 237 nm (log ϵ 4.35), 252 (4.41), 391 (3.94); nmr ($CDCl_3$) τ 7.82 (s, 3, C_4 CH_3), 6.94 (s, 3, C_4 CH_3), 3.55 (s, 1, C_3 H), 3.54 (s, 1, C_7 H), 2.7–2.0 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 382 (100, M·+).

Anal. Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.29; H, 4.74; N, 7.14.

4,6-Dimethyl-2-methylaminopyrimidine (**1**).—2-Chloro-4,6-dimethylpyrimidine (9.0 g, 6.33 mol) and methylamine (15 ml of 40% solution) were heated in a bomb for 16 hr (oil bath temperature 100°). After cooling the colorless solid was collected, washed with water, and recrystallized from hexanes, forming colorless needles, 7.38 g (90%), mp 99° (lit.[5] mp 99°).

Hydrolysis of *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide.—The betaine (0.8 g) was refluxed in water (50 ml) for 2 hr. After cooling, the aqueous solution was extracted with chloroform and the organic phase was evaporated to dryness leaving a pale yellow oil. The oil was chromatographed on Florisil F-100 using ethyl acetate–chloroform as eluent. The product was recrystallized from hexanes giving colorless needles as described for **1** above.

Registry No.—**1**, 15231-64-8; **2**, 41108-47-8; **5** (R = $COOCH_3$), 41108-48-9; **5** (R = CN), 41108-49-0; **5** (R = COPh), 41108-50-3; dimethyl acetylenedicarboxylate, 762-42-5; 2-chloro-4,6-dimethylpyrimidine, 4472-44-0; methylamine, 74-89-5.

(10) Spectral characterizations were carried out with the following instrumentation: ir, Perkin-Elmer Model 337 infrared spectrophotometer, uv, Cary Model 14 spectrophotometer; nmr, Varian T-60 spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV using the direct insertion probe at a temperature of *ca.* 150°. Evaporations were done under reduced pressure using a rotatory evaporator and melting points were determined in capillaries. Microanalyses are by Instranal Laboratories Inc., Rensselaer, N. Y.

(11) A. Stock and H. Stolzenberg, *Ber.*, **50**, 498 (1917).

Heterocyclic Syntheses *via* the Intramolecular Acylation of Enamines Derived from Amino Acids[1]

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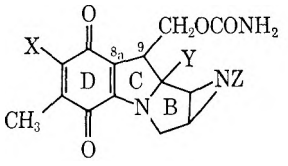
A general heterocyclic synthesis using enamines derived from amino acids is described. The use of salts of amino acids in the enamine-forming step is developed. The preparations of dihydroorcinol and dehydroproline, potential starting materials for the heterocyclic synthesis, are described. Asymmetric induction, ultimately observed in the heterocycle, caused by the chiral amino acids, is discussed.

Enamine derivatives of amino acids have been used as blocking groups[2] and as asymmetric catalysts for alkylations.[3] There is a great deal of literature on the acylation of enamines.[4] In this report, we wish to describe the incorporation, into heterocyclics, of enamines derived from the reaction of natural amino acids with cyclic diketones. The key step in this synthesis is an intramolecular acylation reaction. Of particular interest to us was the accessibility of frameworks related to the mitomycins (**1**). Removal of the bond between 8a and 9 generates structure **2**;



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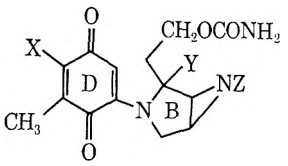

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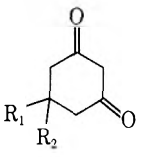
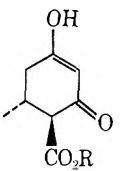
thus the conceptual basis of this program was the preparation of intermediates of this type and the reformation of the bond in question.[5]

Results and Discussion

The carbonyl compounds used in this study are the cyclohexane-1,3-diones known as dihydroresorcinol (**3**), dihydroorcinol (**4**), and dimedone (**5**). Compounds **3** and **5** are commercially available and there is a well-known preparation of **4**, namely, condensation of ethyl crotonate with ethyl acetoacetate to form diketo ester **6**. Finally, alkaline saponification and decarboxylation afford the desired diketone.[6] However, the penultimate saponification, plagued with reverse Claisen and Dieckmann reactions, is highly irreproducible. We found it convenient to circumvent this problem by employing the expedient of using *tert*-butyl acetoacetate, thus affording diketo ester **7**. Cleavage and decarboxylation of this intermediate



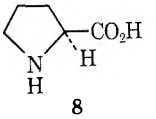
3, $R_1 = R_2 = H$
4, $R_1 = H$; $R_2 = CH_3$
5, $R_1 = R_2 = CH_3$



6, $R = CH_2CH_3$
7, $R = C(CH_3)_3$

can be done entirely in dilute aqueous acid, affording a reproducible 52% overall yield of **4**.

Of the amino acids used in this work, L-proline (**8**) and L-hydroxyproline (**9**) were commercial samples. *N*-Benzylglycine (**10**) and 4-chloroproline (**11**) were



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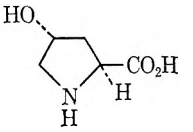

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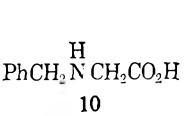

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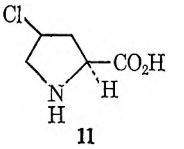

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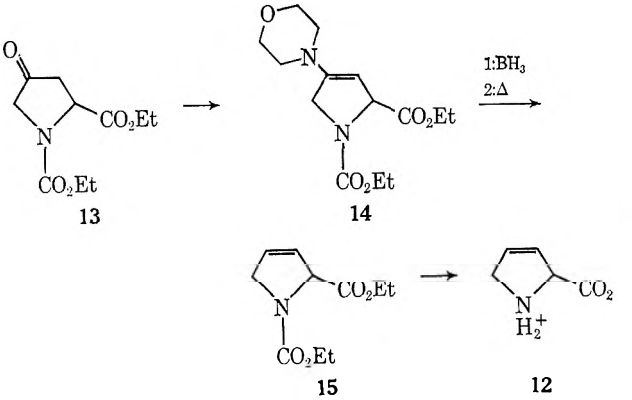
prepared using modifications of literature procedures.[7] Racemic dehydroproline (**12**) was obtained as a gift from Ravizza S. A. Milan. Prior to the availability of **12** from this source, a route to this amino acid was developed as outlined in Scheme I. The key step

SCHEME I



13 **14** **15** **12**

(1) (a) Portions of this article are taken from the Ph.D. Theses of R. J. F and J. M. G., Fordham University, 1970 and 1972, respectively, and the undergraduate report of R. P. S., 1971. (b) A preliminary communication of some of this research has been published: R. W. Franck, R. J. Friary, and J. F. Tobin, *Chem. Commun.*, 283 (1969). (c) The support of the National Cancer Institute, Grant 11421, is gratefully acknowledged.

(2) (a) B. Halpern and L. James, *Aust. J. Chem.*, **17**, 1282 (1964); (b) B. Halpern, *ibid.*, **18**, 417 (1965); (c) B. Halpern and L. James, *Nature (London)*, **202**, 592 (1964); (d) P. Crabbe, B. Halpern, and E. Santos, *Tetrahedron*, **24**, 4299 (1968); (e) *ibid.*, **24**, 4215 (1968).

(3) (a) K. Hiroi, K. Achiwa, and S.-I. Yamada, *Chem. Pharm. Bull.*, **20**, 246 (1972). An intramolecular cyclization such as our work describes is mentioned in this paper. (b) K. Hiroi and S.-I. Yamada, *ibid.*, **21**, 47 (1973).

(4) A. G. Cook, Ed., "Enamines: Their Synthesis, Structure, and Reactions," Marcel Dekker, New York, N. Y., 1969.

(5) This analysis of the problem was reported previously: L. Mandell and E. C. Roberts, *J. Heterocycl. Chem.*, **2**, 479 (1965).

(6) (a) A. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 605 (1915); (b) R. V. Schilling and D. Vorlander, *Justus Liebigs Ann. Chem.*, **308**, 192 (1899); (c) D. Vorland and F. Kalkow, *Ber.*, **30**, 1801 (1897); (d) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, **289**, 170 (1896).

(7) (a) J. A. King and F. McMillan, *J. Amer. Chem. Soc.*, **72**, 1236 (1950); (b) J. Kerwin, G. Hall, F. Milnes, I. Witt, R. McLean, E. Macko, E. Fellows, and G. Ullyot, *ibid.*, **73**, 4162 (1951); (c) R. H. Andreatta, V. Nair, A. V. Robertson, and W. R. J. Simpson, *Aust. J. Chem.*, **20**, 1493 (1967).

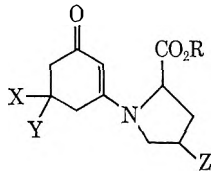
TABLE I

DATA FOR ENAMINE ESTERS, YIELDS, ANALYSES, AND UV DATA

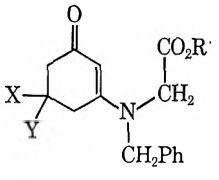
Compd	Mp, °C	Yield, %	Formula	Calcd (found), % C	H	N	Uv, λ_{max}, nm (ϵ)
16a	58.5–59	70	$C_{14}H_{21}NO_3$	66.9 (67.0)	8.4 (8.5)	5.6 (5.5)	310 (14,700)
17a	Oil	76					
18a	55.5–57.5	91					
19a	98.5	76	$C_{18}H_{23}NO_3$	71.7 (71.6)	7.7 (7.6)	4.7 (4.6)	214 (6960), sh 290 (13,800), 306 (16,100)
20a	94	37	$C_{19}H_{25}NO_3$	72.4 (72.5)	8.0 (8.0)	4.4 (4.4)	208 (4800), 298 (16,000)

was the one-pot conversion of a ketone to an alkene in the presence of ester and urethane functions in 53% yield using the method of Lewis and Pearce.[8]

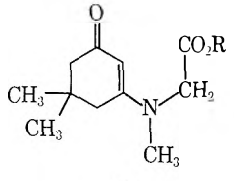
Previous workers[2,3] had used esters of amino acids in the enamine-forming reaction to circumvent the problems presented by the zwitterionic nature of the free acids, *viz.*, insolubility in aprotic organic solvents and lack of basicity of the protonated amino group. Although the technique was satisfactory for enamine formation, the desired synthons were the acids **18–21b**. Thus, we were in the uneconomic position of having to esterify our commericial amino acids so as to synthesize enamines **16–21a** (Table I) and then treat these intermediates under carefully defined hydrolysis conditions so as to remove the ester group. With this in mind, a direct method was developed using the sodium salts of the desired amino acids, formed by treating the free acid with NaH. These salts were sparingly soluble in DMF at room temperature. However, upon heating the mixture of DMF, diketone, and acid salt, a clear solution developed. In most cases, the salt of the enamino acid was less soluble in DMF than its precursors. Thus, the desired products usually crystallized from the hot DMF. The salts **16c**, **17c**, **22c**, **23c**, and **24c** (Table II) were simply



16, X = CH_3; Y = Z = H
17, X = Y = CH_3; Z = H
22, X = CH_3; Y = H; Z = OH
23, X = CH_3; Y = H, Z = Cl



18, X = Y = H
19, X = CH_3; Y = H
20, X = Y = CH_3



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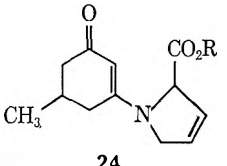


24

a, R = CH_2CH_3
b, R = H
c, R = Na

characterized by their identifiable ir bands. Then they were either converted to free acids by protonation to be compared with samples prepared from the ester pathway which were more carefully characterized

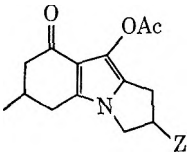
(8) J. W. Lewis and A. A. Pearce, *J. Chem. Soc. B*, 863 (1969).

TABLE II

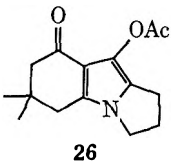
YIELDS AND INFRARED SPECTRAL DATA FOR THE ENAMINE ACID SALTS

Salt	Yield, %	ν_{max}, cm^{-1} -COO⁻	NC=CC=O
16c	59	1541, 1393	1603
17c	71	1529, 1391	1587
21c	72	1538, 1391	1603
22c	97	1524, 1416	1592
23c	76	1530, 1400	1605
24c	64	1525, 1430	1600

or, more usefully, they were directly cyclized in hot acetic anhydride to the desired ketotetrahydroindoles **25–30** (Table III). We speculate that first formed



25, Z = H
29, Z = OAc
30, Z = Cl



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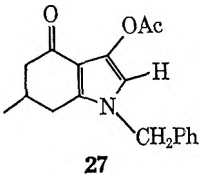

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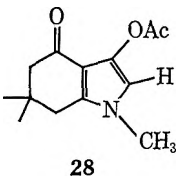

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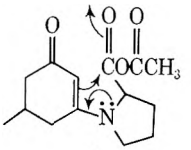
TABLE III

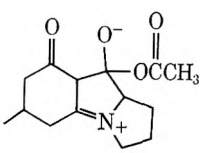
YIELDS, MELTING POINTS, AND ANALYSES FOR ACETOXYTETRAHYDRO- AND ACETOXYHEXAHYDROPYRRCLOOXINDOLES[a]

Compd	Mp, °C	Yield, %	Formula	Calcd (found), % C	H	N	Cl
25	113–114.5	40	$C_{14}H_{17}NO_3$	68.0 (67.9)	6.9 (6.8)	5.7 (5.5)	
26	117–118	57	$C_{15}H_{19}NO_3$	68.9 (69.1)	7.3 (7.3)	5.4 (5.4)	
27	124–124.5	85	$C_{18}H_{19}NO_3$	72.7 (72.7)	6.4 (6.4)	4.7 (4.6)	
28	121–122.5	63	$C_{13}H_{17}NO_3$	66.4 (66.5)	7.3 (7.3)	6.0 (5.9)	
29	110–111	38	$C_{15}H_{19}NO_5$	62.9 (63.0)	6.3 (6.2)	4.6 (4.6)	
30	123–124	10	$C_{14}H_{15}ClNO_3$	59.7 (59.6)	5.7 (5.7)	5.0 (5.0)	12.6 (12.5)

[a] At the request of the editor and referees, the tables of nmr and ir assignments have been omitted. They are all consistent with those reported for **25** in the Experimental Section.

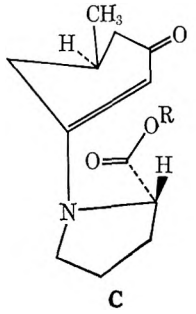
is a mixed anhydride intermediate A which acylates the enamine carbon to form B. Subsequently, elim-


A


B

ination of water or acetic acid results in the formation of the tetrahydroindole. Experiments using isopropenyl acetate or dicyclohexylcarbodiimide failed to produce cyclization. Most disappointing to our program was the failure of salt **24** to afford cyclized product when subjected to hot acetic anhydride. An examination of models suggests that the two trigonal carbons in the dehydroproline ring of the salt confer rigidity to the amino acid framework. Thus, the carboxyl carbon cannot approach the enamine double bond so as to overlap well with the π bond.

The tricyclic **25** was examined by CD to determine if any detectable asymmetric induction had taken place, either in the formation of **16c** or in the cyclization. A rotation at λ_{max} 305 nm ($\Delta\epsilon$ +0.33) and a broad, noisy maximum centered at 265 nm ($\Delta\epsilon$ −0.24) were observed. That this rather small rotation was not due to contamination by the precursor **16c** was demonstrated by its CD spectrum, λ_{max} 292 nm ($\Delta\epsilon$ −9.1) and 214 (+3.3), which is behavior expected for these derivatives of amino acids.[9] Spectra of appropriate model compounds do not seem to be available for assignment of absolute configuration. Use of the chiral nmr shift reagent, trisheptafluorobutyrylcamphoratoeuropium (Regis Chemical Co.) revealed an optical purity of 10%. One can speculate that the asymmetric induction involves preferred cyclization of the diastereomer C depicted so as to minimize repulsions between the methyl and the mixed anhydride. Thus, the absolute configuration of the product should be *R* as illustrated. It is interesting to note that the CD of pulegone (**31**) is λ_{max} 330 nm ($\Delta\epsilon$ +0.38).[10]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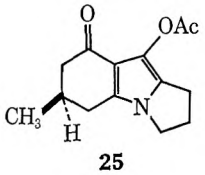
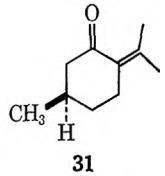

25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In the cases of the tricyclics derived from hydroxyproline and chloroproline, one expects the formation of diastereoisomeric mixtures. In fact, single isomers seem to have been isolated. The nmr spectrum of **29** at 60 MHz revealed a doubling of the A portion of the ABX spectrum assigned to protons at carbon 3. However, spectra at 100 and 220 MHz[11] showed the splitting unchanged. Thus, the doubling of lines is simply long-range spin–spin coupling to a proton at C-5. We cannot identify hydrogens at C-5 in the spectrum. We are able to observe protons at C-1 and are thus able to discount them as the partners in the long-range coupling. If one assumes the same sense of asymmetric induction of methyl stereochemistry at C-6, owing to the identical chirality of the carboxyl portions of both proline and hydroxyproline, and also takes into account the trans relationship of the hydroxyl and carboxyl, then one is able to predict that the absolute configuration and relative stereochemistry of **29** (Table IV) are as drawn.

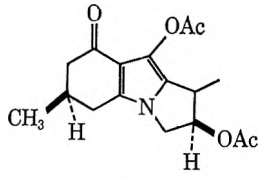
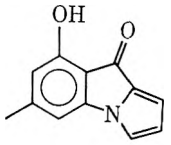

29

TABLE IV
SOME NMR DATA FOR 29

Assignment	δ_A	δ_B	J_{AB}	J_{AX}	J_{BX}
H_A' | | $NCCH_X(OAc)CH_2$ | H_B'	4.23[a]	3.90	12.3	5.85	2.65
H_A | $>NCH_2CH_X(OAc)C-$ | H_B	3.21	2.88	17.0	6.80	2.80

[a] Further long-range splitting, J = 1.9 Hz; *cf.* M. Barfield, *J. Chem. Phys.*, **48**, 4463 (1968); G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).

Although the cyclization yields in this work were not high, it was thought that this rather direct preparation of tricyclics could be applied to the synthesis of aromatic substrates for use in other mitomycin schemes underway in these laboratories. There are several reports of catalytic dehydrogenations of keto-tetrahydroindoles.[12] In the event, **25** afforded the completely aromatized **32** in variable yields when


32

treated with palladium on carbon in refluxing mesitylene. The structural assignment was made by comparison of data to those of similar 9-keto-9*H*-pyrrolo[1,2-*a*]-indoles that had been prepared in this laboratory.[13]

(9) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 311.

(10) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism, Principles, Measurements, and Applications," Academic Press, New York, N. Y., 1965, p 207.

(11) We are indebted to the Analytical Laboratory of Ciba-Basel for these spectra.

(12) (a) S. Hauptmann, G. Clume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 183 (1966); (b) H. Plieninger and K. Klinge, *Chem. Ber.*, **101**, 2605 (1968); (c) W. A. Remers, R. H. Roth, G. J. Gibbs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971).

(13) V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.*, **32**, 486 (1967).

Experimental Section[14,15]

5-Methylcyclohexane-1,3-dione (4).—A solution of 34.2 g (0.300 mol) of ethyl crotonate, 47.8 g (0.303 mol) of *tert*-butyl acetoacetate (Aldrich Chemical Co.), and 0.306 mol of sodium ethoxide, prepared from sodium hydride mineral oil dispersion and 105 ml of absolute ethanol, was refluxed for 2.5 hr, when a precipitate was deposited. After an additional 1 hr at reflux, the precipitate was collected and washed thoroughly with anhydrous ether to afford 59 g (79%) of the sodium enolate of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (7) as a chalk-colored powder: ir ν_{max} 1701, 1639, 1248, 1220 cm^{-1}; nmr (D_2O) δ 1.03 (d, J = 6 Hz, 3 H), 1.47 (s, 9 H), 1.72–2.66 (br envelope, 3 H), 2.95 (d, J = 10 Hz, 1 H), 5.10 ppm (s, 1 H).

A solution of 14.2 g of salt in 50 ml of water was filtered and acidified with 5 ml of concentrated hydrochloric acid. The resulting white precipitate was washed with water and air dried to give 11.1 g (86%) of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (7): mp 130–131.5°; ir ν_{max} 3484–3311, 2778–2128, 1718, 1590, 1242, 1198 cm^{-1}; nmr (DMSO-d_6) δ 1.02 (d, J = 6 Hz, 3 H), 1.45 (s, 9 H), 2.00–2.66 (br envelope, 3 H), 2.94 (d, J = 11 Hz, 1 H), 5.28 ppm (s, 1 H). Two recrystallizations of a specimen of **3** from ethyl acetate containing a little acetone gave the analytical sample, mp 138.5–141.5°.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.55; H, 7.94.

To 160 ml of vigorously stirring and boiling 0.05 N sulfuric acid was added 20.8 g of the *tert*-butyl ester 7 in small portions over 22 min. Slow addition was necessary to avoid material loss due to extensive foaming. Residual ester was rinsed into the reaction mixture with 35 ml of 0.05 N sulfuric acid and 15 ml of water. The mixture was refluxed for 50 min, when the evolution of gas had nearly ceased. The resulting hot solution was decolorized with charcoal, filtered, seeded, and refrigerated overnight at −5° to afford 8.76 g of 4, identified by comparison of its ir spectrum with that of an authentic sample.[6] Recrystallization of a sample from ethyl acetate gave a 78% return of long, white needles of 4, mp 125.5–127° (lit.[6] mp 126–127°). The yield of 4 was found to decrease with increasing acid concentration.

1,2-Dicarbethoxypyrrolidinone-4 (13).—Previously reported methods[16] were modified as follows: 29.8 g of ethyl N-carbethoxyglycinate in 10 ml of benzene was added dropwise over 30 min to a suspension of 7.9 g of 50% NaH mineral oil dispersion (prewashed with anhydrous benzene) in 450 ml of benzene. This was stirred vigorously for 14 hr under an inert atmosphere. At the end of this period, 29.4 g of diethyl maleate in 40 ml of benzene was added over a 20-min period. After an additional 6 hr the reaction mixture was diluted with 100 ml of ether and extracted with ice water (4 × 100 ml). The combined aqueous layers were backwashed with 100 ml of ether and carefully added to a mixture of 20 ml of concentrated H_2SO_4 in about 100 ml of ice. This was extracted with ether (5 × 100 ml), and the combined ether layers were washed with 100 ml of brine, dried over $MgSO_4$, and evaporated to yield 40.5 g (82% if pure) of 1,2,3-tricarbethoxypyrrolidinone-4 as an orange oil. This material was refluxed for 30 min in a mixture of 125 ml of concentrated HCl and 125 ml of water. The water was evaporated and the resultant red-brown oil was dissolved in 250 ml of absolute ethanol. After the addition of 1 ml of concentrated HCl this mixture was allowed to reflux for 8 hr and the volatile materials were removed on a rotary evaporator. The resultant oil was dissolved in 250 ml of chloroform, washed with 100 ml of water, 100 ml of saturated $NaHCO_3$ solution, and 100 ml of brine, dried over $MgSO_4$, and evaporated. Distillation yielded 22.5 g (57%) of a water-white liquid, bp 120–124° (0.05 mm) [lit.[16] bp 116–122° (0.02 mm)].

1,2-Dicarbethoxy-3-pyrroline (15).—A mixture of 5.17 g (22.6 mmol) of 1,2-dicarbethoxypyrrolidinone-4 (13), 1.96 g (22.6 mmol) of morpholine, and 10 mg of *p*-toluenesulfonic acid was dissolved in 50 ml of benzene and the mixture was refluxed under an inert atmosphere for 2 hr, during which time 1 equiv of water was collected in a Dean–Stark trap. After solvent was removed, the resultant enamine was dissolved in 25 ml of dry THF. The solution was transferred to a round-bottom flask equipped with septum and gas valve. After introduction of an inert atmosphere, the flask was immersed in an ice bath and 22.6 ml of 1 M BH_3–THF (Alfa Inorganics) was injected while the mixture was stirred with a magnetic stirring bar. The ice bath was removed and the mixture was stirred for 7 min; 6.0 g of ethanol was injected; and the mixture was stirred for an additional 15 min. The solvents were removed under vacuum without detaching the flask from the gas supply apparatus. An inert atmosphere was reintroduced and 50 ml of benzene was added through the septum. The mixture was refluxed for 1 hr, cooled, diluted with 100 ml of ether, washed with 100 ml of water, 100 ml of $NaHCO_3$ (saturated solution), and 100 ml of brine, and dried over $MgSO_4$, and the solvents were evaporated. Distillation yielded 2.01 g (42%) of a water-white liquid: bp 87° (0.10 mm); ir (CCl_4) 1748, 1712 cm^{-1}; nmr (CCl_4) δ 4 (m), 5.90 (2 H), 4.93 (1 H), 4.22 (6 H), 1.20 (6 H).[17]

Anal. Calcd for $C_{10}H_{15}O_4N$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.25; H, 6.93; N, 6.72.

3,4-Dehydroproline (12).—A sample of 268 mg of 1,2-dicarbethoxy-Δ^3-pyrrolidine (15) was dissolved in 15 ml of 57% HI in H_2O and the solution was refluxed under an inert atmosphere for 2 hr. The HI solution was removed under reduced pressure (0.3 mm) at room temperature until only a gummy residue remained. This was taken up in 2 ml of distilled water and passed through a 2-g column of Dowex 50 W-X8 ion exchange resin in the H^+ form. The column was washed with distilled water until the eluent became neutral and then the dehydroproline was eluted with 25 ml of 0.5 N NH_4OH. This was evaporated at room temperature and reduced pressure to give 112 mg (73%) of light brown material identified as 3,4-dehydroproline by means of its identical mobility on paper chromatography, characteristic and unusual color reaction with ninhydrin, and its ir, which was superimposable on that of a small sample of 3,4-dehydroproline graciously supplied by Ravissa S. A.

Typical Preparation of an Enamine Ester. 3-(2-Carboethoxypyrrolidino)-5-methylcyclohex-2-en-1-one (16a).—To a hot solution of 5.00 g (3.97 × 10^{-2} mol, 10% excess) of 5-methylcyclohexanedione-1,3 (4) (freshly recrystallized from ethyl acetate), mp 128–129.5, in 114 ml of benzene was added, rapidly in 1–2-ml portions, a solution of 5.16 g (3.61 × 10^{-2} mol) of ethyl prolinate in 30 ml of benzene. The resulting solution became yellow; a Dean–Stark trap was attached, and a condenser was affixed to it. The reaction mixture was magnetically stirred under reflux for 2.25 hr, after which the separation of water had ceased. The cooled solution was washed twice with one-half saturated aqueous sodium bicarbonate solution and twice with water. The aqueous layers were back-extracted with ether, and the combined organic layers were washed with brine, dried, filtered, and evaporated. A light yellow oil was obtained which, when seeded and scratched, exothermically crystallized to afford 6.39 g (70%) of bright yellow crystals of 16a, mp 54.5–59°, homogeneous to tlc in chloroform–acetic acid, ethyl acetate–acetic acid, and acetone–acetic acid. Crude 16a, whether crystalline or oily, from various runs always showed a single component to tlc in the foregoing solvent pair Exemplary melting points of such samples were 54.5–58, 55.5–57.5, and 54.5–59°. On one occasion, the nmr spectrum in $CDCl_3$ of oil, crude 16a was found, with the exception of slight solvent shifts and the presence of a trace of benzene, to be identical with that of the analytical sample in pyridine.

Recrystallization of a sample of crude 16a, mp 54.5–58°, from ether gave pale yellow crystals (89% recovery), mp 46–54°, homogeneous to tlc in the aforementioned solvent pairs. Recrystallization from the same solvent gave a 67% return of solid, mp 57–60°. Two additional recrystallizations from ether gave

(14) Commercially available starting materials were used as supplied, except where noted. Liquids were distilled through a vacuum-jacketed, 4-in. Vigreux column; melting points were determined on a Fisher-Johns block, and, like boiling points, are uncorrected. Thin layer chromatograms (tlc) in at least two different solvents or solvent pairs were performed on microscope slides coated with silica gel or alumina, and were visualized with iodine vapor. Merck acid-washed alumina and Fisher 100–200 mesh silica gel were used for elution chromatography. Woelm fluorescent alumina and silica gel (activity II–III) were used for dry-column chromatography. Solutions were dried by washing with saturated sodium chloride solution (brine), followed by treatment with anhydrous sodium sulfate. Solvents were removed by rotary evaporation. Where noted, an atmosphere of dry nitrogen was maintained by use of the apparatus described by W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1954). We thank the Fisher Scientific Co. for a generous gift of chemicals.

(15) Only representative examples of enamine formation and cyclization are included. For the details of each preparation, *in extenso*, the reader is referred to the experimental sections of the Ph.D. Theses of R. J. F. and J. M. G., Fordham University, 1970 and 1972, respectively.

(16) (a) R. Kuhn and C. Osswald, *Ber.*, **89**, 1423 (1956); (b) H. Rapoport and C. Willson, *J. Amer. Chem. Soc.*, **84**, 630 (1962).

(17) *Cf.* A. Cambrella, P. Gariboldi, and G. Jommi, *Chem. Ind. (London)*, 583 (1969).

material (73% recovery), mp 58.5–59.5°, and the analytical sample (74% return) as fine white needles: mp 58.5–60.5°; ir ν_{max} (KBr) 1715 and 1608 ($CHCl_3$), 1733, and 1600 cm^{-1}; nmr (C_5H_5N) δ 0.97 (br m, $W_{1/2}$ = 9 Hz) and 1.09 (t, J = 7 Hz) (total 6 H), 1.58–2.76 (br envelope, 9 H), 3.08–3.42 (br, 2 H), 4.19 (q, J = 7 Hz) and 4.47 (s) (total 3 H), 5.19 ppm (s, 1 H); uv λ_{max} 310 nm (ϵ 14,700).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.96; H, 8.45; N, 5.52.

Typical Preparation of Enamine Acid. 3-(2-Carboxypyrrolidino)-5-methylcyclohex-2-en-1-one (16b).—A mixture of 2.75 g (1.05×10^{-2} mol) of crystalline **16a** and 25 ml of 10% (w/w) aqueous sodium hydroxide solution was magnetically stirred at 27° for 5 min. The mixture was then warmed over 15 min to 47°; at the end of this time, all of the solid had dissolved to give a reddish yellow solution. The solution was cooled during 5–8 min to room temperature, diluted with 40 ml of water, and extracted with ether, which was discarded. The vigorously stirred basic aqueous layer, admixed with 50 ml of dichloromethane, was acidified with cold, concentrated hydrochloric acid to pH 2. The layers were separated, and the aqueous layer was extracted with two 50-ml portions of dichloromethane. The combined organic layers were washed twice with 50-ml portions of water, dried, filtered, and evaporated to give 0.901 g (37%) of creamy powder, mp 220–221° (gas evolution at the melting point), homogeneous to tlc in methanol. The infrared spectrum (ν_{max} 1698, 1536–1502 cm^{-1}) of this material was identical with that of a sample of **16a**, mp 225.5–227°, prepared by condensation of sodium prolinate with 5-methylcyclohexanedione-1,3 in 1,2-dimethoxyethane, followed by acidification.

Typical Preparation of Enamine Acid Salt. 3-(Sodium pyrrolidino-2-carboxylate)-5-methylcyclohex-2-en-1-one (16c).—To a solution of 5.70 g (4.25×10^{-2} mol, 10% excess) of 5-methylcyclohexanedione-1,3 (**4**) and 30 ml of *N*,*N*-dimethylformamide in a 125-ml erlenmeyer flask was added 5.62 g (4.11×10^{-2} mol) of sodium prolinate (from L-proline and sodium hydride in 1,2-dimethoxyethane). The flask was tightly stoppered and heated for several minutes on the steam bath, when most of the solid dissolved. The remaining lumps of solid were crushed with the aid of a spatula, whereupon they dissolved, and the resulting orange solution was heated on the steam bath for 20 min, when crystals were deposited. After an additional 12 min on the steam bath, the mixture was allowed to cool over about 30 min to room temperature. The light yellow powder was collected by filtration, washed with *N*,*N*-dimethylformamide, acetone, and finally ether, and dried at reduced pressure at 100° for 20 min. In this manner there was secured 5.93 g (59%) of the desired **16c**, ir ν_{max} 1603, 1541, 1393 cm^{-1}. Without purification, this material was used in the next step.

Typical Cyclization. 9-Acetoxy-6-methyl-8-oxo-1,2,5,6,7,8-hexahydro-3*H*-pyrrolo[1,2-*a*]indole (25).—To 38 ml of hot (80°) acetic anhydride was added 3.80 g (1.55×10^{-2} mol) of the salt **16c**, prepared as described above. The resulting light yellow suspension was stirred in an atmosphere of dry nitrogen at 80–83° for 3.75 hr, and thereafter at 25° for 21 hr. After 20 min at 80–83°, the supernatant liquid had become orange. A small amount of solid adhering to the walls of the vessel above the reaction mixture was washed into it with 10 ml of acetic anhydride.

Thin layer chromatography (ethyl acetate–acetic acid) after 1 hr at 80–83° revealed that the mixture contained the desired **25** as the major component, as well as lesser amounts of a more mobile impurity, and two nearly immobile impurities. After 2.67 hr one of the nearly immobile constituents appeared to have been consumed, and after 3.75 hr at 80–83° and 21 hr at 25°, the composition of the mixture was essentially unchanged.

The reaction mixture was diluted with 200 ml of toluene, and the solvents were evaporated. Two repetitions of this process gave a semisolid residue which was partitioned between ether and water. The organic layer was washed with water, and the aqueous phase was back-extracted with ether. The combined organic layers were washed with one-half saturated aqueous sodium bicarbonate solution, water, and brine. The solution was dried, filtered, and evaporated to give a crystalline residue. A solution of this residue in ether–hexane was refrigerated to afford 1.55 g (40% from **16c**) of light brown prisms, mp 107.5–111.5°, homogeneous to tlc in ethyl acetate–acetic acid.

In another experiment, the suspension of **16c** was heated at gentle reflux for 0.75 hr. After processing as described above, light brown prisms of **25**, mp 107.5–109°, were obtained in 34% yield from **16c**. The crude product was homogeneous to tlc in dichloromethane–acetic acid and in ethyl acetate–acetic acid; its ir spectrum was sufficiently indistinguishable from that of a sample of **25** which had been repeatedly recrystallized.

Several recrystallizations of a specimen of crude **25** gave fine, tan needles: mp 108–109°; ir ν_{max} 1767, 1640 cm^{-1}; uv λ_{max} 255 nm (ϵ 12,300); nmr δ 1.00–1.23 (br, $W_{1/2}$ = 7 Hz, 3 H), 2.27 (s), and *ca.* 2.34–2.97 (br envelope) (total of 12 H), 3.86 ppm (t, J = 7 Hz, 2 H). Several additional recrystallizations from ether containing a little dichloromethane gave the analytical sample as diamond-shaped white prisms, mp 113–114.5°. The medium-resolution mass spectrum of material of this quality exhibited the correct molecular ion at m/e 247.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.79; N, 5.51.

6-Methyl-8-hydroxy-9-keto-9*H*-pyrrolo[1,2-*a*]indole (32).—9-Acetoxy-6-methyl-8-oxo-1,2,5,6,7,8-hexahydro-3*H*-pyrrolo[1,2-*a*]-indole (**25**) (0.146 g, 0.59 mol) in 20 ml of purified mesitylene was refluxed in the presence of 0.20 g of 30% palladium on carbon catalyst in an atmosphere of dry nitrogen. The reaction was followed by ir. After 13.5 hr of reflux, it appeared that the absorbances due to the acetate carbonyl and to the ketone carbonyl had almost completely disappeared. The reaction was allowed to continue at reflux for an additional 5 hr, and was subsequently stirred for 48 hr at room temperature. The ir at the end of this length of time revealed the complete disappearance of the two aforementioned bands. The reaction mixture was filtered through a Celite 545 pad and the latter was washed thoroughly with hot mesitylene. The filtrate was distilled to a small volume under reduced pressure. Thin layer chromatography revealed the presence of three components having mobilities exhibiting R_f values of 0.3, 0.5, and 0.7. The crude reaction products were absorbed on 1.0 g of Woelm dry column silica gel and subjected to descending column chromatography over a 14.5 × 1.5 in. column of 90.0 g of silica gel, dry packed in nylon tubing. The column was developed with chloroform. A distinct 6.25-in yellow band was apparent followed closely by a 1-in. deep red-brown band. In order to effect better separation of these two bands, elution was continued until the aforementioned yellow band reached the bottom of the column. It was sectioned and extracted with approximately 250 ml of chloroform by means of a Soxhlet extraction apparatus over an 18-hr period. Drying over sodium sulfate, filtering, and evaporation of the solvent yielded 0.06 g (50.4%) of 6-methyl-8-hydroxy-9-keto-9*H*-pyrrolo[1,2-*a*]-indole. Sublimation at 115° afforded material of analytical purity: ir (CCl_4) 1254, 1644, 1689, and 3399 cm^{-1}; nmr (chloroform-d_3) δ 2.32 (s, 3 H) and 6.21–7.43 ppm (m, 6 H); uv max (95% C_2H_5OH) 212 mμ (log ϵ 3.69), 251 (3.83), 286 (3.29), 297 (3.70), and 360 (3.25).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.17; H, 4.68; N, 6.91.

Registry No.—**3**, 504-02-9; **4**, 4341-24-6; **5**, 126-81-8; **7**, 41263-40-5; **7** Na salt, 41263-41-6; **12**, 3395-35-5; **13**, 41263-42-7; **15**, 41263-43-8; **16a**, 41263-45-0; **16b**, 41263-46-1; **16c**, 41263-47-2; **17a**, 41263-48-3; **17c**, 41263-49-4; **18a**, 41263-50-7; **19a**, 41263-51-8; **20a**, 41263-52-9; **21c**, 41263-53-0; **22c**, 41263-54-1; **23c**, 41263-55-2; **24c**, 412-56-3; **25**, 41263-57-4; **26**, 41263-58-5; **27**, 41312-36-1; **28**, 41312-37-2; **29**, 41263-59-6; **30**, 41312-38-3; **32**, 41263-60-9; *tert*-butyl acetoacetate, 1694-31-1; ethyl *N*-carboethoxyglycinate, 999-30-4; 1,2,3-tricarbethoxypyrrolidinone-4, 41263-63-2; ethyl prolinate, 5817-26-5; sodium prolinate, 33006-43-8; ethyl *N*-benzylglycinate, 6436-90-4.

The Removal and Displacement of the Thiazolidine Ring of Penicillin. III.[1] Reconstruction of the Penam Ring System

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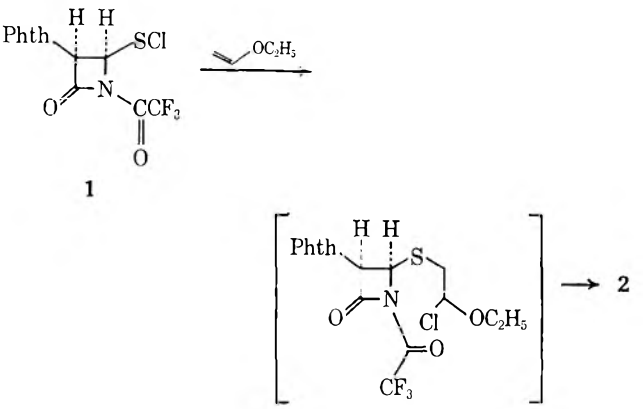
The sulfenyl chloride 1 reacts with ethyl vinyl ether to give 2 and with appropriate ketones to give 6. The ring-closed form (3) of 2 can be trapped by treatment with acetic anhydride–pyridine. Compounds 6 reacted with mercuric chloride in methanol to give the penam ring structures 9.

In 1963, after the numerous side chain variations of penicillin had been demonstrated to produce medically useful modifications in activity, and after the biological activity of the cephalosporins had shown that the thiazolidine ring was not inviolate, it was suggested that penicillin research could be directed toward modification of the ring system to produce clinically useful compounds.[2] Since that time, considerable effort has been expended in this direction.[3] Much of it has focused on the conversion of the thiazolidine ring of the penicillins to the dihydrothiazine ring of the cephalosporins. In contrast, very little progress has been reported in making modifications of the thiazolidine ring itself.[4] This paper reports some recent efforts toward that goal.

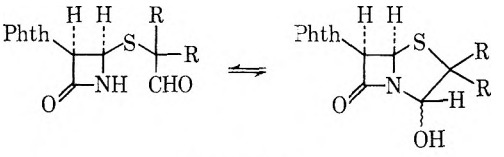
In the conversion of penicillin to cephalosporin, the most economical methods are those which utilize rearrangements of the five-carbon, fused ring system. In order to make substantial modifications of the thiazolidine ring, it becomes necessary to remove the five-carbon skeleton, replacing it with a new carbon framework. Several methods now exist for removal of the skeleton while retaining the sulfur atom and the requisite cis stereochemistry of the azetidine ring.[1,5] The utilization of the sulfenyl chloride **1**[1] is unique in providing an isolable, reactive intermediate which can be treated with a number of different types of reagents, two of which have already been reported.[1]

Details of the preparation of the sulfenyl chloride **1** are given in the Experimental Section. The potential of this intermediate for reconstruction of the thiazolidine ring is demonstrated in the reaction of **1** with ethyl vinyl ether. The course of the reaction is easily followed by watching the disappearance of the characteristic yellow color of a solution of **1**. In this case the color was discharged immediately upon addition of the vinyl ether,[6] and chromatography of the addition product effected hydrolysis of the sensitive α-chloro ether function as well as removal of the trifluoracetyl group.



Phth = phthalimido

No NH or aldehyde proton is detectable in the nmr spectrum of the product. It shows a simple AB pattern in the δ 5–6 region (J = 4 Hz), a straightforward ABX pattern for the thiazolidine ring protons, and an aryl proton multiplet and OH singlet. In contrast, **3**[7] shows characteristic aldehyde and NH absorptions



2, R = H
3, R = CH_3

as well as an AB pattern with a larger coupling constant (5 Hz) and further splitting of the low-field portion by NH ($J \cong 1$ Hz). From this data it appears that the aldehyde–carbinolamide equilibrium is shifted well toward the ring-closed form in **2** as compared to **3**. This equilibrium has been discussed by Heusler.[5b] Based on variations of the C_6 substituent, he postulated that larger substituents shift the equilibrium toward the aldehyde owing to increased interaction between $C_{2\beta}$ and C_6 substituents in the carbinolamide. The comparison of **2** and **3** supports this view, in that removal of the $C_{2\beta}$ methyl shifts the equilibrium toward the carbinolamide. The unexpected favoring of the closed penam system in the absence of steric interference is encouraging when considering the prospect of reconstruction of the penam system from a monocyclic β-lactam.

Further encouragement was obtained when it was found that the reaction of **3** with acetic anhydride–

(1) Part II: J. C. Sheehan, D. Ben-Ishai, and J. U. Piper, *J. Amer. Chem. Soc.*, **95**, 3064 (1973).

(2) J. C. Sheehan, "Molecular Modifications in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 15.

(3) For a review, see R. D. G. Cooper and D. O. Spry in "Cephalosoporins and Penicillins," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, Chapter 5.

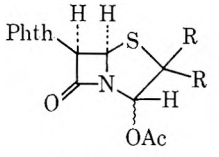
(4) For an exception see R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969).

(5) (a) J. C. Sheehan, U. S. Patent 3,487,074 (1969); *Chem. Abstr.*, **72**, 66933z (1969); (b) K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972); (c) R. D. G. Cooper and F. L. Jose, unpublished results cited in ref 3, pp 235–236; (d) I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *Chem. Commun.*, **601** (1972); (e) J. H. C. Naylor, M. J. Pearson, and R. Southgate, *ibid.*, **57**, 58 (1973).

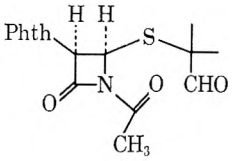
(6) The reaction of **1** with cyclohexene takes *ca.* 1 hr to lose the yellow color, and with ethyl acrylate several hours are required. This is the order expected for the electrophilic sulfenyl chloride.

(7) J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, **87**, 5468 (1965).

pyridine produced **4a** as an oil containing only about 10% of **5** as a contaminant. The faster rate of O-



4a, R = CH_3
b, R = H



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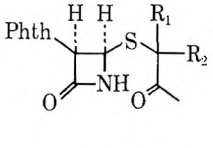
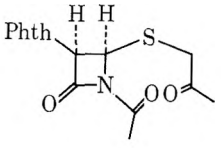
acylation *vs.* N-acylation serves to pull the equilibrium toward the closed system. Thus it became of interest to investigate the applicability of this type of ring closure to other systems.

In a known reaction of sulfenyl chlorides,[8] **1** reacted with acetone at room temperature to give, after chromatography, **6a** in 77% yield. Similarly, methyl



6a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



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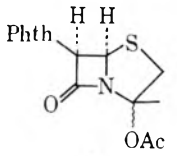

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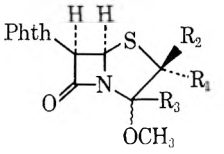
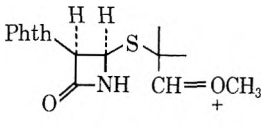
ethyl ketone and methyl isopropyl ketone gave **6b** and **6c**, respectively. In the latter two cases the crude products were slightly contaminated by the products resulting from attack of **1** at the methyl group of the ketones, but recrystallization gave pure products. Ketone **6b** was obtained as a mixture of C_2 epimers (penam numbering) in unequal amounts. The nmr spectra of these three compounds give no indication of the presence of any carbinolamide. Further, treatment of **6a** with acetic anhydride–pyridine gave **7** as the only isolated product. The distinction between structures **7** and **8** is easily made in several ways. In the nmr spectrum the chemical shifts of the *O*- and *N*-acetyl methyl protons are δ 2.1–2.2 and 2.5, respectively. As indicated above, the coupling constant for the azetidine ring protons decreases from *ca.* 5 Hz in **3** and **6** to 4 Hz in **2**, **4a**, and **4b**. On the other hand, N-acylation causes an increase in the coupling constant to *ca.* 6 Hz. In the ir spectra of compounds **2** and **4** the β-lactam carbonyl occurs at 1790–1795 cm^{-1}. The most obvious difference between **7** and **8**, that of the presence or absence of a ketone carbonyl, is not useful in the phthalimido derivatives, since the ketone carbonyl is usually masked by the lower frequency imide band.

The failure of the acetylation procedure to effect closure of **6a** to a penam system indicates that the difference in rates between O- and N-acylation is not large enough to offset the low concentration of carbinolamide.

In considering alternative ring closure methods, an earlier attempt at 1–5 bond cleavage was useful. The use of mercuric salts had been investigated for this purpose, in a manner similar to that recently reported by Stoodley.[9] In contrast to these authors the reaction of **3** with mercuric chloride in methanol gave mainly the dimethyl acetal of **3**. Reinvestigation of this reaction resulted in the isolation of **9a** in 28% yield when equimolar amounts of **3** and mercuric chloride were stirred at 50° in methanol. An intermediate related to **10** in which the electrophilic char-



9a, $R_1 = R_2 = CH_3$; $R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_2 = H$



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acter of the potential C_3 is increased may be involved, although it is not clear whether the ring closure is a kinetic or equilibrium process.

Application of this procedure to ketone **6a** gave **9b** in 40% yield. Assignment of the penam structure is in accordance with the criteria used above: a lack of NH absorption in the ir and nmr spectra, β-lactam carbonyl absorption at 1780–1785 cm^{-1}, and azetidine ring proton coupling constants of 4 Hz. When **6c** was similarly treated, the corresponding penam system was not formed in isolable quantities. The difference in reactivity of **6a** and **6c** is directly analogous to the previous comparison made between **2** and **3**. Here again, the $C_{2\beta}$ methyl inhibits ring closure because of its spatial proximity to the bulky phthalimido group in the penam system[10]

In view of this, it is not surprising that the reaction of the epimeric mixture of ketones **6b** gives a single closed product, and on steric grounds the structure **9c** with the $C_{2\alpha}$ methyl group can be assigned. This assignment is supported by the chemical shift data presented in Table I. There is a substantial differ-

TABLE I
CHEMICAL SHIFTS FOR THE C_2 PROTONS IN PENAM SYSTEMS

Structure	δ ($H_{2\alpha}$)	δ ($H_{2\beta}$)
2	3.25	3.78
4b	3.26	3.86
9b	3.31	3.51
9c		4.06

ence in the chemical shifts of the α and β protons at C_2. Taking the effect of a methyl group into account, the C_2 proton of **9c** absorbs within the range of the $C_{2\beta}$ protons. On the basis of the above steric arguments, the lower field absorptions should be assigned to the β protons. (In the case of C_2 *gem*-dimethyl groups in the penam system, the lower field absorption has been assigned to the β-methyl.[11])

This assignment is also consistent with the H_2–H_3 couplings observed in the nmr spectra of **2** and **4b** if the following two assumptions are made: (1) the

(8) For a review, see I. B. Douglass in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Elmsford, N. Y., 1961, Chapter 30.

(9) R. J. Stoodley and N. R. Whitehouse, *J. Chem. Soc., Perkin Trans. 1*, 32 (1973).

(10) That **3** should close more readily than **6c** follows from the comparison of carbinolamide equilibria in **2** and **6a** and from the expected greater reactivity of the aldehyde *vs.* the ketone.

(11) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

C_3 substituent occupies the less crowded α side of the molecule, and (2) $J_{cis} > J_{trans}$. The latter assumption is usually reliable for five-membered rings which do not deviate appreciably from planarity,[12] a situation dictated here by the fused β-lactam ring. In both 2 and **4b** the C_2 and C_3 protons give rise to an ABX pattern with $J_{AX} \cong 0$ and $J_{BX} = 5$ Hz (A is the higher field C_2 proton, X is H_3). This leads to the conclusion that, if H_3 is β (assumption 1), the higher field proton at C_2 must be α (trans) and the lower field proton β (cis). Examination of models for the conformation which has been assigned to phenoxymethylpenicillin[11] indicates that a dihedral angle between H_2 and H_3 of 90–100°, for which J would be expected to approach 0 Hz, is not unreasonable. The arguments presented here are self-consistent and follow the expected pattern for "well-behaved" molecules. The assignments remain tentative, however, and the configuration at C_3 in **9b** and **9c** remains ambiguous.

Experimental Section

Melting points, determined on a Fisher-Johns hot stage, are corrected. Ir spectra were recorded in methylene chloride solution on a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were determined in deuteriochloroform unless otherwise noted, using tetramethylsilane as an internal standard. Nmr spectra were recorded on Varian T-60 or Hitachi Perkin-Elmer R-20B spectrometers. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Sulfenyl Chloride 1. 3-Phthalimido-4-(2′-hydroxy-1′,1′-dimethylethylthio)azetidin-2-one.—A solution of 3.0 g (9.4 mmol) of **3**[7] in 50 ml of tetrahydrofuran was cooled in an ice bath, and 2.0 ml (4.1 mmol) of a solution of 386 mg of sodium borohydride in 5 ml of water was added. The solution was stirred in the ice bath for 3 min and brought to pH 3–4 with 1 *N* hydrochloric acid. The resulting solution was poured into 150 ml of methylene chloride and washed with three 50-ml portions of water. The methylene chloride solution was dried and evaporated to a white foam. This was redissolved in methylene chloride and the solution was concentrated to give 2.6 g (97%) of white solid. Recrystallization from methylene chloride–hexane gave the crystalline alcohol: mp 196–197°; $[\alpha]^{23}D$ −6° (*c* 0.91, $CHCl_3$); ir 3600–3420 (broad), 3400, 1785, 1770, 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 7.04 (broad s, 1, NH), 5.65 (dd, 1, $J_{1,4} = 1$ Hz, $J_{3,4} = 4.8$ Hz, H-4), 5.40 (d, 1, $J = 4.8$ Hz, H-3), 3.50 (s, 2, CH_2), 2.40 (broad s, 1, OH), 1.08 and 1.07 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74; S, 10.01. Found: C, 55.99; H, 5.13; N, 8.60; S, 10.00.

***N*-Trifluoroacetyl-3-phthalimido-4-(2′-trifluoroacetoxy-1′,1′-dimethylethylthio)azetidin-2-one.**—A solution of 2.0 g of the above alcohol and 10 ml of trifluoroacetic anhydride in 200 ml of methylene chloride was stirred with 1.5 g of anhydrous potassium carbonate for 64 hr at room temperature. The mixture was filtered and the filtrate was evaporated to a white solid. This was recrystallized from methylene chloride–hexane at −78° to give 2.67 g (83%) of the trifluoroacetyl derivative: mp 148–149°; $[\alpha]^{23}D$ −125° (*c* 1.2, $CHCl_3$); ir 1825, 1775, 1730 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.80 (AB quartet, 2, $J = 6.4$ Hz, H-3 and H-4), 4.31 (AB quartet, 2, $J = 11$ Hz CH_2), 1.45 and 1.35 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{19}H_{14}N_2O_6SF_6$: C, 44.54; H, 2.75; N, 5.47; S, 6.26; F, 22.25. Found: C, 44.57; H, 2.73; N, 5.55; S, 6.41; F, 22.36.

To a solution of 500 mg (0.98 mmol) of the above trifluoroacetyl derivative in 10 ml of methylene chloride was added 3.5 ml (2.1 mmol) of a solution of chlorine in carbon tetrachloride (44 mg/ml). The solution stood for 9–16 hr at room temperature and was concentrated *in vacuo* to a yellow oil: ir 1830, 1775, 1725 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.06 (s, 2, H-3 and H-4); in C_6D_6 an AB quartet appeared at δ 5.25 (J = 6.8 Hz). This oil was used without further purification.

3-Hydroxy-6-phthalimidopenam (2).—The sulfenyl chloride 1 from 500 mg of the trifluoroacetyl derivative was dissolved in 5 ml of methylene chloride and 0.2 ml of ethyl vinyl ether was added. The yellow color of the solution disappeared immediately. The solution stood for 1 hr and was concentrated to a colorless oil which was chromatographed on 25 g of Florisil. After washing the column with 200 ml of methylene chloride, the product eluted in 2.5 l. of 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from methylene chloride–hexane to give 96 mg (34%) of amorphous white solid. Recrystallization gave an analytical sample: mp 146–147°; $[\alpha]^{23}D$ 134° (*c* 0.67, $CHCl_3$); ir 3600, 1790, 1770 and 1720 cm^{-1}; nmr (acetone-d_6) δ 7.98 (s, 4, aryl), 6.06 (d, 1, $J = 5$ Hz, H-3), 5.77 and 5.52 (two d, 2, H = 4 Hz, H-5 and H-6), 3.68 (dd, 1, $J_{gem} = 11$ Hz, $J_{vic} = 5$ Hz, H-2β), 3.22 (d, 1, $J = 11$ Hz, H-2α), 2.95 (s, 1, OH).

Anal. Calcd for $C_{13}H_{10}N_2O_4S$: C, 53.79; H, 3.47; N, 9.65; S, 11.05. Found: C, 53.57; H, 3.36; N, 9.54; S, 11.03.

2,2-Dimethyl-3-acetoxy-6-phthalimidopenam (4a).—A solution of 66 mg of **3** in 0.6 ml of acetic anhydride and 0.1 ml of pyridine stood at room temperature for 3 hr and was concentrated at 0.5 mm to a clear oil. This was dissolved in methylene chloride and reconcentrated to a white foam. A 50-mg sample was chromatographed on 6 g of Florisil. After the column was washed with 100 ml of methylene chloride, the product was eluted with 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil: ir 1795, 1775 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.50 (s, 1, H-3), 5.65 and 5.50 (two d, 2, H = 4 Hz, H-5 and H-6), 2.20 (s, 3, OAc), 1.81 and 1.55 [two s, 6, $(CH_3)_2$]. Small signals (±10%) are visible which correspond to those expected for the *N*-acetyl derivative of **3**.

3-Acetoxy-6-phthalimidopenam (4b).—A solution of 50 mg of **2** in 0.6 ml of acetic anhydride and 0.1 ml of pyridine stood for 3 hr at room temperature and was concentrated at 0.5 mm to a white solid. This was chromatographed on 6 g of Florisil. The product eluted in the first 50 ml of 9:1 methylene chloride–ethyl acetate and was recrystallized from methylene chloride–hexane to give 35 mg (61%) of white crystals: mp 195–196°; $[\alpha]^{23}D$ 179° (*c* 0.89, $CHCl_3$); ir 1795, 1775, 1745, and 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 6.89 (d, 1, $J = 5$ Hz, H-3), 5.68 and 5.47 (two d, 2, $J = 4$ Hz, H-5 and H-6), 3.86 (dd, 1, $J_{gem} = 11$, $J_{vic} = 5$ Hz, H-2β), 3.26 (d, 1, $J = 11$ Hz, H-2α), 2.14 (s, 3, OAc).

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.63; N, 8.42; S, 9.64. Found: C, 54.28; H, 3.65; N, 8.35; S, 9.51.

3-Phthalimido-4-(2′-keto-1′-propylthio)azetidin-2-one (6a).—The sulfenyl chloride 1 from 500 mg of trifluoroacetyl derivative was dissolved in 5 ml of benzene, and 0.5 ml of acetone was added. The solution stood for 24 hr and was concentrated to a yellow oil, which was chromatographed on 25 g of Florisil. After the column was washed with 125 ml of 9:1 methylene chloride–ethyl acetate, the product was eluted with 750 ml of 4:1 and 100 ml of 7:3 methylene chloride–ethyl acetate. Evaporation of the solvents left a solid which was recrystallized from methylene chloride–hexane to give 228 mg (77%) of white crystals: mp 189–90°; $[\alpha]^{23}D$ −26° (*c* 0.55, $CHCl_3$); ir 3380, 1790, 1770, and 1725 cm^{-1}; nmr (pyridine-d_5) δ 7.5–8.0 (m, 4, aryl), 6.16 (dd, $J_{1,4} = 1$, $J_{3,4} = 4.8$ Hz, H-4), 5.50 (d, 1, $J = 4.8$ Hz, H-3), 5.05 (broad, s, 1, NH), 3.58 (s, 2, CH_2), 2.07 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.98; N, 9.21; S, 10.54. Found: C, 55.26; H, 3.99; N, 9.00; S, 10.61.

3-Phthalimido-4-(2′-keto-1′-methyl-1′-propylthio)azetidin-2-one (6b).—In the same manner as for **6a**, the sulfenyl chloride from 500 mg of trifluoroacetyl derivative in 5 ml of benzene and 0.5 ml of 2-butanone gave a colorless oil. After chromatography and recrystallization, 210 mg (68%) of white crystals were obtained: mp 154–155°; ir 3380, 1790, 1770, and 1725 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 7.17 (broad s, 1, NH), 5.71 (broadened doublet, 1, $J = 5$ Hz, H-4), 5.20 (d, 1, $J = 5$ Hz, H-3, 3.5 (two overlapping q, 1, $J = 7$ Hz, SCHCO), 2.25 (s, 3, CH_3CO), 1.4 (two overlapping d, 3, $J = 7$ Hz, CH_3CS).

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.65; H, 4.64; N, 8.78; S, 10.29.

3-Phthalimido-4-(2′-keto-1′,1′-dimethyl-1′-propylthio)azetidin-2-one (6c).—In the same manner as for **6a**, the sulfenyl chloride from 500 mg of trifluoroacetyl derivative in 5 ml of benzene and 0.5 ml of 3-methyl-2-butanone gave a black oil. After chromatography and recrystallization, 170 mg (52%) of white crystals were obtained: mp 176–177°; $[\alpha]^{23}D$ −35° (*c* 0.99, $CHCl_3$); ir 3390, 1790, 1770, 1725, and 1690 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.82 (broad s, 1, NH), 5.70 (dd, 1, $J_{1,4} = 1$, $J_{3,4} = 5$ Hz, H-4),

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 288.

5.05 (d, 1, J = 5 Hz, H-3), 2.26 (s, 3, CH_3CO), 1.46 and 1.38 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.64; H, 4.90; N, 8.38; S, 9.74.

N-Acetyl-3-phthalimido-4-(2′-keto-1′-propylthio)azetidin-2-one (7).—A suspension of 60 mg of **6a** in 1 ml of acetic anhydride and 0.5 ml of pyridine was stirred at 52° for 16 hr. The resulting light-brown solution was concentrated at 0.5 mm to an oil which was chromatographed on 15 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product was eluted with 250 ml of 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from methylene chloride–hexane to give 30 mg (44%) of delicate crystals: mp 181–182°; $[\alpha]^{23}D$ −77° (c 1.1, $CHCl_3$); ir 1800, 1775, 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.73 and 5.45 (two d, 2, J = 6 Hz, H-3 and H-4), 3.73 (AB quartet, 2, J = 16 Hz, CH_2), 2.50 (s, 3, NAc), 2.23 (s, 3, CAc).

Anal. Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.07; N, 8.08; S, 9.25. Found: C, 55.29; H, 3.92; N, 7.98; S, 9.12.

2,2-Dimethyl-3-methoxy-6-phthalimidopenam (9a).—A solution of 250 mg (0.7 mmol) of **3** and 190 mg (0.7 mmol) of mercuric chloride in 12 ml of methanol was stirred at 52° for 16 hr. Evaporation of the solvent left an oily residue which was triturated with benzene. The benzene extracts were concentrated to an oil which was chromatographed on 20 g of Florisil. The column was washed with 650 ml of methylene chloride, and the product was eluted with 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from ethyl acetate–hexane to give 65 mg (28%) of long needles: mp 125–126°; $[\alpha]^{23}D$ 215° (c 1.2, $CHCl_3$); ir 1790, 1775, 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.60 and 5.40 (two d, 2, J = 4.0 Hz, H-5 and H-6), 4.97 (s, 1, H-3), 3.52 (s, 3, OCH_3), 1.64 and 1.54 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 58.00; H, 4.90; N, 8.40; S, 9.80.

3-Methyl-3-methoxy-6-phthalimidopenam (9b).—In the same manner as for **9a**, the oil from 144 mg (0.47 mmol) of **6a** and 129 mg (0.47 mmol) of mercuric chloride was chromatographed on 14 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and evaporation left a crystalline solid. Recrystallization from ethyl acetate–hexane gave 60 mg (40%) of needles: mp 170–172°; $[\alpha]^{23}D$ 149° (c 0.91, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.63 and 5.33 (two d, 2, J = 4 Hz, H-5 and H-6), 3.41 (AB quartet, 2, J = 10.5 Hz, CH_2), 3.36 (s, 3, OCH_3), 1.96 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.69; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.29; H, 4.34; N, 8.57; S, 10.31.

2,3-Dimethyl-3-methoxy-6-phthalimidopenam (9c).—In the same manner as for **9a**, the oil from 134 mg (0.42 mmol) of **6b** and 115 mg (0.42 mmol) of mercuric chloride was chromatographed on 13 g of Florisil. After the column was washed with 110 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and the product was obtained as an oil which crystallized from ethyl acetate–hexane to give 23 mg (16%) of needles: mp 130–131°; $[\alpha]^{23}D$ 191° (c 1.1, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.57 and 5.25 (two d, 2, J = 4 Hz, H-5 and H-6), 4.06 (q, 1, J = 7 Hz, H-2), 3.36 (s, 3, OCH_3), 1.83 (s, 3, C_3CH_3), 1.32 (d, 3, J = 7 Hz, C_2CH_3).

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.55; H, 4.85; N, 8.17; S, 9.77.

Acknowledgment.—We wish to thank the Sloan Basic Research Fund No. 27609 for support of this work. J. U. P. acknowledges partial support by Simmons College for a leave of absence.

Registry No.—**1**, 41189-52-0; **2** open form, 41189-53-1; ring form, 41189-54-2; **3** open form, 41189-55-3; **3** ring form, 41189-56-4; **4a**, 41189-57-5; **4b**, 41189-58-6; **6a**, 41189-59-7; **6b**, 41189-60-0; **6c**, 41189-61-1; **7**, 41189-62-2; **9a**, 41189-63-3; **9b**, 41189-64-4; **9c**, 41189-65-5; 3-phthalimido-4-(2′-hydroxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-66-6; *N*-trifluoroacetyl-3-phthalimido-4-(2′-trifluoroacetoxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-67-7; acetone, 67-64-1; 2-butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4.

Benzimidazoles from Preformed Imidazoles. A Novel Approach

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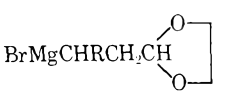
Benzimidazole derivatives **5a–e** are prepared in a two-step procedure by successive reactions of readily available imidazole-5-carboxaldehydes with reagents $BrMgCHRCH_2CHOCH_2CH_2O$ (R = H, CH_3) and cyclization of the resulting carbinols **3a–e** under controlled conditions. Alcohol $ArCHOHCH_2CH_2CHOCH_2CH_2O$ (Ar = 1-benzyl-2-methyl-5-imidazolyl) has been oxidized (MnO_2) to the ketone; addition of Grignard reagents thereto and ring closure of the new carbinols to compounds **9** and **10** illustrates a general preparation of 7-substituted benzimidazoles.

Benzimidazoles are traditionally synthesized by ultimate construction of the imidazole moiety, whereby the prerequisite *o*-phenylenediamines are cyclized with carboxylic acids and/or derivatives thereof. An alternative assembly, commencing with preformed and suitably functionalized imidazoles, has, to the best of our knowledge, hitherto escaped attention. Such an approach is herewith illustrated. It is, by its nature, complementary to existing methods, thereby allowing entry into systems otherwise found to be difficultly accessible.

In a recent[1] report concerning the hydroxymethylation of 1,2-disubstituted imidazoles, the preparation of the imidazolyl-5-methanols and 4,5-dimethanols was described. The reaction, carried out in refluxing aqueous CH_2O, proved to be pH sensitive and produced satisfactory results only in buffered (NaOAc–AcOH) milieu. Subsequent oxidation [$Pb(OAc)_4$] of the products to the aldehydes proceeded cleanly, thus providing an efficient and cheap two-step route to many imidazole-5-carboxaldehydes.

Grignard reagents **1a** and **1b** have, since 1969, found application in the synthesis of (±)-nuciferal[2]

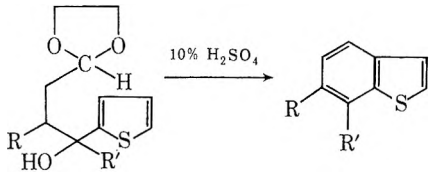


1a, R = H
b, R = CH_3

(1) E. F. Godefroi, H. J. J. Loozen, and J. Th. J. Luderer-Platje, *Recl. Trav. Chim. Pays-Bas*, **91**, 1383 (1972).

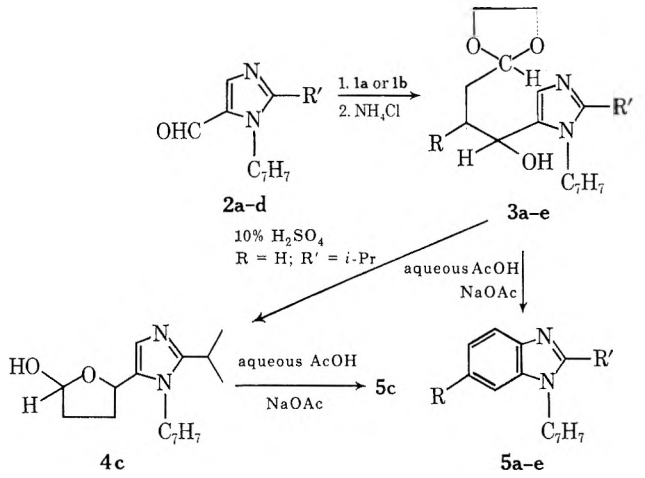
(2) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).

and in a general preparation of benzo[*b*]thiophenes.[3] In the present work, **1a** was allowed to react with imidazole-5-carboxaldehydes **2a–d**[1] in tetrahydrofuran, furnishing in good yields alcohols **3a–d**; similar treatment of **2b** with **1b** gave **3e**. Compound **3c** was chosen as a protoype in establishing conditions required for benzimidazole formation. Refluxing of **3c** in 10% H_2SO_4 resulted in removal of the acetal group, thereby furnishing hemiacetal **4c**. This is not surprising. Whereas these conditions had been effective in bringing about ring closure in related thiophene systems,[3] such pronounced acidic circumstances



will protonate the more basic imidazoles, thus inactivating them toward electrophilic processes. Treatment, however, of **3a–e** with refluxing NaOAc–AcOH buffer solution did produce benzimidazoles **5a–e**. Such conditions also sufficed for converting **4c** to **5c** (Scheme I).

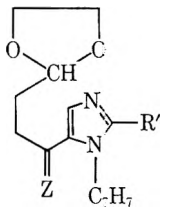
SCHEME I



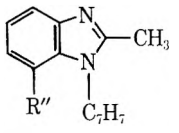
a, R = H; R′ = CH_3
b, R = H; R′ = C_2H_5
c, R = H; R′ = *i*-C_3H_7
d, R = H; R′ = *t*-C_4H_9
e, R = CH_3; R′ = C_2H_5; C_7H_7 = benzyl

The method also proved to be of value in preparing 7-substituted benzimidazoles, as the following examples indicate. Oxidation (MnO_2–$CHCl_3$) of alcohols **3a** and **3c** produced ketones **6a** and **6b**. Of these, **6a** was treated with methyl- and isopropylmagnesium halides; the resulting tertiary alcohols (**7a** and **8a**) cyclized smoothly and provided benzimidazoles **9** and **10**.

Related reactions were found to be of particular value in gaining entry into di- and tetrahydrobenzimidazoles. To this end ketones **6a** and **6b** were reduced under Wolff–Kishner conditions to methylene derivatives **11a** and **11b**. Cyclizations were, in both cases, conducted in refluxing NaOAc–AcOH buffer (15 hr), whereby tetrahydro-4-hydroxybenzimidazoles **12a** and

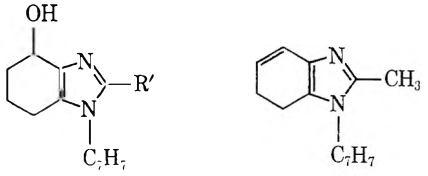


6a, R′ = CH_3; Z = O
b, R′ = *i*-C_3H_7; Z = O
7a, R′ = CH_3; Z = (CH_3)(OH)
8a, R′ = CH_3; Z = (*i*-C_3H_7)(OH)
11a, R′ = CH_3; Z = (H)(H)
b, R′ = *i*-C_3H_7; Z = (H)(H)



9, R″ = CH_3
10, R″ = *i*-C_3H_7; C_7H_7 = benzyl

12b were produced in moderate yields. Moreover, from the reaction mixture arising from **11a** a second component was isolated by column chromatography. Nmr spectra (see Experimental Section) and analytical data left no doubt as to its being **13**. Utilization of



12a, R′ = CH_3
b, R′ = *i*-C_3H_7

13

this approach into partially hydrogenated benzimidazoles is presently under investigation.

Experimental Section

General.—Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra (Varian A-60, TMS as internal standard) and ir data (Perkin Elmer 337) were consistent with assigned structures. Microanalyses were performed by Messrs. P. van den Bosch and H. Eding from our laboratories.

Starting Materials.—Grignard reagents **1a**, **1b**, and imidazole-5-carboxaldehydes **2a–c** were prepared as reported.[1] Aldehyde **2d** was obtained analogously (a) from 1-benzyl-2-*tert*-butylimidazole[1] to the 5-hydroxymethyl derivative (aqueous CH_2O, AcOH, NaOAc; 16-hr reflux; 47%), mp [EtOH–(*i*-Pr)$_2$O] 183–184°; (b) from oxidation [$Pb(OAc)_4$–pyridine] of the carbinol to **2d** (43%), mp [$CHCl_3$–(*i*-Pr)$_2$O] 181–182°, nmr ($CDCl_3$) δ 9.28 (s, 1, CHO).

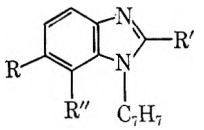
All benzimidazoles and their open-chained precursors have been compiled in Tables I and II, respectively. Experimental details for preparing **3b** and **5b** are given.

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3(1-benzyl-2-ethylimidazol-5-yl)propane (3b).—To a THF solution of **1a**, prepared from 5.0 g (0.026 mol) of the bromide[2] and 0.65 g (0.026 g-atom) of Mg was introduced slowly and with stirring at 30–35° 4.0 g (0.019 mol) of **2b** in 10 ml of THF. After 5 hr the mixture was poured onto 10% NH_4Cl solution. Extraction of the product into $CHCl_3$ and washing, drying, and stripping of solvent left a viscous oil which crystallized on addition of (*i*-Pr)$_2$O: yield 4.1 g (85%); mp [EtOH–(*i*-Pr)$_2$O] 88–89°; nmr ($CDCl_3$) δ 4.38 (t, 1, CHOH).

1-Benzyl-2-ethylbenzimidazole (5b).—Compound **3b**, 2.0 g (0.006 mol), in a solution of 6 ml of AcOH, 8 g of NaOAc, and 50 ml of H_2O, was refluxed for 16 hr. The solution was rendered basic (NaOH) and the product was extracted into $CHCl_3$. Drying and solvent removal left 1.1 g (70%) of essentially pure, oily product: nmr ($CDCl_3$) δ 1.30 (t, 3, CH_3), 2.70 (q, 2,

(3) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 1056 (1973).

TABLE I



Compd	Yield,[a] %	Mp, °C	Derivative	Mp, °C	Empirical formula[e]
5a[c]	77		Picrate	185–189	$C_{15}H_{14}N_2$
5b[d]	70		Picrate	178–180	$C_{16}H_{16}N_2$
5c	92		Picrate	177–178	$C_{17}H_{18}N_2$
5d[b]	33	163–165			$C_{18}H_{20}N_2$
5e	94		Picrate	208–209	$C_{17}H_{18}N_2$
9	75	68–72	Picrate	218–219	$C_{16}H_{16}N_2$
10	62	128–129			$C_{18}H_{20}N_2$

[a] Yields are based on crude product of more than 95% purity (nmr). [b] Crude product chromatographed over silica. [c] N. S. Koslov and M. N. Stepanova, *Dokl. Akad. Nauk Beloruss. SSR*, B(6), 541 (1969); *Chem. Abstr.*, **71**, 124337a (1969). [d] K. Kondal Reddy, N. V. Subba Rao, and C. V. Ratna, *Indian J. Chem.*, **1**, 96 (1963). [e] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

CH_2CH_3), 5.08 (s, 2, $CH_2C_6H_5$), 7.52 (m, 1, H-4 proton), 6.62–7.20 (m, 8, remaining aromatic protons).

4-Hydroxy-4-(1-benzyl-2-isopropylimidazol-5-yl)butyraldehyde (as Hemiacetal 4c).—A solution of 1.0 g (0.003 mol) of **3c** in 10 ml of 10% H_2SO_4 was refluxed for 40 min. The solution was rendered alkaline and was extracted with $CHCl_3$. Drying, solvent evaporation, and trituration of the residual oil with $(i\text{-Pr})_2O$ gave 0.650 g of product: mp 138–139°; ir (KBr) 3000–3500 cm^{-1} (OH), no C=O absorption.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.60; H, 7.69; N, 9.79. Found: C, 71.33; H, 7.68; N, 9.59.

Refluxing of 0.5 g of **4c** in a buffer consisting of 2 g of NaOAc, 2 ml of AcOH, and 15 ml of H_2O and isolation of the product as for **5b** gave 0.3 g of an oil, spectrally (nmr) indentical with **5c**.

1-(1,3-Dioxolan-2-yl)-3-oxo-3-(1-benzyl-2-methylimidazole-5-yl)propane (6a).—A mixture of 32 g (0.11 mol) of **3a**, 150 g of activated MnO_2,[4] and 300 ml of C_6H_6 was stirred and monitored (tlc) for 24 hr. Removal of MnO_2 and solvent evaporation left 26 g (81%) of essentially pure, oily **6a**: nmr ($CDCl_3$) δ 2.30 (s, 3, CH_3), 3.74 (m, 4, dioxolane protons), 5.47 (s, 2, $CH_2C_6H_5$), 7.62 (s, 1, imidazole, 4 H); ir (Nujol) 1685 cm^{-1} (C=O), no OH absorption.

Compound 6b, the isopropyl analog of **6a**, was prepared analogously. The ketone, an oil, was characterized *via* the oxime, mp 184–185°.

Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.45; H, 7.42; N, 12.49.

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3-(1-benzyl-2-methylimidazol-5-yl)butane (7a).—Dropwise addition of 6.0 g (0.02 mol) of crude **6a** to 20 ml of 1 *M* MeMgI in Et_2O and customary work-up of the mixture after 2 hr with 10% NH_4Cl afforded an oil. This was triturated with $(i\text{-Pr})_2O$ to give 3.2 g (51%) of **7a**, mp 115–118°.

1-(1,3-Dioxolan-2-yl)-3-(1-benzyl-2-methylimidazol-5-yl)propane (11a).—To a solution of 20 g (0.066 mol) of **6a** in 150 ml of diethylene glycol was added 15 g of powered KOH and 10 ml of $N_2H_4 \cdot H_2O$. The mixture was refluxed for 1 hr, whereupon solvent was removed until the internal temperature had reached 200°. Hereupon heating was continued for an additional 5 hr. The reaction was quenched by addition to water from which the product was isolated by ether extraction. Drying and solvent removal then left crude, oily product, which, on distillation gave 13.2 g (70%) of product: bp 170–180° (0.02 mm); nmr ($CDCl_3$) δ 2.28 (s, 3, CH_3), 3.03 (m, 4, dioxolane protons), 5.01 (s, 2, $CH_2C_6H_5$), 6.74 (s, 1, imidazole 4 H), 6.80–7.40 (m, 5, C_6H_5); ir no C=O.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 72.19; H, 7.87; N, 10.38.

Compound 11b, bp 180–184° (0.03 mm), was similarly prepared from **6b**. It solidified on standing; analytical material [petroleum ether (bp 30–60°)] had mp 57–58°.

Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.48; H, 8.08; N, 8.83.

1-Benzyl-2-isopropyl-4-hydroxy-4,5,6,7-tetrahydrobenzimidazole (12b).—A solution of 1.0 g (0.0034 mol) of **11b**, 4 g of NaOAc, and 3 ml of AcOH in 20 ml of H_2O was refluxed for 12 hr. The solution was rendered alkaline and the resulting oil was taken up in Et_2O. Drying and evaporation of the organic phase left an oil, which, on addition of $(i\text{-Pr})_2O$ surrendered 0.35 g (40%) of product: mp (C_6H_6–petroleum ether) 147–149°; nmr ($CDCl_3$) δ 1.26 (d, 6, CH_3), 4.41 (s, 1, OH), 5.02 [m, 1, CH(OH)], 5.13 (s, 2, CH_2Ar).

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.51; H, 8.16; N, 10.89.

Reaction of 11a in Refluxing Aqueous NaOAc–AcOH.—Treatment of 2.0 g (0.0071 mol) of **11a** in a refluxing solution of 8 g of NaOAc and 6 ml of AcOH in 40 ml of H_2O for 12 hr and work-up of the mixture as described for **12b** gave 0.42 g (25%) of **12a**, mp 165–169°.

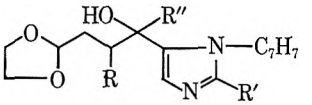
Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.33; H, 74.37; N, 11.38.

Column chromatography of the mother liquors of **12a**, using 2% MeOH in $CHCl_3$ as eluent, provided *ca.* 0.10 g of dihydrobenzimidazole **13**: nmr ($CDCl_3$) δ 2.28 (s, 3, CH_3), 4.95 (s, 2, $CH_2C_6H_5$), 6.45 (d, 1, olefin H_4), 5.56 (m, 1, olefin H_5), 6.90–7.45 (m, 5, C_6H_5).

The picrate salt, prepared in the usual way, had mp 148–152°.

Anal. Calcd for $C_{15}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 55.63; H, 4.22; N, 15.45. Found: C, 55.44; H, 4.41; N, 15.44.

TABLE II



Compd	Yield,[a] %	Mp, °C	Empirical formula[c]
3a	66	108–110	$C_{17}H_{22}N_2O_3$
3b	85	88–89	$C_{18}H_{24}N_2O_3$
3c	68	90–91	$C_{19}H_{26}N_2O_3$
3d	79	138–140	$C_{20}H_{28}N_2O_3$
3e	80	197–99	$C_{19}H_{26}N_2O_3$
7a	51	118–120	$C_{18}H_{24}N_2O_3$
8a[b]	61	159–161	$C_{20}H_{28}N_2O_3$

[a] Yields based on crude, triturated ($i\text{-Pr}_2O$) products of more than 95% purity (nmr). [b] Prepared analogously to **7a** (see Experimental Section). [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

Acknowledgment.—The authors wish to thank the BASF, Ludwigshafen, West Germany, for generous gifts of 1-benzyl-2-methylimidazole and 2-ethyl- and isopropylimidazole.

Registry No.—**2a**, 39269-74-4; **2b**, 39269-75-5; **2c**, 39269-79-9; **2d**, 41030-00-6; **3a**, 41030-01-7; **3b**, 41030-02-8; **3c**, 41030-03-9; **3d**, 41030-04-0; **3e**, 41030-05-1; **4c**, 41030-06-2; **5a**, 5805-83-4; **5a** picrate, 24103-24-0; **5b**, 23982-79-8; **5b** picrate, 24107-49-1; **5c**, 41030-11-9; **5c** picrate, 41030-12-0; **5d**, 41030-13-1; **5e**, 41030-14-2; **5c** picrate, 41030-15-3; **6a**, 41030-16-4; **6b**, 41030-17-5; **6b** oxime, 41030-18-6; **7a**, 41030-19-7; **8a**, 41030-20-0; **9**, 41030-21-1; **9** picrate, 41030-22-2; **10**, 41030-23-3; **11a**, 41030-24-4; **11b**, 41030-25-5; **12a**, 41047-21-6; **12b**, 41030-26-6; **13**, 41030-27-7; **13** picrate, 41030-28-8; 1-(1,3-dioxolan-2-yl)-2-bromoethane, 18742-02-4.

(4) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

Novel Lossen Rearrangements of 3-Benzenesulfonyloxy(1*H*- and 1-methyl)-2,4-quinazolinediones Induced by Alkoxide Ions[1]

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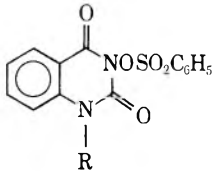
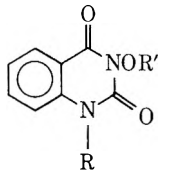
Unexpected Lossen rearrangement products are obtained when sodium alkoxides are added slowly to a solution of the title compounds, **1a** and **1b**, in either alcoholic or DMF media. The slow addition of sodium methoxide to a solution of **1a** in hot methanol furnished *o*-$C_6H_4(CO_2CH_3)NHNHCO_2CH_3$ (45%). A by-product of this reaction is 3-hydroxy-2,4-quinazolinedione (**2a**, 34%), which becomes the major product when **1a** is boiled (3 min) either in aqueous sodium hydroxide or a methanol solution containing sodium methoxide. However, the reaction of **1a** with sodium hydride or methoxide in DMF gave 2-benzimidazolone (88%). The 1-methyl analog, **1b**, was rearranged by various alkoxide ions to 3-indazolone derivatives (40–78%) together with 1-methyl-3-hydroxy-2,4-quinazolinedione (10–35%). Mechanisms are advanced to explain these rearrangements.

The almost spontaneous rearrangement of 3-benzenesulfonyloxy-5,6-dihydrouracil to give ethylenediamine takes place in an aqueous solution containing 1 equiv of sodium hydroxide.[2] In contrast, the aromatic analog, 3-benzenesulfonyloxy-2,4-quinazolinedione (**1a**), is quite stable in a cold 10% aqueous sodium hydroxide solution, but is hydrolyzed to the *N*-hydroxy heterocycle **2a** (77%) after the solution is boiled for several minutes.[2] This nucleophilic substitution reaction involves attack by the base on sulfur with the release of the anion of **2a**. The sulfonate group was also lost when a methanol solution of **1a** containing 2 equiv of sodium methoxide was boiled briefly to furnish **2a** in 78% yield.



1a, R = H
b, R = CH_3



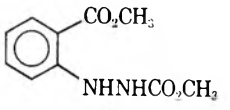
2a, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3
d, R = R′ = CH_3

Rearrangements of 1a.—The *slow* addition of sodium methoxide to a solution of **1a** in hot methanol led to the interesting observation that, besides **2a** (34%), there is formed the *o*-hydrazino ester **3** (45%) and 3-methoxy-2,4-quinazolinedione (**2c**, 7%). The structure of **3** was established by pmr and mass spectra and its transformation to 3-indazolone (**4a**). The identity of **2c** was established by comparison with a sample synthesized by methylating **2a**.

A further departure from the reactions described so far was realized when a solution of sodium methoxide was added to a solution of **1a** in *N*,*N*′-dimethylformamide (DMF) at 100°. There was isolated 2-benzimidazolone (**5a**) in 88% yield. This rearrangement perhaps closely parallels the one described for the conversion of 3-benzenesulfonyloxy-5,6-dihydrouracil to ethylenediamine.[2] Confronted with three different reactions for **1a** with bases, we investigated this matter further as a function of the bases and solvents.

(1) Presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 10, 1973.

(2) C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955). Initially, this reaction produces water-soluble derivatives (probably ureas) since no amides were formed with benzoyl chloride. However, acid- or base-catalyzed hydrolysis formed ethylenediamine, characterized as the benzamide.



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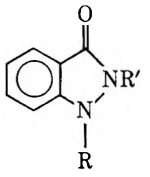
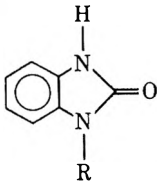
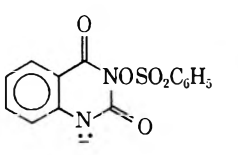


4a, R = R′ = H
b, R = CH_3; R′ = H
c, R = CH_3; R′ = CO_2CH_3



5a, R = H
b, R = $CO_2C_2H_5$
c, R = $CO_2CH(CH_3)_2$

On boiling **1a** in DMF for 3 hr, it was recovered unchanged, which indicated that a strong base was necessary to initiate these observed reactions. Sodium hydride in DMF was chosen as the least nucleophilic base and one most likely to neutralize the acidic NH proton of **1a** to form the anion **6**. Such a step would induce a Lossen rearrangement if **6** opens to **7**, which can be considered a precursor to *o*-benzene diisocyanate (**8**). Since solvents were removed prior to an aqueous work-up, it is suggested that **8** cyclized in DMF solution to benzimidazolone, *or* a substance capable of facile hydrolysis to benzimidazolone.



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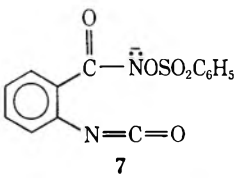

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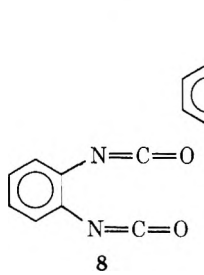

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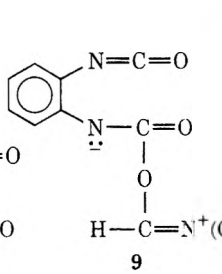

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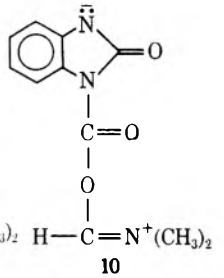

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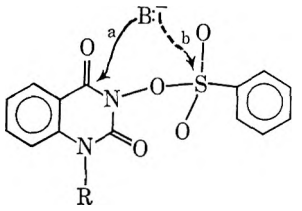
The cyclization of **8** to **5a** in DMF can be explained if DMF, acting as a nucleophilic reagent, adds to **8** to create an intermediate, **9**, which cyclizes to **10**. The latter can be hydrolyzed during an aqueous work-up.

TABLE I

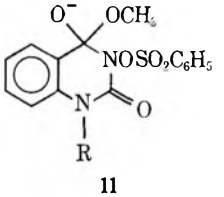
SUMMARY OF RESULTS OF NUCLEOPHILIC ATTACK OF A BASE B:⁻ ON 1



R	Base	Predominant solvent	Yield of product(s), %, due to attack on NH (R = H)	C-4 (path a)	S (path b)
H	NaH	DMF	82		
H	$NaOCH_3$	DMF	88		
H	$NaOCH_3$	CH_3OH		45	41
H	$NaOC_2H_5$	C_2H_5OH	93		5
H	$NaOCH(CH_3)_2$	$(CH_3)_2CHOH$	86		7
CH_3	$NaOCH_3$	CH_3OH		58	17
CH_3	$NaOCH_3$	DMF		78	10
CH_3	$NaOC_2H_5$	C_2H_5OH		41	32
CH_3	$NaOC_2H_5$	DMF		40	35
CH_3	$NaOCH(CH_3)_2$	$(CH_3)_2CHOH$		31	45

It would then appear that hydride or methoxide ions in DMF, acting as strong bases, neutralize, the acidic proton in **1a** and do not attack the sulfonate sulfur atom. In methanol, methoxide ion is less basic and considerably more solvated: the process of neutralization is suppressed while nucleophilic attack on the sulfonate group to give **2a** (path b, top of Table I) produces the anion of **2a** and methyl benzenesulfonate ($C_6H_5SO_3CH_3$). In this medium, the anion of **2a** can undergo an SN2 displacement reaction leading to **2c** and benzenesulfonate anion, which accounts for the 7% of **2c** isolated in that reaction.

However, nucleophilic attack on sulfur competes with one on the highly electrophilic carbon at position 4 in the quinazoline ring[3] (path a on top of Table I). Such an attack of methoxide anion on the C=O group at C-4 of **1a** would create a σ complex, **11** (R = H), which can collapse to form **12**. The latter is the Lossen type of precursor for **13**. The final step in the formation of **3** is the addition of methanol to the isocyanate group of **13** (R = H).



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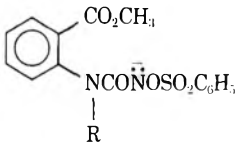

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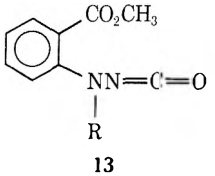
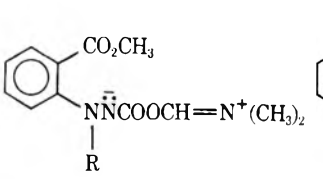


13

In anticipation that sodium ethoxide or isopropoxide, in their respective alcohols, would participate in similar reactions, it was rather surprising to discover that these alkoxide ions in their alcohols produced almost exclusively 2-benzimidazole derivatives **5** (see Table I). It is rather difficult to rationalize how a subtle structural change from methoxide to ethoxide ion would induce two different kind of reactions. The size of the solvated anion and the relative acidity of the methanol solution could expedite attack at C-4 *or* S, to the exclusion of the neutralization of NH in **1a**. The data in Table I summarize the results and the reaction in methanol appears outstandingly different.

Rearrangement of 1b.—The 1-methyl analog **1b** was subjected to a series of analogous reactions, to test if alkoxide ions would attack C-4 once the acidic proton was absent. Methylation of **1a** in cold DMF furnishes **1b** in excellent yield. The reaction of **1b** with sodium methoxide in DMF yielded fewer products than a comparable reaction in methanol. In DMF, there was formed **2b** (11%) and 1-methyl-3-indazolone (**4b**, 78%). The formation of **4b** is explained by attack of methoxide ion at C-4 of **1b** to create **11**–**13** (R = CH_3), which may cyclize in DMF *via* some plausible intermediates **14** and **15**. Methanolysis of the ester group at N-2 can then convert **15** to **4b**.



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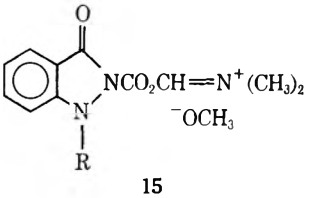

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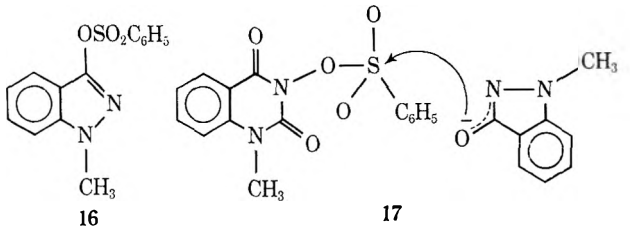
The analogous reaction of **1b** with methoxide ion in methanol furnishes **2b** (12%), **4b** (44%), **4c** (14%), and **2d** (5%). The formation of **4c** is visualized as proceeding *via* a urethane derived from **13** (R = CH_3) and subsequent cyclization. The mechanism suggested for the conversion of **1a** to a small quantity of **2c** (see above) can be applied to the transformation of **1b** to a small amount of **2d**.

We hypothesized that, in the absence of an acidic NH proton, ethoxide and isopropoxide ions would attack either C-4 or S. This premise was verified when **1b** was treated with sodium ethoxide in ethanol. As is evident (Table I) the attack on S increased over that on C-4 to give **2b** (32%) and **4b** (41%). However, the reaction of **1b** with sodium ethoxide in DMF

(3) The high electrophilicity at C-4 in quinazolines is discussed by A. Albert and W. L. F. Armarego in "Advances in Heterocyclic Chemistry," Vol. 4, A. R. Katrizky, Ed., Academic Press, New York, N. Y., 1965, p 1.

gave besides **2b** (35%) a mixture of 1-methyl-3-indazolone (11%) and its corresponding *o*-sulfonate **16** (29%).



16 17

A synthesis of **16** was accomplished by treating **1b** with **4b** in the presence of NaH in DMF. The ambident 1-methyl-3-indazolone anion attacks the sulfonate group as is drawn in **17**. It is therefore quite likely that, in DMF, the 3-indazolone anion, once produced, competes with the ethoxide ion in attacking **1b** to produce **16**.

In order to test the effect of increasing the bulk of the alkoxide ion, **1b** was treated with sodium isopropoxide in 2-propanol. Alcoholysis of the sulfonate group to give **2b** increased over the formation of indazole derivatives (**4b** and **16**) (Table I).

It is clear that the reactions of **1b** with ethoxide and isopropoxide ion still involve attack at C-4 and are not inhibited by the bulk of these nucleophiles.

Experimental Section[4]

Materials.—Methanol and ethanol refer to commercial grade absolute alcohols. Small quantities of sodium alkoxide solutions were prepared by diluting a stock solution of 1.2 g of sodium in 100 ml of the required alcohol.

3-Benzenesulfonyloxy-2,4(1*H*,3*H*)-quinazolinedione (1a).[5]—Finely powdered **2a**[6] (17.8 g, 0.1 mol) was dissolved in aqueous sodium hydroxide solution (8 g in 400 ml) and finally on a steam bath to dissolve traces of insoluble material. This solution was cooled to 5°, while benzenesulfonyl chloride (26 ml, 0.2 mol) was added dropwise, with stirring over 1 hr. The ice bath was then removed and the mixture was stirred at 25° for 3 hr. The solid was collected, washed with water and 95% ethanol, and recrystallized from 95% ethanol to give **1a** (25.8 g, 81%), mp 234–235° (lit.[2] mp 235–236°), ir identical with that of a literature sample.[2]

1-Methyl-3-benzenesulfonyloxy-2,4(1*H*,3*H*)-quinazolinedione (1b).—To a stirred solution of **1a** (9.7 g, 0.03 mol) in 100 ml of cold DMF and 20 ml of methyl iodide was added dropwise 0.03 mol of sodium ethoxide in 100 ml of ethanol over 2 hr at 25°. The mixture was stirred for 1 hr longer and then poured into 2 l. of ice–water. After 30 min, the white solid was collected, washed with water, and recrystallized from 95% ethanol to furnish pure **1b** (9.4 g, 93%): mp 187–189°; ir (Nujol) 1748, 1725 cm^{-1} (C=O); pmr (TFA) δ 8.46–7.40 (m, aromatic protons), 3.94 (s, NCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 334 (4), 333 (9), 332 (51), 176 (12), 161 (8), 142 (6), 141 (88), 134 (5), 133 (17), 132 (13), 105 (32), 104 (28), 92 (6), 90 (5), 78 (20), 77 (100), 64 (5), 51 (18), 50 (6), 39 (5).

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: N, 8.43. Found: N, 8.43.

Hydrolysis of **1b** (1 g) was achieved by heating it in 5% NaOH solution (10 ml) on a steam bath until a clear solution was obtained (about 5 min). The mixture was filtered to remove traces of insoluble material. The filtrate was cooled to 5° and acidified with concentrated HCl to pH 2. The wall of the flask was scratched and the solution was stored at 0° (3 days) and **2b** was deposited (0.37 g, 64%): mp 223–225° (lit.[7] mp 227°); its ir spectrum was identical with that of an authentic sample prepared by the other route;[7] mass spectrum (70 eV) *m/e* (rel intensity) 193 (12), 192 (100), 176 (27), 175 (6), 162 (38), 148 (5), 133 (11), 132 (62), 119 (5), 105 (32), 104 (33), 92 (80), 90 (8), 78 (16), 77 (28), 76 (8), 64 (10), 51 (13), 50 (10), 39 (8).

3-Methoxy-2,4(1*H*,3*H*)-quinazolinedione (2c).—A solution of **2a** (3.56 g, 0.02 mol) was stirred at 80°, while methyl sulfate (6.3 g, 0.05 mol) was added dropwise over 1 hr. After 2 hr another portion of methyl sulfate (6.3 g) was added and the mixture was stirred for 1 hr longer. The suspension was cooled, and the product (3.3 g 86%) was collected and washed with ice–water: mp 224–226°; ir (Nujol) 3250 (NH), 1750, 1720, 1690 cm^{-1} (C=O); pmr (TFA) δ 8.45–7.43 (4, m, aromatic protons), 4.41 (3, s, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 193 (4), 192 (31), 163 (7), 162 (41), 147 (6), 146 (46), 120 (12), 119 (100), 92 (30), 91 (9), 90 (20), 64 (13), 63 (11), 39 (6).

Anal. Calcd for $C_9H_8N_2O_3$: N, 14.58. Found: N, 14.50.

1-Methyl-3-methoxy-2,4-(1*H*,3*H*)-quinazolinedione (2d).—A mixture of **2a** (0.89 g, 0.005 mol) in 25 ml of water containing NaOH (0.8 g, 0.02 mol) and methyl sulfate (6.3 g, 0.05 mol) was stirred at 80° for 2 hr. The clear solution was chilled in an ice–water bath. The product was collected, washed with a little ice–water, and recrystallized from water to furnish **2d** (1.05 g, 100%): mp 150–152°; ir (Nujol) 1720, 1690 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.45–7.14 (4, m, aromatic protons), 4.10 (3, s, OCH_3), 3.65 (3, s, NCH_3); mass spectrum (70 eV) (rel intensity) 207 (9), 206 (82), 177 (10), 176 (51), 147 (11), 146 (5), 134 (19), 133 (29), 132 (34), 131 (7), 119 (9), 106 (10), 105 (100), 104 (70), 92 (10), 90 (10), 78 (25), 77 (36), 64 (10), 63 (10), 51 (13), 50 (7), 39 (8).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 13.59. Found: N, 13.79.

Reactions of 1a with Sodium Alkoxides. A. Sodium Methoxide in Methanol (Slow Addition).—To a stirred boiling solution of **1a** (3.2 g, 0.01 mol) in methanol (300 ml) was added dropwise (1 hr) a solution of sodium methoxide (0.23 g of sodium in 78 ml of methanol). The suspension[8] was stirred for 0.5 hr longer and then evaporated to dryness *in vacuo*. The residue was extracted with chloroform (3 × 20 ml). The chloroform-insoluble material was suspended in 20 ml of water and acidified with HCl to pH 2. After 18 hr at 5°, there was obtained **2a** (0.6 g, 34%), identical with a prior sample.[2]

The combined chloroform solution was extracted successively with ice-cold 5% NaOH (2 × 20 ml), 5% HCl (2 × 20 ml), and water (2 × 20 ml) and then evaporated to dryness *in vacuo*. The oily residue was dissolved in 10 ml of hot 95% ethanol, and 30 ml of boiling water was added. The hot solution was scratched to effect crystallization. After several hours at 5°, **3** (1.0 g, 45%, mp 106–108°) was obtained as white needles: ir (Nujol) 3315 (NHNH), 1710 cm^{-1} (C=O); pmr ($CDCl_3$) δ 9.26 (1, s, one of the NHNH protons, the other one is buried among the aromatic proton multiplet, as is evident by D_2O exchange), 8.08 (1, dd, H-6, $J_{5,6}$ = 8.0, $J_{4,6}$ = 1.8 Hz), 7.72–6.70 (4, m, H-3, H-4, H-5, NH), 4.23 (3, s, CH_3), 4.08 (3 s, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 225 (8), 224 (56), 193 (6), 192 (30), 160 (7), 150 (5), 149 (9), 148 (57), 147 (10), 134 (17), 133 (100), 120 (5), 119 (12), 106 (7), 105 (74), 104 (16), 92 (10), 91 (10), 90 (6), 79 (5), 78 (14), 77 (91), 76 (15), 65 (8), 64 (9), 63 (8), 59 (55), 52 (9), 51 (25), 50 (10), 39 (9).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: N, 12.49. Found: N, 12.26.

Compound **3** (100 mg) was dissolved in 2 ml of methanol and 3 ml of 5% NaOH. The clear solution was refluxed for 0.5 hr. The pH of the solution was then adjusted with concentrated HCl to 2 and the mixture was boiled under reflux for 10 min. It was then evaporated, *in vacuo*, almost to dryness. The resi-

(4) All melting points are uncorrected and were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. Analyses for N were determined with the use of a Coleman nitrogen analyzer in this department. Infrared spectra were obtained on a Perkin-Elmer 337 recording infrared spectrophotometer. Pmr spectra were recorded by means of a Varian A-60 spectrometer in parts per million (δ), downfield from $(CH_3)_4Si$. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak, using a Hitachi Perkin-Elmer RMU-6D single-focusing mass spectrometer. Usually, ions with 5% of base peak or more are recorded only, from *m/e* 39. Thin layer chromatographs (tlc) were developed on slides over 7.2 cm (15 min) coated with silica gel and a fluorescent indicator (Eastman chromagram sheet 6060) using the following solvent systems, designated by letters: A, ethyl acetate; B, methanol. Spots were detected by uv light.

(5) The original preparation of **1a** from sodium phthalohydroxamate (ref 2) has been modified and the method described by L. Bauer and C. S. Mahajanshetti [*J. Heterocycl. Chem.*, **4**, 325 (1967)] is perhaps more *a propos*.

(6) Prepared in 88% yield from *N*-benzenesulfonyloxyphthalimide, utilizing the method of E. Kühle and R. Wegler [*Justus Liebigs Ann. Chem.*, **616**, 183 (1958)].

(7) C. B. Shapira and S. Lamdan [*J. Heterocycl. Chem.*, **9**, 569 (1972)] have described the synthesis of 1-methyl-3-hydroxy-2,4(1*H*,3*H*)-quinazolinedione from *N*-methylanthranilic acid.

(8) The methanol-insoluble solid was shown to be the sodium salt of **2a** (ir comparison with an authentic sample).

due was dissolved in 2 ml of water and the pH was adjusted with sodium carbonate to 7. The crystalline product was collected, washed with ice-cold water, and recrystallized from methanol to give 3-indazolone (50 mg, 83%): mp 244–247° (lit.[9] mp 246–249°); tlc (solvent B) R_f 0.73; its ir was identical with that of the authentic sample prepared by the literature method,[9] and its mass spectrum was identical with the published one.[10]

The alkaline extract from the $CHCl_3$ solution above was acidified with HCl to pH 2 and extracted with chloroform (5 × 20 ml). After evaporation of the solvent, the residue was triturated with benzene to give **2c** (0.13 g, 7%), mp 220°, identical with the sample prepared above.

B. Sodium Methoxide in Methanol (Fast Addition).—A suspension of **2** (1.6 g, 0.05 mol) in 10 ml of boiling methanol was treated with sodium methoxide (0.23 g of sodium) in 18 ml of methanol, all at once. An emulsion resulted which was boiled for 3 min. After solvents were removed *in vacuo*, the residue was dissolved in 50 ml of water, acidified with HCl to pH 2, and stored at 0° for 18 hr to give **2a** (0.7 g 78%) identical with sample above.

C. Sodium Methoxide in DMF.—To a stirred solution of **1a** (3.1 g, 0.01 mol) in DMF (100 ml) on a steam bath was added sodium methoxide (0.23 g of sodium in 78 ml of methanol) dropwise over 2 hr, and the mixture was heated for an additional 0.5 hr. The solution was evaporated to dryness *in vacuo*, and the residue was diluted with ice-water. The product was filtered and recrystallized from methanol to give 2-benzimidazolone (1.15 g, 88%, white plates): mp 311–313° (lit.[11] mp 309–310°); tlc (solvent B) R_f 0.80; ir identical with that of a sample prepared by Hershenson, *et al.*[11]

D. Sodium Hydride in DMF.—To a solution of **1a** (3.18 g, 0.01 mol) in 100 ml of DMF was added 0.48 g of sodium hydride in mineral oil (50%). It was then stirred and heated on a steam bath for 1 hr. Solvent was removed *in vacuo*, and the residue was triturated with 25 ml of water and 25 ml of petroleum ether (bp 30–60°). The product proved to be **5a** (1.10 g, 82%).

E. Sodium Ethoxide in Ethanol.—A stirred suspension of **1a** (3.2 g, 0.01 mol) in boiling ethanol (300 ml) was treated with sodium ethoxide (0.23 g of sodium in 78 ml of ethanol) dropwise (1.5 hr). The turbid solution was evaporated to dryness *in vacuo*. The residue was extracted with chloroform (4 × 30 ml) and then ether (20 ml) and after removal of these, the oily residue was crystallized by the addition of 2 ml of 95% ethanol. After 1 hr at 5°, the white needles were collected and washed several times with ice-cold 95% ethanol. These proved to be **5b** (1.0 g, mp 148–152°); a second batch (0.2 g, mp 148–154°) was obtained from the mother liquors and ethanol washings after 18 hr at 5°. The combined yield of **5b** was 59%, tlc (solvent A) R_f 0.53. The product was recrystallized from ethanol (50% recovery): mp 158–160°; ir (Nujol) 3275 (NH), 1790 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.10–7.60 (1, m, H-7), 7.14–6.94 (3, m, H-4, H-5, H-6), 4.66 (2, q, CH_2), 1.49 (3, t, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 206 (23), 147 (7), 135 (9), 134 (100), 133 (12), 106 (39), 105 (7), 79 (9), 78 (11), 52 (7), 51 (8).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 14.43. Found: N, 14.21.

The chloroform-insoluble residue was triturated with 10 ml of water, and the precipitate was collected, washed with ice-cold water several times, and then dissolved in 15 ml of 5% NaOH. The solution was filtered to remove insoluble substances. The filtrate was acidified with acetic acid to produce, after 30 min at 0°, 2-benzimidazolone (0.45 g, 34%).

The aqueous solution from triturating the chloroform-insoluble residue was acidified with HCl to pH 2 to yield some **2a** (0.08 g, 4.5%), mp 325°.

The structure of **5b** was proved by heating a suspension of it (0.10 g) with 3 ml of 5% NaOH at 95° for 30 min. The solution was then acidified with glacial acetic acid to produce 2-benzimidazolone (0.05 g, 73%), identical with the product of C.

F. Sodium Isopropoxide in 2-Propanol.—The reaction of **1a** (3.2 g, 0.01 mol) with sodium isopropoxide in boiling 2-propanol, as described under E, provided, from the corresponding chloroform extract, **5c**, which was crystallized from 50% ethanol (1.52 g, 69%): mp 149–151°; ir (Nujol) 3150 (NH), 1780, 1700 cm^{-1} (C=O); pmr (DMSO-d_6) δ 1.38 (6, d, CH_3) 5.15 (1, q, CH), 7.09–7.49 3, m, H-4, H-5, H-6), 7.75–8.02 (1, m, H-7); mass spectrum (70 eV) *m/e* (rel intensity) 221 (2), 220 (15), 178 (11), 161 (6), 160 (6), 135 (10), 134 (100), 133 (8), 106 (15), 43 (18). The analytical sample was recrystallized from 20% ethanol, mp 152–153.5°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.82.

In another run, the oily residue, after 2-propanol was removed, was hydrolyzed directly by refluxing with 30 ml of 10% NaOH for 30 min. Acidification with acetic acid gave **5a** (1.15 g, 86%).

Reactions of 1b with Sodium Alkoxides. G. Sodium Methoxide in DMF.—Addition of $NaOCH_3$ to **1b** (3.22 g, 0.01 mol) was carried out as described for C. The residue, after solvents were evaporated, was extracted with boiling ether (5 × 50 ml). Removal of ether afforded 1-methyl-3-indazolone (**4b**, 1.15 g, 78%), mp 146–150°, tlc (solvent A) R_f 0.38. Recrystallization from aqueous acetone (80% recovery) provided a pure sample, mp 154–155° (lit.[12] mp 151–153°) with ir and mass spectra identical[10] with those of a sample prepared by the literature method.[12]

The ether-insoluble material was suspended in water (10 ml), acidified with 1:1 HCl to pH 2, and collected after 18 hr at 5° (0.2 g, 10%), identical with **2b**.

H. Sodium Methoxide in Methanol.—The reaction of **1b** (3.22 g, 0.01 mol), as performed under the conditions of A, worked up as described under G, gave from the ether-insoluble material **2b** (0.23 g, 12%).

The ether extract was worked up differently. The crystalline residue, after removal of ether, was suspended in benzene and was extracted with 5% NaOH. The aqueous alkaline layer yielded, upon acidification with acetic acid, **4b** (0.65 g, 44%) identified as in G.

The benzene extract was concentrated to 1 ml and chromatographed on a column (54 × 2.5 cm) of silica gel (70–325 mesh ASTM, Brinkmann) packed in benzene–ethyl acetate (3:1). Elution (1 ml/min) with the same solvent mixture was monitored every 20 ml by tlc The fraction from 225 to 275 ml was evaporated *in vacuo* to produce **4c** (0.28 g, 14%): mp 93–95°; ir (Nujol) 1740 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.00–7.05 (4, m, aromatic protons), 4.04 (3, s, CH_3), 3.33 (3, s, CH_3); tlc (solvent A) R_f 0.39; mass spectrum (70 eV) *m/e* (rel intensity) 207 (15), 206 (54), 175 (5), 162 (25), 161 (7), 148 (23), 147 (100), 133 (7), 119 (27), 105 (34), 104 (13), 92 (5), 78 (13), 77 (25), 76 (20).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 13.59. Found: N, 13.92.

A suspension of **5c** (0.2 g) in 3 ml of 5% NaOH was refluxed for 1 hr, and the solution was just acidified with HOAc to yield, after 18 hr at 5°, **5b** (0.11 g, 77%).

From the eluent, 300–335 ml, there was obtained **2d** (0.1 g, 5%), tlc (solvent A) R_f 0.34, identical with specimen prepared above.

I. Sodium Ethoxide in Ethanol.—This experiment, when carried out as per A and G, gave on acidifying the ether-insoluble material **2b** (32%). The ether-soluble material was hydrolyzed with 5% NaOH for 1 hr and worked up as for 1-methyl-3-indazolone (41%).

J. Sodium Ethoxide in DMF.—This experiment was performed as under C and G. The residue, after removal of DMF, was extracted with ether (3 × 50 ml) and acetone (30 ml). The insoluble material was suspended in water and acidified to produce **2b** (35%). The organic extract was evaporated, triturated with water (10 ml) and 1-methyl-3-benzenesulfonyloxyindazole (**16**, 0.83 g, 29%), and recrystallized from 50% aqueous MeOH to give product (90% recovery): mp 103–105°; its ir spectrum (Nujol) lacked bands above 1620 cm^{-1} indicative of the sulfonate ester rather than the sulfonamide type, **4** (R = CH_3; R′ = $SO_2C_6H_5$); pmr ($CDCl_3$) δ 3.90 (3, s, CH_3) and aromatic protons 7.11–7.55 (7, m), 7.90 (1, d), 8.06 (1, d); mass spectrum (70 eV) *m/e* (rel intensity) 288 (11), 147 (100), 119 (4), 105 (13), 77 (14), 76 (10).

Anal. Calcd for $C_{14}H_{12}N_2O_3S$: N, 9.72. Found, N, 9.66.

From the aqueous filtrate of **16** there was deposited on standing (24 hr) some additional **4b** (0.16 g, 11%).

Synthesis of 16.—A solution of the sodium salt of **4b** in DMF was prepared by adding 96 mg of 50% sodium hydride in oil to a solution of **4b** (269 mg, 0.0018 mol) in 20 ml of DMF. There

(9) E. F. M. Stephenson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1955, p 475.

(10) J. M. Desmarchelier and R. B. Jones, *Org. Mass Spectrom.*, **2**, 37 (1969).

(11) F. M. Hershenson, L. Bauer, and K. F. King, *J. Org. Chem.*, **33**, 2543 (1968).

(12) J. Schmutz, F. Hunziker, and W. Michaelis, *Helv. Chim. Acta*, **47**, 1986 (1964).

was then added 500 mg (0.0015 mol) of **1b** and the mixture was heated on a steam bath for 0.5 hr with occasional shaking. The suspension was evaporated to dryness and the residue was extracted with $CHCl_3$ (3 × 20 ml) and ether (20 ml). The combined extract was evaporated to dryness and the oily residue was partitioned between water (20 ml) and petroleum ether (20 ml). The insoluble solid was collected, washed with water, and dried. It weighed 376 mg (87%), mp 103–105°, and was identical with compound **16** isolated from **J**.

The chloroform-insoluble residue was suspended in 10 ml of water and acidified with dilute HCl (1:1) to pH 2. After several hours, pure **2b** was collected and washed with acetone (310 mg 94%).

K. Sodium Isopropoxide in 2-Propanol.—This experiment was performed as described in E. The corresponding chloroform extract was evaporated to dryness. The residue was triturated with ether (3 × 30 ml). The ether-insoluble residue was triturated with water (10 ml) to give **16** (0.2 g). The ether extract was evaporated to 10 ml to obtain a second batch of **16** (0.4 g, combined yield was 21%).

The ether filtrate was evaporated to dryness and the residue was refluxed with 5% NaOH (6 ml) for 30 min to give **4a** (0.15 g, 10%) after acidification.

The chloroform-insoluble residue was dissolved in 20 ml of water and acidified by pH 2 to afford **2b** (0.86 g, 45%).

Registry No.—**1a**, 41120-14-3; **1b**, 41120-15-4; **2a**, 5329-43-1; **2b**, 37833-99-1; **2c**, 41120-18-7; **2d**, 41120-19-8; **3**, 41120-20-1; **4b**, 41120-21-2; **4c**, 41120-26-7; **5a**, 615-16-7; **5b**, 41120-23-4; **5c**, 41120-24-5; **16**, 41120-25-6.

Quinazolines and 1,4-Benzodiazepines. LIX.[1] Preparation of Pyrrolo[2,1-*c*]-1,4-benzodiazepines

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10-Substituted 7-chloro-5,10-dihydro-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines (**5**) were obtained from the corresponding 3-allylbenzodiazepine 4-oxides (**2**) with acetic anhydride. Oxidative cleavage of the pyrrole ring of **5h** gave the known compounds **6** and **9**. The pyrrolidinobenzodiazepine **11** was prepared by conventional reactions *via* the 3-(2-methoxycarbonylethyl)benzodiazepines **4** and **7**. Compound **4** was obtained by base catalyzed addition of methyl acrylate to the benzodiazepine **1a**. The 5-methyl analog of **5** was not accessible through the corresponding 3-allylbenzodiazepine 4-oxide (**14**) since the Polonovsky rearrangement led to compounds **15c–e** instead.

In the course of other studies connected with the synthesis of 3-substituted benzodiazepines,[2,3] a 3-allyl-1,4-benzodiazepine 4-oxide, compound **2a** (Scheme I), was also prepared. It was found that under Polonovsky conditions this compound was converted to the pyrrolo[2,1-*c*]benzodiazepine **5h**. The structure of the pyrrolobenzodiazepine was derived from the spectroscopic and analytical data and was further substantiated by chromic acid oxidation to the known benzodiazepine-2,3-dione **6**[4] and the quinazolinone **9**.[5] Treatment of **5h** with lithium aluminum hydride reduced the amide carbonyl and led to compound **8**. In the nmr spectrum the 11-methylene group of this compound appeared as an AB system with a coupling contant of 15 Hz.

Treatment of the *N*-methoxymethyl derivative **5k** (prepared from **2d**) with ethanolic hydrogen chloride did not result in the expected replacement of the methoxymethyl group by a proton[2] but only in the exchange of the methoxy group by ethoxy to yield compound **5m**.

A plausible mechanism for the conversion of the 3-allylbenzodiazepine to the pyrrolobenzodiazepine is depicted in Scheme II. The first step is no doubt the formation of the Polonovsky rearrangement product, the 3-acetoxy derivative A. Loss of the acetic acid would then yield the diene B. The intermediate diene B could then rearrange thermally *via* the aziridine C or with participation of acetate *via* D to the pyrrolobenzodiazepine **5h**. The transformation D → **5h** involves a 1,3-hydride shift while the thermal rearrangement of C may be formulated as a proton or a hydride shift. Evidence for the formation of a diene such as B was obtained by the isolation of the diene **3f** from the reaction of the dimethylallyl derivative **2c** with acetic anhydride. As anticipated, this particular diene did not convert to a pyrrolobenzodiazepine even under forcing conditions. In addition to being sterically less favorable, the transformation of this diene to the pyrrolobenzodiazepine would also require a methyl shift. The 3-crotylbenzodiazepine **2b** also underwent the conversion to the pyrrolobenzodiazepine **5i**, although in lower yield. The previously described 3-benzylbenzodiazepine **2e**[3] could not be transformed analogously to an indolobenzodiazepine. Instead a mixture of the two isomeric 3-benzylidenebenzodiazepines **3g** was obtained. The major component was readily isolated by crystallization and had been prepared earlier by condensation of 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one with benzaldehyde.[6] The minor component was isolated by chromatography. Based on the chemical shift difference of the benzylidene protons, we have assigned the configuration of phenyl trans to the carbonyl group to the major product.

The pyrrolidinobenzodiazepine **11** was prepared as outlined in Scheme I. Addition of methyl acrylate to **1a** yielded the ester **4**, which was reduced with zinc and acetic acid to afford **7**. Thermal cyclization of this δ-amino ester led to the pyrrolidone **10**. Reduction of both amide carbonyls with lithium aluminum

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(2) A. Walser, G. Silverman, J. Blount, and R. Ian Fryer, *J. Org. Chem.*, **36**, 1465 (1971).

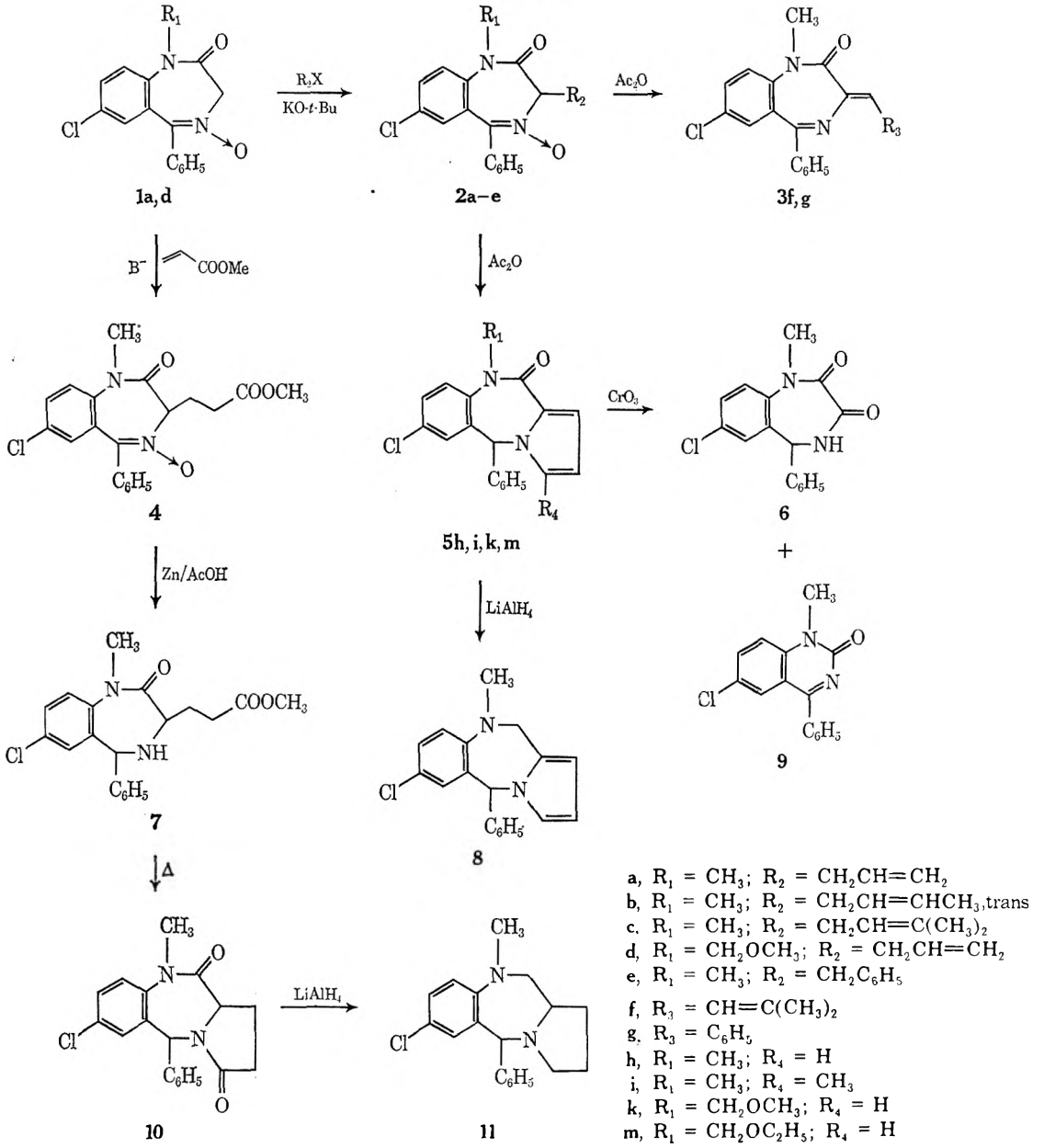
(3) A. Walser, G. Silverman, R. Ian Fryer, L. H. Sternbach, and J. Hellerbach, *J. Org. Chem.*, **36**, 1248 (1971).

(4) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(5) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968).

(6) E. Broger, unpublished work of these laboratories. Analysis provided by courtesy of E. Broger.

SCHEME I



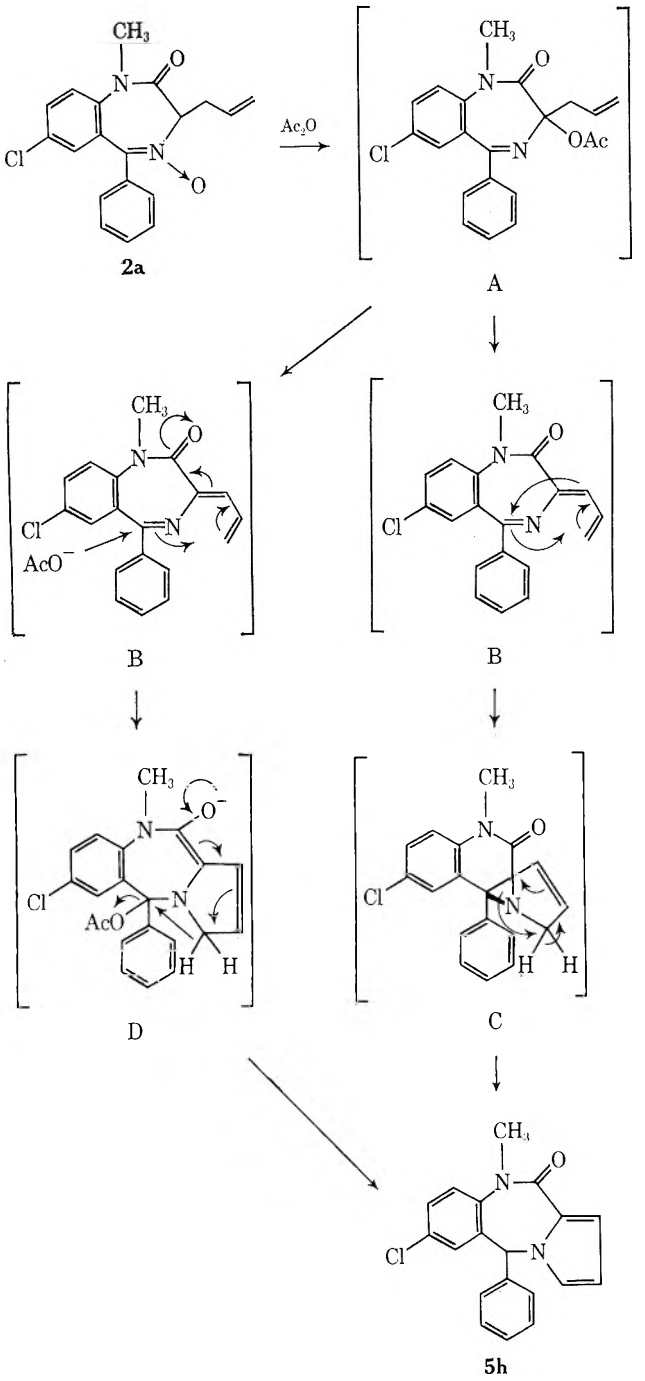
a, $R_1 = CH_3$; $R_2 = CH_2CH{=}CH_2$
b, $R_1 = CH_3$; $R_2 = CH_2CH{=}CHCH_3$,trans
c, $R_1 = CH_3$; $R_2 = CH_2CH{=}C(CH_3)_2$
d, $R_1 = CH_2OCH_3$; $R_2 = CH_2CH{=}CH_2$
e, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$
f, $R_3 = CH{=}C(CH_3)_2$
g, $R_3 = C_6H_5$
h, $R_1 = CH_3$; $R_4 = H$
i, $R_1 = CH_3$; $R_4 = CH_3$
k, $R_1 = CH_2OCH_3$; $R_4 = H$
m, $R_1 = CH_2OC_2H_5$; $R_4 = H$

hydride produced the desired pyrrolidine **11**. Although the stereochemistry has not been unequivocally established it is believed that it is most likely that both the C_3 proton and the C_6 proton of compound **7** take a pseudoaxial orientation. This may also be true for the corresponding protons in the pyrrolidinobenzodiazepines **10** and **11**. The nmr spectra of **7**, **10**, and **11** do not contradict this assignment of stereochemistry.

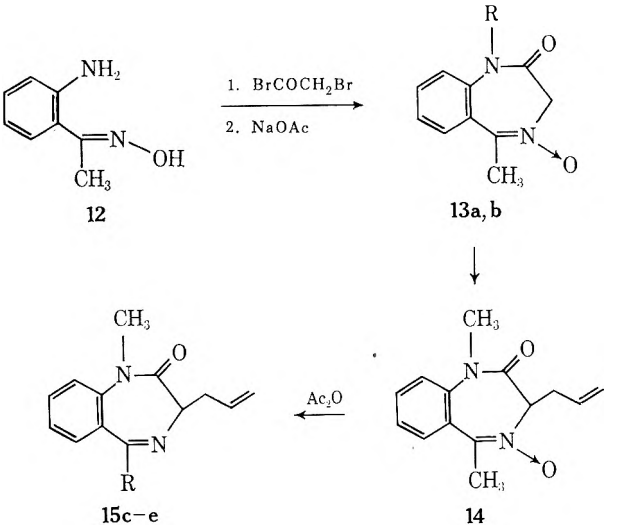
We also looked at the reaction of the 5-methyl analog of **2a**, compound **14**, with acetic anhydride. The benzodiazepine **14** was prepared as shown in Scheme III by alkylation of **13b** with allyl bromide. Compound **13b** was obtained by methylation of **13a**,[7] which in turn was accessible by bromoacetylation of the oxime **12** followed by cyclization of the intermediate bromo acetate. In this case treatment of **14** with acetic anhydride did not give the analogous pyrrolobenzodiazepine. The major product was found to be the 5-acetoxymethyl derivative **15c**. Methanolysis of this acetate produced the rather unstable alcohol **15d**, which was oxidized with manganese dioxide to give the aldehyde **15e**. We observed an unusual long-range coupling between the aliphatic protons of the C_5 substituent and one of the C_3 protons. If it is assumed that in compound **13b** the pseudoaxial proton in the 3 position is more shielded and appears therefore at higher field, then the pseudoequatorial proton would be responsible for the long-range coupling. If this is true it would follow that the allyl group in compounds **14**, **15c**, and **15d** would favor a pseudoaxial orientation. A proton-free 5 substituent seems to be required on the 1,4-benzodiazepine **2** in order to obtain a good yield of the pyrrolobenzodiazepines **5**, since in the Polonovsky reaction the *N*-oxide showed a preference for migration to the 5-methyl group rather than to the 3-methine moiety.

(7) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

SCHEME II



SCHEME III



a, R = H
b, R = CH_3
c, R = CH_2OAc
d, R = CH_2OH
e, R = CHO

Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument in deuteriochloroform with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

3-Allyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2a).—Potassium *tert*-butoxide (13.5 g, 0.12 mol) was added to a solution of 30 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (1a)[8] in 200 ml of dry dimethylformamide cooled to 0°. After stirring for 5 min under nitrogen the mixture was further cooled to −45°, when 14.5 g (0.12 mol) of allyl bromide was added. Cooling was discontinued and the reaction mixture was stirred until it reached room temperature, when it was poured into ice water. The precipitated product was collected, washed with water, and dissolved in methylene chloride. The solution was washed with water, dried over sodium sulfate, filtered, and evaporated The residue was crystallized from ether to yield 24 g (70%) of product, mp 178–180°. The analytical sample was recrystallized from methanol: mp 183–185°; uv λ_{max} 240–241 mμ (ε 30,400) infl 270 (13,500), 316–317 (11,500); ir ($CHCl_3$) 1660 cm^{-1} (CO); nmr δ 3.05 (m, 2, $-CH_2-$), 3.45 (s, 3, NCH_3), 4.26 (t, 1, J = 7 Hz, C_3H), 4.9–6.3 (m, 3, olefinic H), 7–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.25; H, 4.08; N, 8.14.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3-(*trans*-2-butenyl)-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2b).—7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, 30 g (0.1 mol), in 200 ml of dimethylformamide was allowed to react for 20 min at room temperature with 13.5 g (0.12 mol) of potassium *tert*-butoxide and 11 g (0.12 mol) of crotyl chloride. Work-up as described in the previous procedure and crystallization from methanol yielded 10.5 g (30%) of product. The analytical sample was recrystallized twice from methanol: mp 164–167°; nmr ($CDCl_3$) δ 1.63 (d with fine structure, 3, J = 4.5 Hz, CH_3), 3.0 (m, 2, $-CH_2-$), 3.5 (s, 3, NCH_3), 4.2 (t, 1, J = 7 Hz, C_3H), 5.6 (m, 2, olefinic H), 7.1–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.90. Found: C, 67.92; H, 5.50; N, 7.87.

7-Chloro-1,3-dihydro-3-(3-methyl-2-butenyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2c).—Similarly, the alkylation of 30 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide with 12.5 g (0.12 mol) of 3-methyl-1-chloro-2-butene and 13.5 g (0.12 mol) of potassium *tert*-butoxide in 200 ml of dimethylformamide yielded 20 g (57%) of product, crystallized from methanol. The analytical sample was recrystallized from methanol: mp 149–151°; nmr ($CDCl_3$) δ 1.68 (s, 6, CH_3), 3.02 (m, 2, $-CH_2-$), 3.48 (s, 3, NCH_3), 4.15 (t, 1, J = 7 Hz, C_3H), 5.1 (broad t, 1, J = 6 Hz, CH=), 7.1–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; N, 5.74; N, 7.59. Found: C, 68.39; H, 5.81; N, 7.56.

3-Allyl-7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2d).—A solution of 33 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (1d)[2] in 200 ml of dimethylformamide was cooled to −30°. Potassium *tert*-butoxide (13.5 g, 0.12 mol) was added with stirring under nitrogen. After 10 min the reaction mixture was cooled to −50° and 14.5 g of allyl bromide was added. When the temperature had reached 0°, the reaction mixture was poured into ice water. The resinous precipitate was extracted with methylene chloride.

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

The combined extracts were washed with water, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol yielded 18.5 g (50%) of product: mp 137–139°; nmr ($CDCl_3$) δ 3.06 (m, 2, $-CH_2-$), 3.4 (s, 3, OCH_3), 4.30 (t, 1, J = 7 Hz, C_3 H), 4.94 (d, 1) and 5.4 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 4.8–6.2 (m, 3, olefinic H), 7–7.8 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 64.68; H, 5.43; N, 7.82.

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5h).—A mixture of 17 g (0.05 mol) of 3-allyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2a**) and 200 ml of acetic anhydride was refluxed for 3 hr with slow distillation of 100 ml of the solvent (collected in a Dean–Stark trap). The reagent was evaporated under reduced pressure, at the end azeotropically with toluene. Crystallization of the residue from ether yielded 10.6 g (66%) of product, mp 221–222°. The analytical sample was recrystallized from CH_2Cl_2–hexane: mp 223–225°; uv λ_{max} 242 mμ (ε 15,650), 277–278 (10,150); ir ($CHCl_3$) 1620 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.0 (s, 3, NCH_3), 6.16 (s, 1, C_5 H), 6.2–7.6 (m, 11, aromatic H).

Anal. Calcd for $C_{19}H_{15}ClN_2O$: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.70; H, 4.70; N, 8.87.

7-Chloro-5,10-dihydro-3,10-dimethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5i).—7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3-(*trans*-2-butenyl)-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2b**) (3.55 g) was refluxed in 40 ml of acetic anhydride for 48 hr under an atmosphere of nitrogen. The reagent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous ammonia. The methylene chloride layer was dried and evaporated. The residue was chromatographed over 200 g of silica gel with benzene–ether (1:1, v/v). Crystallization of the pure fractions from methylene chloride–petroleum ether (bp 30–60°) yielded 1.25 g (37%) of colorless product: mp 214–216°; uv λ_{max} 244 mμ (ε 17,800), infl 265 (10,400), 288 (12,800); ir ($CHCl_3$) 1630 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.40 (s, 3, CH_3), 2.97 (s, 3, NCH_3), 6.05 (d, 1, J = 4 Hz, pyrrole H), 6.20 (s, 1, C_5 H), 6.6–7.6 (m, 9, 8 aromatic H and pyrrole H).

Anal. Calcd for $C_{20}H_{17}ClN_2O$: C, 71.32; H, 5.09; N, 8.32. Found: C, 71.15; H, 5.10; N, 8.17.

7-Chloro-5,10-dihydro-10-methoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5k).—A mixture of 37 g (0.1 mol) of 3-allyl-7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2d**) and 300 ml of acetic anhydride was refluxed for 3 hr. The reagent was evaporated under reduced pressure and the residue was crystallized from benzene to yield 18.2 g (51%) of product: mp 196–198° after recrystallization from methylene chloride–ethanol; uv λ_{max} 239–240 mμ (ε 17,800), 279 (11,650); ir ($CHCl_3$) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.30 (s, 3, OCH_3), 4.20 (d, 1) and 4.88 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 6.15 (s, 1, C_5 H) 6.25–7.8 (m, 11, aromatic H).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; N, 7.94. Found: C, 68.27; H, 4.92; N, 8.08.

7-Chloro-5,10-dihydro-10-ethoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5m).—Ethanol (10 ml) containing 5% hydrogen chloride was added to a solution of 1 g of 7-chloro-5,10-dihydro-10-methoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**5k**) in 10 ml of methylene chloride. After sitting for 3 days at room temperature the solvents were removed under reduced pressure and the residue was crystallized from ethanol to yield 0.75 g (72%) of product: mp 148–151°; uv λ_{max} 238–239 mμ (ε 16,300), 277–278 (11,100); ir ($CHCl_3$) 1630 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.14 (t, 3, J = 7 Hz, CH_3), 3.5 (m, 2, OCH_2CH_3, protons not equivalent), 4.26 (d, 1) and 4.97 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 6.2 (s, 1, C_5 H), 6.25–8 (m, 11, aromatic H).

Oxidation of 7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5h) with Chromic Acid.—A solution of 6 g of chromium trioxide in 10 ml of water was added to a solution of 2 g of 7-chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one in 70 ml of glacial acetic acid. The mixture was stirred for 16 hr, diluted with ice water, made alkaline with aqueous ammonia, and extracted with methylene chloride. The extracts were dried and evaporated. The residue was chromatographed over 40 g of silica gel with 25% methylene chloride in ethyl acetate. The first eluted product, 0.6 g (32%), mp 224–228°, was found to be identical in every respect with 7-chloro-1-methyl-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3-(1*H*)-dione (**6**).[4] The later eluted compound (0.1 g, 6%) melted at 227–230° and was found to be identical with 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazolin-2-one (**9**).[5]

7-Chloro-1,3-dihydro-3-(3-methyl-2-butenylidene)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3f).—A mixture of 1 g of 7-chloro-1,3-dihydro-3-(3-methyl-2-butenyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2c**) and 10 ml of acetic anhydride was heated to reflux for 15 min. The excess reagent was removed under reduced pressure. The residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was separated, dried, and evaporated. Crystallization of the residue from ether–petroleum ether yielded 0.43 g (45%) of deep yellow crystals, mp 157–161°. The analytical sample was recrystallized from methylene chloride–petroleum ether: mp 163–166°; uv λ_{max} 206 mμ (ε 34,600), sh 230 (26,800), 236 (27,100), sh 255 (22,500), 290 (17,900), 380 (5400); ir ($CHCl_3$) 1660 cm^{-1} (NCO); nmr ($CDCl_3$) δ 1.82 (s, 3, CH_3), 1.90 (s, 3, CH_3), 3.38 (s, 3, NCH_3), 6.25 (d with fine structure, 1) and 6.50 (d, 1) (AB system, J = 11 Hz, =CHCH=), 7–8 (m, 8, aromatic H).

Anal. Calcd for $C_{21}H_{19}ClN_2O$: C, 71.89; H, 5.46; N, 7.98. Found: C, 71.65; H, 5.54; N, 7.92.

3-Benzylidene-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3g).—A solution of 1.95 g (0.005 mol) of 3-benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide[3] in 30 ml of acetic anhydride was refluxed for 1 hr. The reagent was evaporated under reduced pressure. The residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether–petroleum ether yielded 1.3 g (70%) of yellow prisms: mp 189–192°; nmr ($CDCl_3$) δ 3.44 (s, 3, NCH_3), 6.47 (s, 1, $=CHC_6H_5$), 7–8 (m, 13, aromatic H).

Anal. Calcd for $C_{23}H_{17}ClN_2O$: C, 74.10; H, 4.60; N, 7.51. Found: C, 74.26; H, 4.65; N, 7.41.

The evaporated mother liquors were chromatographed over 20 g of silica gel using 5% ethyl acetate in methylene chloride. The fractions containing the slower moving spot were combined and evaporated. Crystallization from methylene chloride–ether–petroleum ether yielded 50 mg of yellow crystals: mp 207–212°; nmr ($CDCl_3$) δ 3.48 (s, 3, NCH_3), 6.2 (s, 1, $=CH-C_6H_5$), 7–8 (m, 13, aromatic H).

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (8).—7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**5h**) (3.2 g, 0.01 mol) was added in portions to a suspension of 2 g (0.05 mol) of lithium aluminum hydride in 100 ml of ether. After 4 hr of reflux the reaction mixture was hydrolyzed by addition of 10 ml of water. The inorganic material was filtered and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from methylene chloride–petroleum ether yielded 2.15 g (70%) of colorless prisms: mp 150–153°; uv λ_{max} 272 mμ (ε 10,500), 310 (2200); nmr ($CDCl_3$) δ 2.78 (s, 3, NCH_3), 3.72 (d, 1) and 4.10 (d, 1) (AB system, J = 15 Hz, C_{11} H), 5.9–6.25 (m, 3, C_5 H and 2 pyrrole H), 6.6–7.5 (m, 9, aromatic H and 1 pyrrole H).

Anal. Calcd for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07. Found: C, 73.94; H, 5.65; N, 9.08.

7-Chloro-1,3-dihydro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (4).—A solution of 4.75 g (0.055 mol) of methyl acrylate in 20 ml of dimethylformamide was added to a mixture of 15 g (0.05 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**1a**), 0.75 g of potassium *tert*-butoxide, and 150 ml of dimethylformamide cooled to −35°. Cooling was discontinued after 10 min and the reaction mixture was stirred overnight under an atmosphere of nitrogen. After neutralization with acetic acid the product was precipitated by dilution with water. The collected precipitate was partitioned between methylene chloride and water. The organic phase was dried and evaporated. The residue was crystallized from ether and recrystallized twice from methylene chloride–methanol to leave 6.6 g (34%) of product: mp 179–182°; nmr ($CDCl_3$) δ 2.2–3.0 (m, 4, $-CH_2CH_2-$), 3.48 (s, 3, NCH_3), 3.62 (s, 3, OCH_3), 4.48 (t, 1, J = 6 Hz, C_3 H), 7.15 (d, 1, J = 2 Hz, C_8 H), 7.2–7.8 (m, 7, C_6H_5, C_8 H, C_9 H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; N, 7.24. Found: C, 62.37; H, 5.01; N, 7.24.

7-Chloro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-1,3,-4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (7).—Zinc dust (30 g) was added in portions to a solution of 19.3 (0.05 mol) of 7-chloro-1,3-dihydro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (4) in 300 ml of glacial acetic acid. After addition, stirring was continued for 2 hr. The reaction mixture was filtered and the filtrate was made alkaline with ice and ammonia and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization from ether yielded 12.3 g (66%) of colorless product, mp 174–178°. The analytical sample was recrystallized from methylene chloride–ether: mp 177–180°; uv λ_{max} 240 mμ (ε 14,900), infl 290 (1300); ir ($CHCl_3$) 3300 (NH), 1740 (COOMe), 1670 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.06 (broad s, 1, NH), 1.8–2.7 (m, 4, $-CH_2CH_2-$), 3.35 (t, 1, J = 6.5 Hz, C_3 H), 3.52 (s, 3, NCH_3), 3.68 (s, 3, OCH_3), 5.25 (s, 1, C_5 H), 6.64 (d, 1, J = 2 Hz, C_6 H), 7.0–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.43; H, 5.67; N, 7.51. Found: C, 64.45; H, 5.54; N, 7.50.

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-1*H*-pyrrolo[2,1-c]-[1,4]benzodiazepine-3,11(2*H*,11a*H*)-dione (10).—A solution of 15 g of 7-chloro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (9) in 100 ml of quinoline was heated at 225–235° for 2 hr. After cooling the reaction mixture was partitioned between 2 *N* hydrochloric acid and methylene chloride. The methylene chloride layer was washed twice with 2 *N* hydrochloric acid and once with water. It was dried and evaporated. Crystallization of the residue from ether–petroleum ether after treatment with charcoal yielded 7.4 g (54%) of product. For analysis it was recrystallized from methylene chloride–methanol: mp 193–195°; uv λ_{max} 240 mμ (ε 11,020), 253 (11,150), infl 290 (800); ir ($CHCl_3$) 1700, 1680 cm^{-1} (NCO); nmr ($CDCl_3$) 1.6–2.9 (m, 4, $-CH_2CH_2-$), 3.41 (s, 3, NCH_3), 4.33 (d, 1, J = 6 Hz, C_3 H), 5.70 (s, 1, C_5 H), 6.46 (d, 1, J = 2 Hz, C_6 H), 7–7.6 (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.93; H, 4.94; N, 8.26.

7-Chloro-10-methyl-5-phenyl-1,2,3,5,11,11a-hexahydro-10*H*-pyrrolo[2,1-c][1,4]benzodiazepine (11).—7-Chloro-5,10-dihydro-10-methyl-5-phenyl-1*H*-pyrrolo[2,1-c][1,4]benzodiazepine-3,11-(2*H*,11a*H*)-dione (10) (6.8 g, 0.02 mol) was added in portions to a suspension of 5 g (0.125 mol) of lithium aluminum hydride in 250 ml of ether. After addition, the mixture was stirred at room temperature for 15 min and was then heated to reflux for 6 hr. The hydride was hydrolyzed by addition of 25 ml of water. The inorganic material was filtered off and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from ether yielded 4 g (64%) of product: mp 145–148° after recrystallization from methylene chloride–methanol; uv λ_{max} 263 mμ (ε 11,030), sh 300 (2390); nmr ($CDCl_3$) δ 2.86 (s, 3, NCH_3), 1.3–3.9 (m, 9, $-CH_2-$, CH), 5.1 (s, 1, C_5 H), 6.60 (d, 1, J = 2 Hz, C_5 H), 6.76 (d, 1, J = 9 Hz, C_9 H), 7.15 (q, 1, J_{AB} = 9, J_{AX} = 2 Hz, C_8 H), 7.35 (broad s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{21}ClN_2$: C, 72.95; H, 6.76; N, 8.95. Found: C, 72.85; H, 6.81; N, 8.96.

1,3-Dihydro-5-methyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (13a).[7]—Bromoacetyl bromide (120 g, 0.6 mol) was added slowly to a vigorously stirred two-phase mixture of 60 g (0.4 mol) of 2-aminoacetophenone oxime, 500 ml of methylene chloride, and 1 l. of saturated sodium bicarbonate solution. After complete addition, stirring was continued for 15 min. The methylene chloride layer was separated, washed with bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residue was dissolved in 1 l. of ethanol. Glacial acetic acid (50 ml) and 50 g of anhydrous sodium acetate were added. The mixture was refluxed with stirring for 1 hr. The solvent was evaporated under reduced pressure and the product was precipitated by addition of water. It was collected, washed with water, and crystallized from acetone–methanol to yield 24 g (31.5%), mp 235–240°.

1,3-Dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (13b).—Potassium *tert*-butoxide (12.5 g, 0.11 mol) was added to a solution of 19 g (0.1 mol) of 1,3-dihydro-5-methyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (13a) in 500 ml of dimethylformamide cooled to 0°. After stirring for 5 min, 15.6 g (0.11 mol) of methyl iodide was added and the mixture was stirred at room temperature for 90 min. Most of the dimethylformamide was removed under reduced pressure. The residue was crystallized by addition of water. The crystals were collected, washed with water, and recrystallized from methylene chloride–ethyl acetate to leave 12.5 g (61%) of product, mp 255–260°. The analytical sample was recrystallized from ethyl acetate–methanol: mp 268–271°; nmr (DMSO) δ 2.50 (d, 3, J = 1 Hz, C_5 CH_3), 3.56 (s, 3, NCH_3), 4.46 (d, 1, J = 14 Hz, C_3 H), 4.95 (d with fine structure, 1, J = 14 Hz, C_3 H) 7.1–7.7 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.93; H, 5.97; N, 13.78.

3-Allyl-1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (14).—A solution of 20.5 g (0.1 mol) of 1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (13b) in 1 l. of dimethylformamide was cooled to −20° with stirring under nitrogen. Potassium *tert*-butoxide (14 g, 0.125 mol) was added and stirring was continued for 5 min. After the solution was cooled further down to −50°, 15 g (0.125 mol) of allyl bromide was added. The reaction mixture was allowed to reach room temperature and was neutralized with glacial acetic acid and evaporated under reduced pressure. The residue was partitioned between methylene chloride and water. The methylene chloride layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 14 g (57%) of product. The analytical sample was recrystallized from ethyl acetate–hexane: mp 138–141°; nmr ($CDCl_3$) δ 2.47 (d, 3, J = 2 Hz, 5 CH_3), 3.04 (m, 2, $-CH_2-$), 3.45 (s, 3, NCH_3), 4.14 (t, 1, J = 7 Hz, C_3 H), 4.9–6.3 (m, 3, $CH=CH_2$), 7.2–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.84; H, 6.60; N, 11.46. Found: C, 68.98; H, 6.55; N, 11.54.

5-Acetoxymethyl-3-allyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (15c).—A mixture of 12.2 g (0.05 mol) of 3-allyl-1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (14), 50 ml of acetic anhydride, and 250 ml of toluene was heated to reflux for 3 hr. During this period 100 ml of toluene was removed by distillation. The reaction mixture was then evaporated and the residue was crystallized from ether–hexane to yield 8.6 g (60%) of product. Recrystallization from ether–hexane yielded colorless crystals: mp 82–84°; uv λ_{max} 227 mμ (ε 34,000), infl 250 (6500), 300 (1600); ir ($CHCl_3$) 1750 (OAc), 1680 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.05 (s, 3, $COCH_3$), 2.92 (m, 2, $-CH_2-$), 3.4 (s, 3, NCH_3), 3.5 (m, 1, C_3 H), 5.15 (d, 2, J = 2 Hz, $-CH_2OAc$), 4.9–6.3 (m, 3, $-CH=CH_2$), 7–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.78. Found: C, 67.07; H, 6.51; N, 9.82.

3-Allyl-1,3-dihydro-5-hydroxymethyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (15d).—Sodium methoxide (0.6 g, 11 mmol) was added to a solution of 2.86 g (10 mmol) of 5-acetoxymethyl-3-allyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (15c) in 50 ml of methanol. After the solution had stood at room temperature for 1 hr the methanol was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. The product was crystallized from ether–hexane and recrystallized from methylene chloride–ether–hexane to yield 1.5 g (61%): mp 100–106°; uv λ_{max} 225 mμ (ε 34,300), infl 250 (6200), 297 (1750); ir ($CHCl_3$) 3375 (OH), 1670 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.90 (t, 2, J = 7 Hz, $-CH_2-$), 3.40 (s, 3, NCH_3), 3.60 (m, 1, C_3 H), 3.87 (broad s, 1, OH), 4.33 (q, 1, J_{AB} = 17, J_{AX} = 2 Hz), and 4.94 (q, 1, J_{AB} = 17, J_{AX} = 2 Hz) (CH_2OH), 4.9–6.3 (m, 3, $CH=CH_2$), 7–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 68.73; H, 6.50; N, 11.44.

This compound was sensitive to air and discolored to red.

3-Allyl-1,3-dihydro-5-formyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (15e).—A mixture of 1 g of 3-allyl-1,3-dihydro-5-hydroxymethyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (15d), 7 g of manganese dioxide, and 30 ml of methylene chloride was stirred at room temperature for 1 hr. The manganese dioxide was removed by filtration. The filtrate was evaporated and the residue was chromatographed over 30 g of silica gel using 2.5% (v/v) ether in methylene chloride. Crystallization of the combined homogenous fractions from ether–hexane yielded 0.55 g (55%) of product: mp 68–71°; uv λ_{max} 234 mμ (ε 19,700), sh 275 (2800), 324 (1180); ir ($CHCl_3$) 1720 (CHO), 1680 cm^{-1} (NCO); nmr ($CDCl_3$) δ 3.07 (t, 2, J = 7 Hz, $-CH_2-$), 3.40 (s, 3, NCH_3), 3.77 (t, 1, J = 7 Hz, C_3 H), 4.9–6.3 (m, 3, $CH=CH_2$), 7.1–7.9 (m, 4, aromatic H), 9.77 (s, 1, CHO).

Anal. Calcd for $C_{14}H_4N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.68; H, 5.81; N, 11.27.

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Registry No.—1a, 2888-64-4; 1d, 28506-53-8; 2a, 41075-53-0; 2b, 40973-75-9; 2c, 40973-76-0; 2d, 41075-54-1; 2e, 28199-30-6; 3f, 40973-78-2; *cis*-3g, 40973-79-3; *trans*-3g, 40973-80-6; 4, 40973-81-7; 5h, 40973-82-8; 5i, 40973-83-9; 5k, 40973-84-0; 5m, 40973-85-1; 6, 3294-96-0; 7, 40973-87-3; 8, 40973-88-4; 9, 20927-53-1; 10, 40973-90-8; 11, 40973-91-9; 12, 4964-49-2; 13a, 40973-93-1; 13b, 40973-94-2; 14, 40973-95-3; 15c, 40973-96-4; 15d, 40973-97-5; 15e, 40973-98-6; allyl bromide, 106-95-6; crotyl chloride, 625-35-4; 1-chloro-3-methyl-2-butene, 503-60-6.

Carboxyalkylthioacrylates[1]

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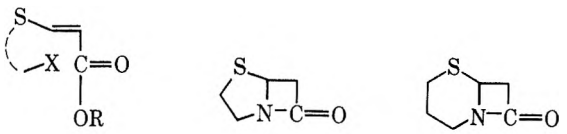
Base-catalyzed addition of mercaptoalkanoic acids and esters to propiolic acid and its esters gives, under mild conditions, carboxyalkylthioacrylic acids and their mono- and diesters. Reaction in protic polar solvents gives predominantly cis thioacrylates whereas aprotic solvents strongly favor the trans products.

It is well known that thioacrylates (I) are produced when thiols add to propiolic acid and its esters.[2]

$$RSH + HC{\equiv}CCOOR' \longrightarrow RSCH{=}CHCOOR'$$

Our interest in these compounds stemmed from the observation that the S—C=C—C=O moiety which they contain simulates a major structural feature of the penicillins (II) and cephalosporins (III). Thus,



I II III

suitably constructed thioacrylates might well be useful intermediates in the synthesis of such fused β-lactam antibiotics, the group X providing the nitrogen atom, and either X or the thioacrylate function the carbonyl group. Thioacrylates, moreover, are conveniently prepared in either the cis or the trans geometry, and preservation of this geometry during cyclization might permit a stereoselective penicillin–cephalosporin synthesis.

Alkyl, as opposed to aryl, thioacrylates seem to have been little studied. We report here upon one group of such compounds, the carboxyalkylthioacrylic acids (I, R = H, X = -COOH), their esters and half-esters, and other derivatives. The compounds (1–15) prepared are listed in Table I.

TABLE I

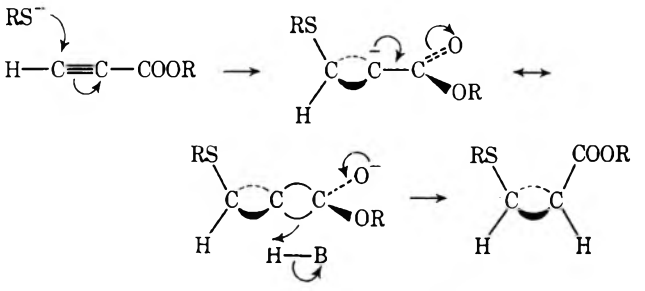
CARBOXYALKYLTHIOACRYLIC ACIDS AND ESTERS

A—CH_2CH_2—S—CH=CH—B

Compound		Group	
cis	trans	A	B
1	2	CO_2H	CO_2Et
3	4	CO_2H	CO_2H
5	6	CO_2Me	CO_2Et
7	8	CH_2CO_2H	CO_2H
9	10	CH_2CO_2H	CO_2Et
11		CO_2Me	CO_2H
12	13	COCl	COCl
14		$CONHC_6H_5$	CO_2Et
15		$CONHC_6H_5$	CO_2Et

The reaction of thiols with propiolates is very slow in the absence of catalysts but is accelerated remarkably by bases. Thus neutral alkanethiols such as benzyl mercaptan, methyl β-mercaptopropionate, and methyl γ-mercaptobutyrate react completely with propiolate esters in alcohol, aqueous alcohol, acetonitrile, or diethyl ether within 30–60 min after addition of catalytic amounts of pyridine or triethylamine at room temperature. Free mercaptoalkanoic acids neutralized to pH ~8 with rather more than 1 mol of aqueous base react equally readily, the pH of the reaction mixture rising to 10–12 as the buffering effect of the thiol group disappears. The reactive entity undoubtedly is the thiolate ion. Rather surprisingly, salts of propiolic acid react with thiols almost as readily as do esters. The carboxylate anion would hardly be expected to activate the acetylene to nucleophilic addition as much as the ester group does, and the question is open as to whether the propiolate anion or the small amount of free propiolic acid in equilibrium with it (at pH 8–9) is the entity which actually undergoes nucleophilic addition.

The predominant initial products from reactions effected in aqueous and alcoholic solvents were the cis alkylthioacrylates. The trans isomers usually could be recovered from mother liquors, with or without deliberate or fortuitous isomerization of residual cis material. The well-known rule of trans addition[3] thus is obeyed. The generally accepted rationalization of this rule involves coordination of thiolate ion at the β carbon of the acetylene to give a resonance-stabilized anion which subsequently accepts a proton from the protic solvent (HB) on its least-hindered side.

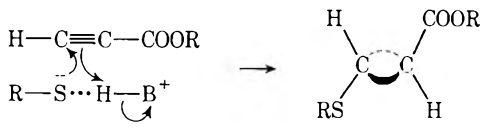


(1) A grant from Bristol Laboratories, Syracuse, N. Y. 13201, in support of this work is gratefully acknowledged.

(2) A comprehensive list of references is given in a recent paper by W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972).

(3) S. Miller, *J. Chem. Chem. Soc.*, **78**, 6091 (1956); C. K. Ingold, *J. Chem. Soc.*, 2991 (1954); W. E. Truce, *J. Amer. Chem. Soc.*, **78**, 695, 2743, 2756 (1956); F. Montanari and A. Negrini, *Gazz. Chim. Ital.*, **87**, 1073 (1957).

It occurred to us that, if protonation on the less hindered side at the expense of proton donor solvent is indeed a major factor in trans addition, a change of solvent might produce a dramatic change in product stereochemistry. An aprotic solvent would be incapable of such involvement and, if, in such a solvent, the thiol and the basic catalyst were to behave as a thiolate–protobase ion pair, protonation by the protobase might, perforce, take place on the same side as thiolate coordination—a cis addition giving trans product. The lower the concentration of reactants,



moreover, the greater would be the likelihood of such quasiintramolecular reaction. This possibility promised not only a revealing test of the accepted mechanism, but also a means of tailoring the reaction, merely by change of solvent, to give a predominance of either the cis or the trans product directly, at will.

The solvent effect was explored using ethyl propiolate and methyl mercaptopropionate as reactants and a trace of triethylamine or pyridine as catalyst since these reactants, and the products, are conveniently soluble in solvents ranging from aqueous alcohol to ether and dichloromethane. Results are detailed in Table II. In dilute aqueous ethanol the

TABLE II

SOLVENT AND CONCENTRATION EFFECTS IN THE TRIETHYLAMINE-CATALYZED REACTION OF METHYL MERCAPTOPROPIONATE WITH ETHYL PROPIOLATE

Solvent	Solvent/reactant ratio (w/v)	% cis[a]	% trans[a]
None		48	52
EtOH-H_2O (1:10)	100	85	15
EtOH-H_2O (1:1)	10	85	15
EtOH	5	70	30
Et_2O	5	33	67
Et_2O	125	20	80
MeCN	5	33	67
MeCN	50	20	80
MeCN	100	20	80

[a] Determined by nmr analysis of crude mixtures after evaporation and dissolution in CCl_4.

usual product ratio (85% cis, 15% trans) was obtained. In absolute ethanol, this ratio fell to 7:3, and, in ether or acetonitrile at ordinary concentrations (20%), inverted completely to a 1:2 ratio. The extreme case, reaction in dilute (1%) solution in ether or acetonitrile gave 80% of trans and only 20% of cis product. Similar results are being obtained in other cases currently being studied, and the results obtained in a large number of thiol addition reactions which we had previously effected in aqueous, alcoholic, and aqueous–alcohol solutions, with variable isomer ratios being produced, are satisfactorily rationalized in terms of the solvent effect. We venture to predict, therefore, that base-catalyzed additions of thiols to propiolates and related activated acetylenes in dilute solution in aprotic solvents and poorly protic solvent mixtures will, in general, favor the formation of trans enesulfides.

The diacids (**3**, **4**) and their half-esters (**1**, **2**) reacted smoothly with oxalyl chloride. No indication of cis–trans isomerization was revealed by nmr spectra of the unpurified acid chlorides. The cis compounds were characterized as the anilide–ester (**14**) and the dianilide (**15**).

Experimental Section[4,5]

Structures (cis or trans) were determined by nmr,[6] vinyl proton coupling constants of 10–11 and 15–16 Hz being assigned to the cis and the trans isomers, respectively.

Ethyl 3-(2′-Carboxyethylthio)acrylate. Cis (1) and Trans (2) Isomers.—Ethyl propiolate (19.6 g, 0.2 mol) in EtOH (25 ml) was added to a solution of 3-mercaptopropionic acid (21.2 g, 0.2 mol) and KOH (11.2 g, 0.2 mol) in a water (50 ml)–EtOH (175 ml) mixture. The pH was adjusted to 8.5–9.0 and the mixture was stirred overnight, acidified with HCl (16.2 ml of 38%, 0.2 mol), and refrigerated. The white crystals (20.5 g, mp 105–106°) which were deposited were recrystallized from $CHCl_3$ (35 ml) giving *cis*-ethyl 3-(2′-carboxyethylthio)acrylate (**1**): 14.5 g (35.5%); mp 107.5–108°; ir (Nujol) 5.85, 5.95, 6.36, 14.6 μ; nmr (A-60, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.95 (m, 4 H, $-SCH_2CH_2COOH$), 4.25 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.92 (d, 1 H, J = 10.5 Hz, =CHCOOEt), 7.15 (d, 1 H, J = 10.5 Hz, -SCH=); uv $\lambda_{max}^{H_2O}$ 287 nm (ϵ 12,300). The aqueous–alcoholic mother liquor was extracted five times with $CHCl_3$; the extract was dried ($MgSO_4$), combined with the $CHCl_3$ mother liquors, and evaporated to dryness. The residue crystallized from CCl_4 (75 ml) to give additional somewhat less pure cis product (13.2 g, 33%), mp 101–106. Evaporation of the CCl_4 mother liquors gave a yellow oil (6.6 g) which was shown by nmr to be mostly the trans isomer **2**. Distillation of this was attended by considerable decomposition and afforded only 2.0 g (5%) of *trans*-ethyl 3-(2′-carboxyethylthio)acrylate (**2**): bp 152° (0.8 mm); $n^{25}D$ 1.5319; ir (liquid film) 5.87, 6.33, 7.67, 10.6 μ; nmr (A-60, $CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.94 (symmetrical multiplet, 4 H, $-SCH_2CH_2COOH$), 4.17 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.75 (d, 1 H, J = 15 Hz, =CHCOOEt), 7.67 (d, 1 H, J = 15 Hz, -SCH=); uv $\lambda_{max}^{H_2O}$ 278 nm (ϵ 18,300).

***cis*-3-(2′-Carboxyethylthio)acrylic Acid (3).**—Propiolic acid (2.0 g, 29 mmol) and 3-mercaptopropionic acid (3.03 g, 29 mmol) were dissolved in an EtOH–water (1:3) mixture (50 ml) containing KOH (3.2 g, 58 mmol). The pH was adjusted to 9 with aqueous KOH. After 4 hr the mixture was acidified with HCl (4.7 ml of 38%, 58 mmol) in water (50 ml) and chilled. The solid which separated (2.35 g, mp 182°), recrystallized from water (100 ml/g), gave *cis*-3-(2′-carboxyethylthio)acrylic acid (**3**): 2.10 g (42%); mp 187°; ir (Nujol) 5.85, 6.05, 6.38 μ; nmr (4H-100, DMSO-d_6) δ 2.60 (t, 2 H, J = 6 Hz, $-CH_2COOH$), 3.03 (t, 2 H, J = 6 Hz, $-SCH_2-$), 5.88 (d, 1 H, J = 10 Hz, =CHCOOH), 7.44 (d, 1 H, J = 10 Hz, -SCH=); uv $\lambda_{max}^{H_2O}$ 283 nm (ϵ 10,700). Partial evaporation and chilling of the combined mother liquors afforded a cis–trans mixture (2.05 g, 40%), mp 140–160°.

***trans*-3-(2′-Carboxyethylthio)acrylic Acid (4).**—A mixture similar to that used for the preparation of the cis isomer **3** was adjusted to pH 7 and kept at 25° for 30 hr prior to being acidified. Partial evaporation and chilling afforded crystals of fairly pure *trans*-3-(2′-carboxyethylthio)acrylic acid (**4**) (35%), mp 155–156°, a portion or which was recrystallized twice from water and once from C_6H_6–EtOH (10:1) mixture to give pure material: mp 158–159°; ir (KBr pellet) 5.83, 6.02, 6.33, 7.67, 10.4 μ; nmr (4H-100, DMSO-d_6) δ 2.70 (t, 2 H, J = 7 Hz, $-CH_2COOH$),

(4) See paragraph at end of paper regarding supplementary material.

(5) Spectra were determined using Varian A-60, Jeolco 4H-100, Perkin-Elmer 337, and Bausch and Lomb "Precision" instruments. Chemical shifts, δ, are ppm downfield from tetramethylsilane. Melting points are uncorrected. Solvent removal was invariably effected under reduced pressure (5–15 mm) at 30° or below.

(6) W. E. Truce and B. Grotcn, *J. Org. Chem.*, **27**, 128 (1962); H. Hogeveen, G. Maccagnani, and F. Taddei, *Recl. Trav. Chim. Pays-Bas*, **83**, 937 (1964).

3.14 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.83 (d, 1 H, J = 15 Hz, =CH-COOH), 7.73 (d, 1 H, J = 15 Hz, =CHS—); uv $\lambda_{max}^{H_2O}$ 275 nm (ϵ 15,800).

The cis diacid (**3**), dissolved in water containing a little H_2SO_4, was converted into the trans isomer to the extent of 95% in 2 days at 25°. Recovery of the latter acid after evaporation to dryness, washing with ice–water, and recrystallization was 65%.

***cis*-Ethyl 3-(2′-Carbomethoxyethylthio)acrylate (5).**—Triethylamine (1 drop) was added to a solution of methyl 3-mercaptopropionate (2.4 g, 20 mmol) and ethyl propiolate (2.0 g, 20 mmol) in EtOH–water (1:1) mixture (40 ml). After 12 hr, solvent was removed by evaporation under reduced pressure to leave, in practically quantitative yield, an oil which contained (nmr) 85% of the cis and 15% of the trans product. Distillation (Nester–Faust adiabatic spinning band column, 200:1 reflux ratio) afforded *cis*-ethyl 3-(2′-carbomethoxyethylthio)-acrylate (**5**) (3.1 g, 70%, 99% pure) as a slightly yellow oil: bp 114° (0.6 mm); $n^{23}D$ 1.5141; ir (liquid film) 5.73, 5.89, 12.5, 14.1 μ; nmr (A-60, neat) δ 1.17 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.69 (slightly split triplet, 2 H, J = 5.5 Hz, $-CH_2COOMe$), 3.02 (slightly split triplet, 2 H, J = 5.5 Hz, $-SCH_2-$), 3.63 (s, 3 H, $-OCH_3$), 4.12 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.82 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.27 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 284 nm (ϵ 13,000).

***trans*-Ethyl 3-(2′-Carbomethoxyethylthio)acrylate (6).**—Reaction effected as in the preparation of the cis isomer but in dry acetonitrile or ether (200 ml) as solvent gave an oil which contained (nmr) 80% of the trans and 20% of the cis product. Distillation gave *trans*-ethyl 3-(2′-carbomethoxyethylthio)acrylate (**6**) (2.8 g, 64%, 97% pure) as an almost colorless oil: bp 108° (0.6 mm); $n^{23}D$ 1.5107; ir (liquid film) 5.75, 5.87, 6.32, 7.67, 10.5 μ; nmr (A-60, neat) δ 1.21 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.71 (slightly split triplet, 2 H, J = 6 Hz, $-CH_2COOMe$), 3.10 (slightly split triplet, 2 H, J = 6 Hz, $-SCH_2-$), 3.61 (s, 3 H, $-OCH_3$), 4.07 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.72 (d, 1 H, J = 15 Hz, =CHCOOEt), 7.57 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 275 nm (ϵ 17,000).

Reaction effected in the absence of solvent (the mixture became quite warm) gave an equimolar mixture (nmr) of cis and trans isomers. Reactions in other solvents (Table II) gave, in all cases, weights of crude products corresponding to complete consumption of the volatile starting materials. No detectable amounts of side products were revealed by nmr.

***cis*-3-(3′-Carboxypropylthio)acrylic Acid (7).**—γ-Thiobutyrolactone (10.2 g, 0.1 mol) was heated under reflux with NaOH (4.0 g, 0.1 mol) and phenolphthalein solution (3 drops) in water (100 ml) until a clear colorless solution was obtained (30 min). The cooled liquid was mixed with a solution of propiolic acid (7.0 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in water (50 ml), adjusted to pH 8.5 with NaOH, kept 14 hr at 25°, acidified with HCl (16 ml of 38%, 0.2 mol), and chilled. The copious white crystalline precipitate (17.9 g, 94%) melted at 115–118° and contained (nmr) less than 5% of trans material. Pure *cis*-3-(3′-carboxypropylthio)acrylic acid (**7**), crystallized from C_6H_6 containing a little EtOH and then from water, had mp 121–122°; ir (KBr pellet) 5.92, 6.31, 6.36, 14.3 μ; nmr (4H-100, DMSO-d_6) δ 1.80 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.30 (t, 2 H, $-CH_2COOH$), 2.75 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.80 (d, 1 H, J = 10 Hz, =CHCOOH), 7.26 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 283 nm (ϵ 10,600).

***trans*-3-(3′-Carboxypropylthio)acrylic Acid (8).**—The cis isomer (**7**) was dissolved in water (~100 ml/g) containing H_2SO_4 (~5 drops/g), and the solution was kept at 25° for 5 days and then evaporated to near-dryness. The damp solid was washed with ice–water and the crude product (mp 165–170°) was crystallized twice from CCl_4–MeOH (6:1) mixture to give pure *trans*-3-(3′-carboxypropylthio)acrylic acid (**8**) (60%), as white prisms: mp 173–174°; ir (KBr pellet) 5.87, 6.00, 6.35, 7.70, 10.4 μ; nmr (4H-100, DMSO-d_6) δ 1.80 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.32 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.85 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.68 (d, 1 H, J = 15 Hz, =CHCOOH), 7.52 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 276 nm (ϵ 14,500).

Ethyl 3-(3′-Carboxypropylthio)acrylates (9, 10).—γ-Thiobutyrolactone (10.2 g, 0.1 mol) was hydrolyzed by heating (100°, 30 min) with KOH (5.6 g, 0.1 mol) in water (100 ml), and the cooled hydrolysate was mixed with a solution of ethyl propiolate (9.8 g, 0.1 mol) in EtOH (50 ml). The solution was kept 12 hr at 25° and acidified with HCl (8.1 ml of 38%, 0.1 mol), the mixture was extracted with $CHCl_3$ (4 × 50 ml), and the extracts were dried ($MgSO_4$) and evaporated to give a solid residue (19.6 g, mp 52–56°). This was crystallized from pentane (200 ml)–ether (100 ml)–$CHCl_3$ (20 ml) mixture at −20° and recrystallized by Soxhlet extraction with pentane–ether (10:1) mixture giving pure *cis*-3-(3′-carboxypropylthio)acrylic acid (**9**) (14.4 g, 66%) as fluffy white needles: mp 64–64.5°; ir (Nujol) 5.90, 6.38, 14.2 μ; nmr (4H-100, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, $-OCH_2-CH_3$), 1.95 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.48 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.77 (t, 2 H, J = 7 Hz, $-SCH_2-$), 4.13 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.79 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.00 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 289 nm (ϵ 12,800). The combined mother liquors, concentrated and chilled, afforded further crystals (4.0 g, 18%, mp 25°) of largely (95%) *trans*-3-(3′-carboxypropylthio)acrylic acid (**10**). This product was not further purified and elemental analysis was not obtained: ir (liquid film) 5.85, 6.33, 7.67, 10.6 μ; nmr (4H-100, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.00 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.52 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.88 (t, 2 H, J = 7 Hz, $-SCH_2-$), 4.17 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.77 (d, 1 H, J = 15 Hz, =CH-COOEt), 7.63 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 278 nm (ϵ 18,000).

***cis*-3-(2′-Carbomethoxyethylthio)acrylic Acid (11).**—Methyl 3-mercaptopropionate (2.4 g, 20 mmol) in ethanol (5 ml) was added to propiolic acid (1.4 g, 20 mmol) and KOH (1.12 g, 20 mmol) in ethanol–water (1:3) mixture (20 ml). The pH was adjusted to 8 with KOH and the solution was stirred overnight, acidified with HCl (1.6 ml of 38%, 20 mmol), and chilled, when it set to a slurry of fine white needles (2.8 g, 73%, 95% cis, mp 91.5–92°). Pure *cis*-3-(2′-carbomethoxyethylthio)acrylic acid (**11**) was crystallized from carbon tetrachloride as needles: mp 94–95°; ir (Nujol) 5.78, 5.98, 6.40 μ; nmr (A-60, $CDCl_3$) δ 2.96 (m, 4 H, $-SCH_2CH_2COOMe$), 3.75 (s, 3 H, $-OCH_3$), 5.97 (d, 1 H, J = 10.5 Hz, =CHCOOH), 7.40 (d, 1 H, J = 10.5 Hz, —SCH=), 11.18 (s, 1 H, $-COOH$); uv $\lambda_{max}^{H_2O}$ 275 nm (ϵ 10,000).

Dianilide (15) and Diacid Chloride (12) of *cis*-3-(2′-Carboxyethylthio)acrylic Acid (3), and Diacid Chloride (13) of the Trans Diacid (4).—The cis (**3**) and trans (**4**) diacids (0.35 g, 2 mmol) were heated under reflux 2 hr with oxalyl chloride (2 ml). Removal of excess reagent under reduced pressure gave very pale green viscous oils. The nmr spectra (A-60, $CDCl_3$, Table I, compounds **12** and **13**) of these were readily distinguishable from each other and from the starting materials, indicated the essential absence of isomerization of either to other, and were entirely consistent with smooth conversion into the desired diacid chlorides. The cis product, in ether, was treated with an ethereal solution of aniline (0.37 g, 4 mmol) and pyridine (0.32 g, 4 mmol). A gummy solid separated. After 12 hr, the supernatant ether was removed by decantation and the residue was crystallized, successively, from acetone–water (1:1) and EtOH–water (1:1) mixtures to give the cis dianilide (**15**) (0.33 g, 50%) as colorless leaflets: mp 165°; ir (Nujol) 3.03, 5.99, 6.08, 6.22, 6.27 μ.

Anilide (14) of *cis*-Ethyl 3-(2′-carboxyethylthio)acrylate (1).—The cis acid–ester (**1**) (0.36 g, 1.8 mmol) dissolved with vigorous effervescence in warm oxalyl chloride (1 ml). The solution was kept at 25° overnight and evaporated, and the residue in ether (15 ml) was treated with a solution of aniline (0.17 g, 1.9 mmol) and pyridine (0.14 g, 1.9 mmol) in ether (25 ml). Isolation with ether and recrystallization from EtOH–water (1:4) mixture gave the cis anilide–ester (**14**) (0.20 g, 38%) as white crystals with a pale-green cast: mp 125–125.5°; ir (Nujol) 3.03, 5.90, 6.00, 6.23, 6.36, 13.3, 14.4 μ; nmr (A-60, $CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.75 (t, 2 H, J = 6.5 Hz, $-CH_2CO-NHPh$), 3.15 (t, 2 H, J = 6.5 Hz, $-SCH_2-$), 4.21 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.88 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.40 (m, 6 H, $-C_6H_5$ and —SCH=), 8.30 (s, 1 H, PhNH–); uv $\lambda\lambda_{max}^{CH_3OH}$ 245 nm (ϵ 16,000), 285 (15,700).

Registry No.—**1**, 41108-51-4; **2**, 41108-52-5; **3**, 41108-53-6; **4**, 41108-54-7; **5**, 41108-55-8; **6**, 41108-56-9; **7**, 41108-57-0; **8**, 41108-58-1; **9**, 41108-59-2; **10**, 41108-60-5; **11**, 41108-61-6; **12**, 41108-62-7; **13**, 41108-63-8; **14**, 41108-64-9; **15**, 41108-65-0; ethyl propiolate, 623-47-2; 3-mercaptopropionic acid, 107-96-0; methyl 3-mercaptopropionate, 2935-90-2; γ-thiobutyrolactone, 1003-10-7.

Supplementary Material Available.—Elemental analysis are given in Table III which will appear following these pages in the

microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3507.

The Stringent Requirement for Electrophiles in the Facile Solvolytic Hydrolysis of Neutral Sulfate Ester Salts[1]

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The facile desulfation of neutral sulfate ester salts in boiling moist dioxane is well known. The present studies provide evidence that the solvolysis requires initiation by traces of impurities presumably behaving as electrophiles. The surface of a glass containing vessel is adequate to initiate a reaction which is precipitously catalyzed to completion by the acidic products produced. In clean *Teflon* vessels but *not in glass*, 2-octanol (potassium sulfate) (I) and the cholestan-3β-ol analog (II) are stable for prolonged periods in hot moist dioxane, but are almost instantly solvolyzed following addition of almost any trivial potentially acidic contaminant encountered in a laboratory environment. At ambient temperature, dioxane solutions–suspensions of I and II are solvolyzed in less than 1 hr after addition of a trace of H_2SO_4 or other electrophilic reagents.

Sulfate esters of steroids,[2,3] many carbohydrates,[4,5] and simple alcohols[6,7] are notably resistant to hydrolysis in neutral or acidic aqueous systems; however, under appropriate conditions many of these are rapidly solvolyzed in relatively nonpolar, nucleophilic solvents, especially moist (<1% H_2O) ether, dioxane, and tetrahydrofuran. In these solvents, the *free acid esters* desulfate easily at *ambient temperature* while neutral alkali metal salts, with modest exceptions,[2,8] are ordinarily stable.[9]

Ammonium salts (but not sodium salts) of specific sulfatides elaborated by *Mycobacterium tuberculosis* also undergo facile solvolytic hydrolysis at ambient temperature in reagent-grade "anhydrous" ether (H_2O content ~0.005%).[10,11] The principal mycobacterial sulfatide (SL-I) is a complex tetraacyl trehalose-2-sulfate.[12] Studies with these sulfatides led us to the inference that alkali metal sulfate ester or sulfatide salts in general should ordinarily be stable in ether solvents, that a trace of mineral acid or appropriate electrophile should *initiate* solvolysis, and that the reaction would accelerate to completion, since each desulfation event generates a strongly acidic anion (HSO_4^-). For various salts of the mycobacterial SL-I, these deductions were verified.[11]

In earlier studies of steroid sulfate esters Burstein and Lieberman concluded that the species undergoing reaction is the free steroid hydrogen sulfate, and offered a probable mechanism as reproduced in Figure 1.[3] Conclusions of Batts[7] also implicate the zwitterion (of Figure 1) as the reactive species. The proposed mechanisms of our own studies and of Figure 1 have in common the requirement of an intermediate in which the sulfate ester oxygen has accepted a proton (*cf.* also Benkovic[13] and Benkovic and Dunikoski[14]).

It is well known, however, that alkali metal salts of even simple sulfate esters undergo rapid solvolysis in apparently *neutral* ether solvents at elevated temperature, as, for example, in boiling moist dioxane.[8,15,16] In the Haines' group's studies of the sulfatides of *Ochromonas danica*, the solvolysis of (+)-2-octanol (potassium sulfate) as a model compound was examined. Like many steroid sulfatides, it hydrolyzed in minutes in boiling dioxane–1% H_2O (with retention of optical configuration).[16,17] In their interpretation of the reaction, Haines, *et al.*, proposed a quite different mechanistic model in which the water participating in the reaction was assigned a prominent role in hydrating the sulfate core to generate a species proposed as reactive for the nucleophilic solvent (Figure 2). In this interpretation,[18] the intervention of electrophiles or protons is not required—a concept in contradiction with earlier conclusions. The "neutral" conditions of the solvolysis were implicitly advocated as a means of avoiding complications of acidic hydrolysis.[17]

However, reference to this high-temperature transformation as a solvolysis in *neutral* moist dioxane becomes untenable after the initial few desulfation events. The intermediate dioxane–SO_3 complex must be considered

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(9) The reported ambient-temperature solvolysis of certain apparently neutral steroid sulfates[2,8] may result as a consequence of anchimeric participation of unsaturated functions in appropriate positions, although such participation is contradicted from studies of Burstein and Lieberman.[3] It cannot yet be ruled out that infinitesimal acidic impurities may account for the instability.

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(18) Respecting Figure 2, Mayers, *et al.*,[17] and Haines[16] suggest that a hydrated complex in which the water molecule is bonded to two negatively charged oxygens (rather than as in the reactive complex postulated) would have greater stability. However, this would not lead to the desired products on attack by the solvent. It was suggested therefore that the "heat required for the reaction is necessary to provide the initial reacting species" as formulated in Figure 2.

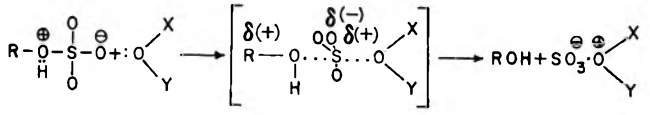

Figure 1.—Mechanism of Burstein and Lieberman for solvolysis of hydrogen sulfate esters.

an electrophile, and hydrolyzes with facility in the moist reaction medium to yield the strongly acidic $KHSO_4$. The reaction mixture therefore quickly assumes the (predictable) character of the acidic low-temperature reaction with the possible disadvantages conferred by the now unnecessary high temperature. Nevertheless, the reaction unquestionably is *initiated* in an apparently neutral system—a seeming paradox which we have sought to resolve in the present study. Beyond this we wished to test in simpler systems our earlier observations that salts of mycobacterial sulfatides which are stable in ether solvents may be gently and completely solvolyzed at ambient temperature following the addition to the stable system of minute amounts of electrophilic reagents.[11]

Results and Discussion

We prepared purified K salts of 2-octanol sulfate (I) and cholestan-3β-ol sulfate (II) for the present studies. These were entirely stable at ambient temperature in moist (<1% H_2O), purified dioxane; however, a gentle, rapid low-temperature desulfation could be initiated with minute traces of appropriate electrophiles—iodine, H_2SO_4, $ZnCl_2$, NH_4Cl, hydrazine sulfate. With precise amounts of H_2SO_4 (0.0025–0.005 equiv relative to sulfate salt) the solvolysis was complete in less than 1 hr (Figure 3). The salt need not be dissolved in the solvent; suspensions are easily desulfated. We conclude that a host of organic sulfate esters, including natural sulfatides, may be effectively hydrolyzed under these gentle conditions without significant degradation such as racemization or inversions, hydrolysis of glycosidic linkages, etc. (*cf.* ref 10, 11, 19–21). The methodology therefore recommends itself for synthesis and for structural investigations.

Solvolysis at High Temperature.—Respecting solvolysis at elevated temperatures we confirmed that I and II solvolyzed in minutes in moist dioxane when heated in glass vessels near the boiling point (as little as 2 min for I). However, our evidence suggests that, under these vigorous conditions, a multiplicity of contaminants can function to *initiate* the desulfation, which then progresses precipitously to completion (in seconds) owing to the acidic product(s) generated: $KHSO_4$, a protonated dioxane–SO_3 complex (?); a dioxane–H_2SO_4 complex (?).[22] Trace contaminants

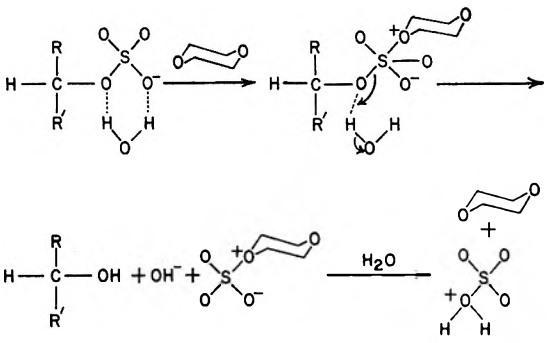

Figure 2.—Proposed mechanism of Haines for solvolysis in neutral dioxane.

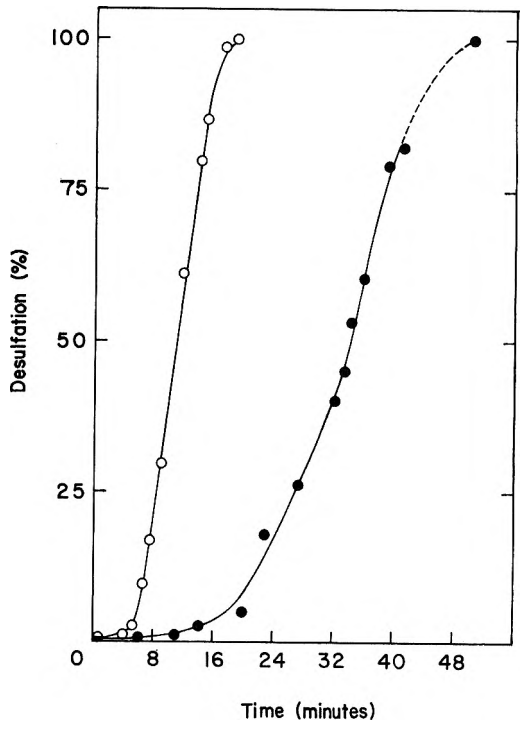

Figure 3.—Solvolysis of potassium sulfate esters in dioxane under acid catalysis: open circles, potassium 2-octyl sulfate ($H^+ \cong 0.25$ mol % with respect to salt); closed circles, potassium β-cholestanyl sulfate ($H^+ \cong 0.5$ mol %).

on the surface of even diligently cleaned glass containing vessels (or perhaps the glass surface itself) seem the most notable culprits. On the other hand, both I and II may be held near reflux in moist dioxane for prolonged periods (as long as 2 hr for I under ideal circumstances) in clean Teflon vessels and recovered unchanged: the reaction mixture remains neutral, and the salt merely recrystallizes from the cooled solvent.[23]

The rationale for the experimental approach anticipated that, if the sulfate salt is contaminated by even undetectable quantities of sufficiently acidic material, these would detrimentally affect the prolonged stability of the sulfate esters even at ambient temperatures.

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(22) The "explosive" behavior which characterizes the desulfation in the experiments described, and which was seen in numerous other experiments not reported here, led us to consider the possible intervention of (transient) intermediates generated by the reaction itself, more potent in catalyzing the solvolysis than hydrated or solvated protons. Although we have no evidence in support of its existence, we speculate that a dioxane–SO_3 complex which is protonated on one of the SO_3 oxygens (or a dioxane–H_2SO_4 complex) might have such characteristics—stemming from the combined nucleophilic and electrophilic properties, which may allow participation in a concerted attack on the ester. These species would also regenerate themselves as well. Although the former protonated complex is entirely speculative, a dioxane–H_2SO_4 complex of appropriate structure is firmly established [Y. K. Syrkin and K. M. Anisimova, *Chem. Abstr.*, **42**, 6593 (1948)]. Similar complexes of dioxane with $HClO_4$ and H_3PO_4 are known.

(23) During this stable period we were unable, in numerous experiments, to detect any measurable amount of solvolysis products, *e.g.*, $KHSO_4$ or any released alcohol (by gas chromatography). If heating is prolonged sufficiently, invariably a sudden desulfation occurs, the reaction being completed in a few seconds. Since our studies show that nanogram amounts of, *e.g.*, H_2SO_4 or $HClO_4$ initiate almost instantaneous desulfation when added to such hot stable systems, it is possible that the "stable period" involves an immeasurably slow solvolysis which eventually produces a *critical* concentration of acidic reaction products, with a resultant cataclysmic completion of the reaction. However, we were unable to obtain any data in support of this interpretation.

Accordingly, extraordinary precautions were taken to mitigate as much as possible against such contaminants. As a point of departure we speculated that the initial desulfation events might simply involve a (probably very slow) hydrolysis at the high temperature. To discriminate against the catalytic influence of the bisulfate which this would generate, the initial high-temperature experiments examined the effects of alkali (KOH) on the solvolytic behavior (in glass). Such alkaline systems were indeed found to be stable, but inordinately subject to abrupt destabilization, *e.g.*, during sampling, removal of the condenser, twisting of the condenser in its joint, insertion of a glass pipet—capricious incidents which made us suspect the possible catalytic intervention of the glass equipment. We therefore examined the reaction in Teflon, first with very small amounts of added alkali, and then in the absence of any added reagents. Completely stable systems were obtained.

Finally, we examined a variety of substances as potential initiators. Hot stable systems in Teflon were almost instantly solvolyzed following the addition of traces of mineral or Lewis acids (nanogram amounts of H_2SO_4 or $HClO_4$ as dilute solutions, salts of Zn or Fe; pyridine–SO_3 complex; precipitated $KHSO_4$ from a previous solvolysis) by apparently "neutral" salts such as $MgSO_4$; sulfur dust, $Na_2S_2O_3$, $Na_2S_2O_4$, citrazinic acid; and, *ad absurdum*, dust from laboratory surfaces. Many substances were inactive: Na_2CO_3, KOH, $NaHCO_3$, 2-pyridone, 2-aminopyridine, isonicotinic acid, acetic acid, 2,4-dichlorophenol, quinhydrone, and pyrogallol. Some were selected to assess possible functionality as both electrophile and nucleophile,[22] others simply because of acidic properties. We can only speculate that dichlorophenol and acetic acid were ineffective initiators because they are too weakly acidic under the specific conditions (acetic acid is principally dimeric in hot dioxane[24]).

Many of the initiators are clearly electrophiles. Others may simply provide solid surfaces that act catalytically to initiate the reaction. We infer, however, that the function is merely *initiative*, and that the reaction then progresses almost explosively owing to the catalytic influence of the geometrically increasing acidic product(s) of the hydrolysis. Although water in excess of about 2% dramatically inhibits the solvolysis,[15-17] a sudden initiation, *e.g.*, with traces of citrazinic acid, pyridine–SO_3, or nanogram quantities of H_2SO_4 in dioxane, effects immediate and quantitative desulfation in systems containing as much as 7% H_2O.[22] We hope to incorporate the results and implications of the latter studies in a subsequent, brief communication.

From our observations we conclude that the high-temperature solvolysis has an absolute requirement for an initiator, presumably behaving as an electrophile, the reaction then progressing almost instantaneously owing to the acidic products generated—and that a facile "neutral" solvolysis as proposed earlier[16,17] is untenable.

Experimental Section

Dioxane was employed almost exclusively in the solvolytic experiments. Baker's reagent grade dioxane was purified according to the method of Hess and Frahm[25] (*cf.* Fieser and Fieser[26]), and finally refluxed for several hours with either Na, $LiAlH_4$, or CaH_2 and distilled. The H_2O content as estimated from examination of the infrared band at 1640 cm^{-1} and comparison with standard samples was below 0.1%. Experiments were performed with this solvent and stable systems in Teflon obtained at high temperature; more often small amounts of water (usually about 0.4–0.5%) were added to aid in dissolving the sulfate ester salts.

2-Octanol (potassium sulfate) (I) was prepared by modification of the procedure described by Mayers, *et al.*[17] The product was recrystallized from absolute ethanol or butanol: it sinters at 165°, foams at 175°, and gives a clear melt at 182°. *Anal.*[27] Calcd for $C_8H_{17}SO_4K$: C, 38.71; H, 6.85; K, 15.74. Found: C, 38.55; H, 6.87; K, 15.8.

Cholestan-3-β-yl potassium sulfate (II) was prepared both by reaction of cholestan-3-β-ol with chlorosulfonic acid in dioxane and by reaction with pyridine–SO_3 complex followed by metathesis.[8] The products were recrystallized several times from hot methanol containing about 3% H_2O. Only the first crops of fine needles which crystallized were collected. The melting point of the vacuum-dried potassium salt depends upon the manner in which it is taken: 234–235° dec, 240–240.5° with gas evolution (reported mp 234–235°,[8] 236°[28]). *Anal.* Calcd for $C_{27}H_{47}SO_4K$: C, 63.98; H, 9.35; K, 7.71. Found: C, 64.37; H, 9.25; K, 8.06.

Equipment.—*All* glassware, precleaned in acid dichromate and washed, and washed Teflon ware were heated in 5–10% aqueous alkali for several hours, exhaustively rinsed with deionized water, wrapped in protective Al foil, and dried. For solvolysis studies in Teflon, we employed Nalgene narrow-mouth "Boston Round" Teflon bottles (4-oz capacity) with fluorocarbon closures.

Methods.—Ordinarily 5–6 ml of dioxane was pipetted into the reaction vessel along with 10–20 μl of deionized H_2O or other reagents dissolved to appropriate concentration. The sulfate salt (40–50 mg) was weighed into a small, clean test tube, which was inserted far into the mouth of the container before the contents were emptied. The reaction vessel with cap or condenser was heated for brief periods with gentle shaking until the salt was in solution and droplets of the dioxane (slightly below its boiling point) were condensing. The vessel was then inserted in a boiling water bath and a stopwatch was started. Solvolysis was recognizable by a sudden turbidity in the clear solution and precipitation of $KHSO_4$. Analysis of these turbid reaction mixtures invariably indicated that solvolysis was complete. Maintenance of clarity was examined so many times as a criterion of stability as to be definitive: many such clear samples, quenched and then analyzed for acidity or, when appropriate, for octanol-2 content (by gas chromatography), were entirely free of either product of solvolysis.

Experiments.—Probably more than 100 solvolyses were examined. A few representative experiments are reported here.

A. Low-Temperature Solvolysis. Catalysis by Electrophiles. 1.—I (193 mg) was suspended in 10.0 ml of dioxane to which 25 μl of H_2O was added and the mixture was stirred (magnetic stirrer) at room temperature. In a period of 6 days the mixture remained neutral. A minute crystal of iodine was added. Within 20 min the suspension of sulfate ester was completely solvolyzed as indicated by titration of the released $KHSO_4$ with standard alkali. Other effective initiators included $ZnCl_2$, $FeCl_3$, mineral acids, and hydrazine sulfate.

2.—The conditions of experiment 1 were duplicated except that 25 μl of 0.02 *N* H_2SO_4 was added instead of water (to 53 mg of I in 15 ml of dioxane). Aliquots were withdrawn at intervals, quenched into 10 ml H_2O, and titrated to the methyl red end point. (The stability of acidified I in such an aqueous mixture was demonstrated in a separate experiment.) The results given in Figure 3 indicate that complete solvolysis occurred in about 18 min.

3.—II (46 mg, 9.13×10^{-5} mol) was suspended in 5 ml of dioxane and stirred at room temperature. After 12 hr the still *neutral* suspension was acidified with 10 μl of 0.05 *N* H_2SO_4 (0.54 mol % H^+ based on II) and 0.1-ml samples were withdrawn peri-

(24) S. Feneant-Eymard, *Chem. Abstr.*, **48**, 7399 (1954).

(25) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 333.

(27) Analyses by Huffman Laboratories, Lakewood, Colo. We thank Donald Papineau for potassium analysis.

(28) A. E. Sobel and M. J. Rosen, *J. Amer. Chem. Soc.*, **63**, 3536 (1941).

odically, quenched as in the preceding experiment, and analyzed. The solvolysis of the acidified K salt suspension was complete in less than 1 hr (Figure 3).

B. Solvolysis at High Temperature (in Glass Vessels).—I (50 mg), 6 ml of dioxane, and 18 μl of H_2O were mixed in a 10-ml Bantam ware flask fitted with a condenser. The mixture desulfated before it had reached maximum temperature on top of a steam bath. In many such experiments solvolysis occurred within 2–4 min. The solvolysis in glass could be prevented for many hours by 10–20 μl of KOH (8–1 *M*), but only if the reaction mixture was not disturbed (*vide supra*). The aqueous alkali does not dissolve in the dioxane, but merely coats the walls of the flask.

C. Stability at High Temperature in Teflon. 1.—A reaction mixture of 50 mg of I, 5 ml of dioxane, and 20 μl of 8×10^{-3} *M* KOH (<0.001 mol/mol sulfate ester) was heated in a Teflon bottle for intermittent brief periods until the sulfate had dissolved, and thence continuously in a steam cone (96°). This concentration of KOH did not prevent desulfation in glass. After 2 hr, the solution was chilled, sampled, and found not acidic to methyl red; nor was octanol-2 detectable by glc. The solution was transferred to a clean, glass round-bottom flask with condenser and heated on the steam bath. Desulfation occurred in about 3 min.

2.—Experiment C-1 was repeated except that 18 μl of deionized water was substituted for the alkali. The mixture was heated at full steam bath temperature for 1 hr, carefully removed, and allowed to cool and crystallize. The crystalline material was recovered by filtration and washing with cold ethanol, 43 mg, sinters at 165°, begins to foam and melt at 174°, and is complete at 182°, *i.e.*, essentially identical with the starting 2-octanol (potassium sulfate). The mother liquor was neutral.

3.—II (40 mg) in 5 ml of dioxane plus 10 μl of H_2O in a Teflon bottle was heated as above. At 21 min the flask was removed, cooled, and sampled. The material had not dissolved completely and the suspension was not acidic to methyl red. It was reheated for an additional 40 min and now was completely desulfated. The insoluble material was identified as $KHSO_4$ (mp 206–208°); cholestan-3-β-ol (mp 143°) was recovered from the organic phase.

4.—The previous experiment was repeated with 51 mg of II. After 20 min, the flask was removed from the steam bath and chilled. A small sample was tested and found to be not acidic. Water (15 ml) was added to the reaction mixture along with a drop of methyl red. A 30-μl portion of 0.01 *N* H_2SO_4 was more than enough to give an intense red color. Accordingly, solvolysis could not have progressed to even 0.3% of the sulfatide charged. In glass the sulfatide solvolyzed completely in the interval between 6.5 and 7.5 min.

From the preceding experiments (1–4) it is evident that the solvolysis occurs only suddenly—there is no evidence of a slow progression.

D. Initiation of Solvolysis by Trace Materials.—In these experiments stable solutions of 2-octanol (potassium sulfate) (50 mg) in 5–6 ml of dioxane plus 10–20 μl of H_2O were maintained in Teflon in a boiling water bath, usually for 20–30 min, at which time minute amounts of test solids or aqueous solutions were dropped in. Quantities of solids were ordinarily those left on the very tip of a microspatula or a needle-pointed capillary tube after insertion into a bottle of reagent and tapping off excess. Liquids were judged to be about 0.5 μl (*cf.* Results and Discussion).

Registry No.—I, 41209-93-2; II, 41209-94-3.

Substituent Effects in Sulfone Carbanions[1a]

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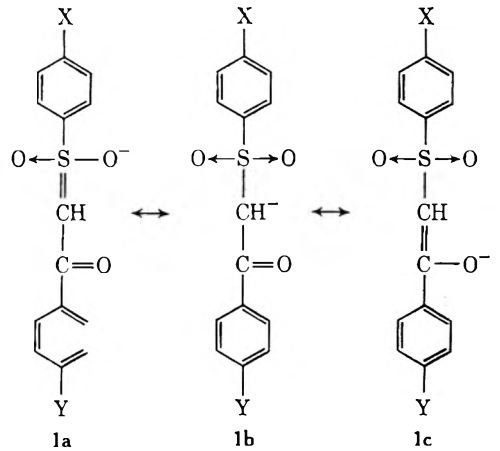
The pK_a's of a series of substituted phenyl phenacyl sulfones (**2**) were determined. With variation of the phenylsulfonyl substituents, the sulfone acidities followed a linear correlation with σ. The ρ value for this correlation was +2.01, indicating that electron-withdrawing substituents increase sulfone acidity and that this system is very responsive to substituent changes. Since correlation of acidity with σ^+ was not obtained, there is no enhanced resonance interaction between the substituent and the electron-deficient sulfone group. Variation of the phenacyl substituents gave linear correlation of acidity with σ and a ρ value of +2.35. Acidifying effects in the sulfones are considered to be identical with the factors stabilizing the corresponding sulfone carbanions. The large positive ρ indicates that the carbanion is stabilized substantially by pπ–dπ overlap with the sulfur. The magnitude of this stabilization depends upon the electronegativity of the sulfur which, in turn, is determined by the electronic effects of the substituents. The interaction of the substituents through the phenyl ring with the sulfur is principally inductive in nature.

It is well established that the sulfone group can stabilize an adjacent carbanion.[2] Sulfone carbanions have been utilized in numerous syntheses, but there has been no quantitative systematic study of their electronic effects. This study was undertaken to determine the nature and magnitude of such carbanion stabilization. Several resonance structures which can be envisioned for β-carbonyl sulfone carbanions are **1a**, utilizing sulfur d orbitals; **1b**, the carbanion structure; and **1c**, the enolate structure. The magnitude of carbanion stabilization afforded through resonance structures **1a** and **1c** was determined by measuring the acidity of the sulfone precursors. Schwarzenbach and



1a **1b** **1c**

Felder[3] determined the pK_a's (in water) of several sulfones [*i.e.*, $CH_3SO_2CH_2COCH_3$, 10; $(CH_3SO_2)_2CH_2$,

(1) (a) This work was presented in part at the Twenty-third Annual Undergraduate Chemistry Symposium of the Chicago Section of the American Chemical Society, Chicago, Ill., May 1972. (b) Author to whom inquiries should be addressed at Department of Chemistry, Viterbo College, LaCrosse, Wis. 54601. (c) Undergraduate Research Participant.

(2) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 351–352.

(3) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).

TABLE I

PROPERTIES OF β-CARBONYL SULFONES[a]

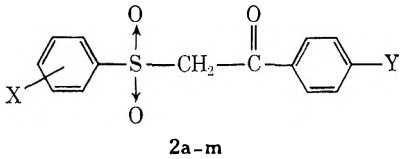
Compd	X[b]	Y	Mp, °C	pK_a	Nmr (CDCl$_3$ solvent), δ, multiplicity[c] Methylene	Aromatic	X or Y
2a	NO_2	H	169–171	9.42	s, 5.90[d]	m, 7.64–8.82	
2b	*m*-NO_2	H	132–134	9.54	s, 5.36	m, 7.80–9.34	
2c	Br	H	122–123	10.33	s, 5.28	m, 7.80–8.56	
2d	Cl	H	131.5–132.5	10.52	s, 5.28	m, 7.80–8.54	
2e	F	H	148–150	10.80	s, 5.26	m, 7.60–8.64	
2f	H	H	89–90	10.97	s, 5.20	m, 7.74–8.44	
2g	CH_3	H	105–107	11.25	s, 5.20	m, 7.64–8.44	s, 2.78
2h	OCH_3	H	105–106	11.42	s, 5.24	m, 7.40–8.54	s, 4.36
2i	H	Br	138.5–139.5	10.44	s, 5.24	m, 7.80–8.50	
2j	H	Cl	129–131	10.53	s, 5.26	m, 7.80–8.50	
2k	H	C_6H_5	147–149	10.85	s, 5.26	m, 7.76–8.64	
2l	H	F	116–117.5	10.90	s, 5.24	m, 7.48–8.60	
2m	H	OCH_3	112–114	11.70	s, 5.20	m, 7.32–8.50	s, 4.34

[a] Satisfactory analytical data were reported for all new compounds listed in the table: Ed. [b] The substituent is in the para position unless indicated otherwise. [c] s, singlet; m, multiplet; all integrations were in accord with theory. [d] Solvent was $(CD_3)_2SO$.

~14; and $(CH_3SO_2)_3CH$, ~0], which indicated the acidifying effect attained by successively adding sulfone groups to a carbon. Bordwell, *et al.*,[4] determined the pK_a's (in DMSO) of several sulfones which were capable of affording little stabilization to the conjugate base [pK_a's ranging from $C_6H_5SO_2C_2H_5$, 29, to $(C_6H_5CH_2)_2SO_2$, 22]. This work showed that when benzyl groups were substituted for methyl groups the pK_a decreased 6.5 units [compare $(C_6H_5CH_2)_2SO_2$, 22, with $CH_3SO_2CH_3$, 28.5] indicating that the phenyl ring was electron withdrawing relative to methyl. When an ethyl group was substituted for a methyl group the pK_a increased 2.0 units [compare $C_6H_5SO_2CH_3$, 27, with $C_6H_5SO_2C_2H_5$, 29], showing that a methyl group provided electron release relative to hydrogen. Bordwell further reported that replacing methyl with phenyl decreased the pK_a 1.5 units [compare $C_6H_5SO_2CH_3$, 27, with $CH_3SO_2CH_3$, 28.5]. The magnitude of this lowering was consistent with the lowering reported by Johnson and Amel[5] for similar sulfonium and phosphonium systems. This paper will describe the linear correlation of sulfone acidities with substituent constants and elaborate the electronic effects involved in the stabilization of phenyl phenacyl sulfone carbanions.

Results

A series of substituted phenyl phenacyl sulfones (2) was prepared. The properties of these sulfones are



2a–m

listed in Table I. The pK_a's of the sulfones were determined potentiometrically in 95% ethanol solution using the method of Speziale and Ratts.[6] The average deviation was ±0.04 pK_a unit.

For sulfones substituted on the phenylsulfonyl end, linear correlation was achieved when log K/K_0 (K_0 is the dissociation constant of the unsubstituted sulfone, 2f) was plotted against σ but not when σ^+ or σ^0 were used (Figure 1). A ρ of +2.01 was calculated using a least-squares treatment of the data. For sulfones substituted on the phenacyl end, linear correlation again was possible with σ and a ρ of +2.35 was calculated (Figure 2).

Discussion

Our research was designed to determine the nature and magnitude of the carbanion stabilization provided by the sulfonyl moiety as well as that provided by the substituted benzoyl group. In order to obtain this information, the relative acidities of a series of sulfones were determined. In this study, the factors determining sulfone acidity were considered to be identical with the factors affording stabilization to the corresponding sulfone carbanion. Only meta- and para-substituted phenyl groups were used so that stabilization differences could be ascribed to electronic effects without intervention of steric effects.

Variation of the Sulfonyl Moiety.—Figure 1 demonstrates that the acidities of phenyl phenacyl sulfones substituted on the sulfonyl moiety could be correlated with σ. The ρ value for this correlation was positive, indicating that electron-withdrawing substituents increased the acidity of the sulfone or decreased the basicity of the sulfone carbanion. For example, the unsubstituted sulfone 2f had a pK_a of 10.97, while with X = NO_2 the acidity was increased to a pK_a of 9.42 and with X = CH_3O the pK_a was 11.42. Craig and Magnusson[7] have proposed that increasing the electronegativity of sulfur, by attaching electron-withdrawing substituents, will contract the sulfur d orbitals, allowing more efficient overlap with the filled 2p orbital of an adjacent carbanion. Employing this idea in our system, the differences in carbanion stabilization as a result of changing substituent X can be explained as differences in the amount of d orbital overlap possible with the sulfonyl group. Consequently, the degree of carbanion stabilization afforded by the sulfonyl moiety is interpreted to be a measure of pπ–dπ overlap, as depicted in the double-bonded structure 1a. Robinson and Gillespie[8] have reported correlation of sulfur electronegativity variation with the amount of pπ–dπ

(4) F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967).
(5) A. W. Johnson and R. T. Amel, *Can. J. Chem.*, **46**, 461 (1968).
(6) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **85**, 2790 (1963).
(7) D. P. Craig and E. A. Magnusson, *J. Chem. Soc.*, 4895 (1956).
(8) E. A. Robinson, *Can. J. Chem.*, **39**, 247 (1961); R. J. Gillespie and E. A. Robinson, *Can. J. Chem.*, **41**, 2074 (1965).

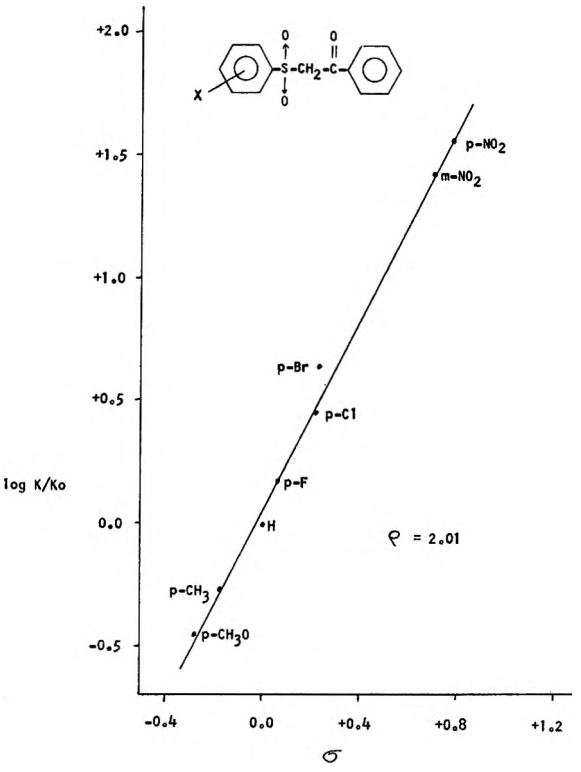


Figure 1.—Acidities of X-phenyl phenacyl sulfones *vs.* σ.

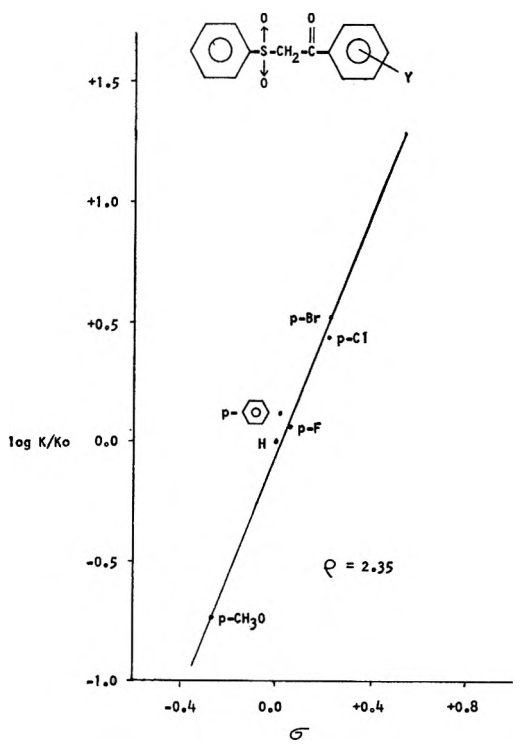


Figure 2.—Acidities of phenyl (Y-phenacyl) sulfones *vs.* σ.

bonding. In their work with sulfones and sulfoxides, they found that increasing the electronegativity or electron-withdrawing capability of groups attached to the sulfur caused stronger S–O bonds, as evidenced by higher vibrational absorption frequencies.

Bordwell and Cooper[9] reported that an enhanced σ constant was required to express the acidifying effect of the 4-methylsulfonyl group on phenol. This indicated an increased stabilization of the phenolate anion by the sulfonyl group. In this case the d orbitals in the electron-deficient sulfur were utilized in conjugatively delocalizing the charge on the phenolate anion. In our system, however, sulfone acidity did not correlate with σ^+, indicating no such enhanced electron donation from the phenyl substituents to the sulfur. In addition, Johnson, *et al.*,[10] reported finding no enhanced interaction between phenyl substituents and the electron-deficient phosphorus in the 9-fluorenyltri(*p*-X-phenyl)-phosphonium bromide system. Johnson explained his results on the basis of steric considerations. With the crowded quaternary phosphorus atom it is understandable that steric requirements would not allow the orbitals of the three phenyl rings to line up properly with the phosphorus 3d orbitals. With our sulfone system, however, steric problems should not be the factor. Wheatly[11] and Speziale and Ratts[12] reported in the molecular structure analysis of $CH_3C_6H_4SO_2CH{=}P(C_6H_5)_3$ that the tolyl ring was nearly perpendicular to a plane containing the tetrahedral sulfur, the carbanion, and the phosphorus. This situation would not appear to preclude, on steric grounds, d orbital overlap with either the phenyl ring or the carbanion.

(9) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **74**, 1058 (1952).

(10) A. W. Johnson, S. Y. Lee, R. A. Swor, and L. D. Royer, *J. Amer. Chem. Soc.*, **88**, 1953 (1966).

(11) P. J. Wheatley, *J. Chem. Soc.*, 5785 (1965).

(12) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **87**, 5603 (1965).

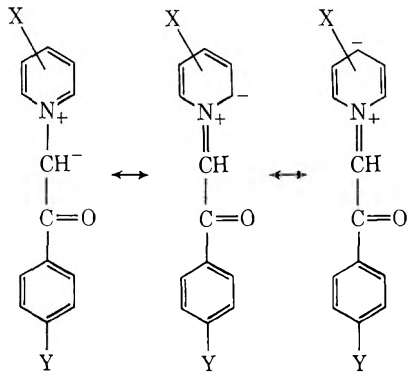
However, since linear correlation was accomplished with σ rather than σ^+, the degree of conjugative electron donation by the substituted phenyl ring to the sulfur in our system must be considerably less than that observed by Bordwell. Johnson and Jones[13] have concluded that in phosphorus systems involving strong $p\pi$–$d\pi$ interaction with one substituent (*i.e.*, a carbanion) there is relatively little such interaction possible with any other substituents. This conclusion is applicable to sulfone systems as well. Consequently, the substituent effects causing electronegativity changes in the sulfonyl sulfur must be principally inductive in nature. The magnitude of these electronegativity changes is significant because it determines the degree of participation of the sulfur d orbitals in bonding with the carbanion.

Figure 1 shows $\rho = +2.01$, indicating that electron-withdrawing groups increased the acidity of the sulfones. The magnitude of ρ shows that the sulfone carbanion required considerable electron delocalization into the sulfur d orbitals. Ratts[14] determined a ρ of +1.23 for the corresponding methylphenylsulfonium ylide system. Johnson, *et al.*,[10] have reported a triphenylphosphonium ylide system with a ρ of +4.8 (for three substituted phenyls attached to phosphorus), which can be broken down into a ρ of +1.7 for each substituted phenyl group. The magnitude of ρ in the sulfone system was higher than the values for the phosphonium and sulfonium systems. Perhaps this is because the sulfone system has a considerably smaller net positive charge on the heteroatom, resulting in diminished coulombic stabilization of the carbanion. This situation may require more stabilization from $p\pi$–$d\pi$ overlap with the sulfur. Because the magnitude of such stabilization is dependent upon the electronegativity of the sulfone groups, the sulfone system is more

(13) A. W. Johnson and H. L. Jones, *J. Amer. Chem. Soc.*, **90**, 5232 (1968).

(14) K. W. Ratts, *J. Org. Chem.*, **37**, 848 (1972).

dependent upon substituent effects for increasing the positive charge on sulfur than are the corresponding onium systems. Ratts and Phillips[15] studied the basicity of substituted pyridinium phenacylides, obtaining a ρ of +2.5. The higher ρ was attributed to the additional carbanion delocalization possible through resonance structures such as **3b** and **3c**.



3a 3b 3c

Variation of the Benzoyl Moiety.—In considering the substituted benzoyl portion of the molecule (Figure 2), a ρ of +2.35 was calculated, again indicating that electron withdrawal stabilized the carbanionic charge and log K/K_0 correlated with σ. This ρ value is similar to values reported by Ratts[14,15] and Fliszar[16] for corresponding pyridium, sulfonium, and phosphonium systems. It should be noted that in this case there can be no direct conjugation between Y and the carbanion. It is perhaps surprising that the ρ values for these four systems should be so similar, since the pK_a's of the analogous ylides vary considerably as a result of the wide differences in acidifying power (or carbanion stabilizing ability) of the heteroatom groups. The order of heteroatom group stabilizing ability can now be extended to include the sulfone system, *i.e.*, $(C_6H_5)_2S^+$ ($pK_a = 5.36$)[5] > $(C_6H_5)_3P^+$ ($pK_a = 5.60$)[5] > $(C_6H_5)_3As^+$ ($pK_a = 8.25$)[5] > $C_5H_5N^+$ ($pK_a = 9.7$)[15] > $C_6H_5SO_2$ ($pK_a = 10.97$).

Even though the sulfone group provided less carbanion stabilization than the other heteroatom groups mentioned, enough stabilization was afforded so that we were able to isolate several sulfone carbanions. Treatment of the precursor sulfones **2a**, **2c**, **2f**, **2g**, **2h**, and **2i** with sodium hydride produced the corresponding carbanions, which could be stored in closed containers for reasonable periods without significant decomposition. They were solids that could be reprotonated to form again the parent sulfone. These ylides showed the typical infrared carbonyl shift of 50–100 cm^{-1} to lower frequencies, indicating the strong contribution of resonance from **1c**. Shifts of the SO_2 vibrational frequencies also were observed. Further characterization of these isolable sulfone carbanions is in progress.

In summary, the same factors that have been suggested for the carbanion stabilization in onium systems appear to apply to the stabilization of sulfone carbanions. Two chief differences in magnitude are observed: (a) less carbanion stabilization is afforded by the sulfone system, as evidenced by the higher pK_a's; (b) the sulfone system has a higher sensitivity to substituent effects than do comparable onium systems, as evidenced by the higher ρ value.

Experimental Section

General.—Analyses were by Galbraith Laboratories, Knoxville, Tenn. Potentiometric measurements were carried out on a Corning Digital 112 research pH meter equipped with glass, saturated calomel, and automatic temperature control electrodes which were standardized with standard pH 4.008 and pH 7.00 buffers in aqueous solutions at 25°. Melting points are uncorrected. Nmr spectra were recorded in $CDCl_3$ on a Varian A-60 spectrometer using TMS as an internal standard with chemical shifts reported as parts per million downfield from TMS. Ir spectra were recorded as KBr pellets on a Beckman IR-10 spectrophotometer.

Preparation of Phenyl Phenacyl Sulfones 2. Method 1.—In this synthesis, reported by Becker and Russell,[17] the appropriate substituted phenyl methyl sulfone in twofold excess was treated with sodium hydride in dry dimethyl sulfoxide under nitrogen. To this was added the substituted methyl benzoate in tetrahydrofuran. Upon quenching with water and acidification with hydrochloric acid, the reaction mixture yielded the sulfone product as crystals. The products were recrystallized from 95% ethanol.

Method 2.—The appropriately substituted sodium benzenesulfinate[18] was treated with the appropriate phenacyl bromide in 95% ethanol and refluxed from 12 to 24 hr to yield the sulfone. The sulfones were recrystallized from 95% ethanol or ethanol–water mixtures.

pK_a Determinations.—Approximately 0.5 mmol of the desired sulfone was dissolved in 100 ml of 95% ethanol and titrated potentiometrically with 0.100 *N* KOH in 95% ethanol prepared by dissolving 6.61 g of potassium hydroxide in 95% ethanol and diluting to 1 l. with more 95% ethanol. The pK_a is taken as the pH at the half-equivalence point. A reverse titration was run using 0.100 *N* HCl prepared by mixing 9.3 ml of concentrated (12%) hydrochloric acid with 40.7 ml of water and 950 ml of absolute ethanol.

Acknowledgments.—We wish to thank the Board of Regents Research Grants and the National Science Foundation for their generous support of this research. We also wish to thank Dr. Edward J. Drexler for his helpful advice regarding the pK_a determinations.

Registry No.—**2a**, 41024-48-0; **2b**, 41024-49-1; **2c**, 41024-50-4; **2d**, 36603-45-9; **2e**, 432-99-5; **2f**, 3406-03-9; **2g**, 31378-03-7; **2h**, 41024-54-8; **2i**, 41024-55-9; **2j**, 38488-19-6; **2k**, 41024-57-1; **2l**, 41024-58-2; **2m**, 27918-37-2.

(15) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **35**, 3144 (1970).

(16) S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).

(17) H. D. Becker and G. H. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

(18) S. Smiles and C. M. Bere, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 7; C. W. Ferry, J. S. Buck, and R. Baltzly, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 239.

Substituent Shift Constants for the Aromatic Protons of Benzene Derivatives in Dimethyl Sulfoxide Solution

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Received April 5, 1973

An empirical set of substituent shift constants for 27 commonly encountered substituents, applicable to dimethyl sulfoxide solutions, for use in predicting the chemical shifts of aromatic protons has been derived. These constants differ from previously published constants determined from chemical shift measurements in relatively nonpolar solvents and yield more accurate predicted chemical shifts when the polar solvent, dimethyl sulfoxide, is required for nmr measurements of materials difficultly soluble in nonpolar solvents. Thus structural assignments can be made on these materials with increased confidence when the polar solvent is used.

A number of studies, summarized by Jackman and Sternhell,[1] have shown that the chemical shifts of ring protons in the nmr spectra of benzene derivatives can be predicted by the relationship

$$\delta = \delta_B - \sum_i S_i \quad (1)$$

The parameters, S, are substituent shift constants whose values depend mainly on the nature of the substituent and its orientation with respect to the ring proton in a given solvent system. δ_B is the chemical shift of benzene in the same system. Both δ_B and the values of S vary with the solvent employed for the nmr measurement.[2] Most of the values of S reported in the literature have been derived from measurements in nonpolar solvents, *e.g.*, carbon tetrachloride, hexane, cyclohexane, etc. A compilation of these is given in the monograph by Jackman and Sternhell. Smith listed S_o and S_m values for a wider variety of substituents from measurements on 1,4-disubstituted benzenes in both nonpolar and polar solvents, no S_p values being given. A fairly restricted set of substituent constants applicable to chloroform solutions is available.[3]

Benzene derivatives with multiple polar substituents are often poorly soluble in nonpolar solvents and nmr measurements on these compounds require polar solvents. Dimethyl sulfoxide-d_6 (DMSO-d_6) is a useful solvent not only for its high solvent power but because it is readily available at a relatively low cost. However, when predicted chemical shifts for ring protons calculated from eq 1 and the shift constants listed by Jackman and Sternhell are compared with the experimental shifts from measurements in DMSO-d_6 solution, large differences are observed in many cases.

In this laboratory, chemical shifts for the protons in several hundred benzene derivatives measured in dilute DMSO-d_6 solutions have been accumulated. These data were analyzed by a multiple regression procedure to obtain substituent shift constants for use in DMSO-d_6 solutions. With these constants it is possible to calculate predicted chemical shifts using eq 1 which closely approximate the observed chemical shifts. In addition, shift constants were derived for several frequently encountered substituents for which constants were not previously available.

(1) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," International Series of Monographs in Organic Chemistry, Vol. 5, 2nd ed, Pergamon Press, Oxford, 1969, p 202.
(2) G. W. Smith, *J. Mol. Spectrosc.*, **12**, 146 (1964).
(3) J. A. Ballantine and C. T. Pillinger, *Tetrahedron*, **23**, 1691 (1967).

Results and Discussion

The substituent constants derived in this work are listed in Table I. With these constants predicted chemical shifts for aromatic protons in a wide variety of benzene derivatives can be calculated using eq 1 and a value of 7.38 for δ_B. The standard deviation of these constants is usually less than δ 0.025. The largest standard deviations are δ 0.05 for S_p of the –NRR group and S_p for the phenyl group; only four chemical shifts involving the para orientation of these substituents were available for the calculation. The standard error

TABLE I
SUBSTITUENT SHIFT CONSTANTS FOR DMSO SOLUTIONS[a]

Substituent	S_o	S_m	S_p
–H	0.00	0.00	0.00
$-CH_3$	0.17 (214)[b]	0.07 (206)	0.18 (71)
$-CH_2R$	0.13 (55)	0.07 (63)	0.15 (20)
–CHRR	0.06 (34)	0.02 (20)	0.19 (11)
–CRRR	−0.03 (50)	0.05 (18)	0.15 (24)
–CH=CH (H, R)	−0.08 (11)	0.03 (12)	0.14 (5)
–CH=CHY[c]	−0.31 (35)	−0.10 (36)	−0.03 (13)
$-C_6H_5$[d]	−0.29 (31)	−0.12 (31)	0.03 (4)
–C(=O)H	−0.52 (39)	−0.20 (35)	−0.31 (18)
–C(=O)R	−0.54 (27)	−0.11 (23)	−0.23 (16)
–C(=O)Y[c]	−0.42 (24)	−0.21 (43)	−0.19 (13)
–C(=O)O– (H, R)	−0.53 (110)	−0.12 (68)	−0.19 (53)
–C(=O)NH– (H, R)	−0.60 (23)	−0.07 (21)	−0.16 (17)
–C≡N	−0.49 (49)	−0.24 (45)	−0.32 (22)
–OH	0.53 (188)	0.14 (267)	0.58 (63)
–OR	0.41 (139)	0.04 (107)	0.37 (40)
–OC(=O)R	0.17 (31)	−0.07 (39)	0.11 (13)
$-NH_2$	0.72 (94)	0.27 (105)	0.84 (32)
–NHR	0.81 (16)	0.15 (18)	0.87 (8)
–NRR	0.67 (34)	0.17 (23)	0.80 (4)
Hindered –NHR, –NRR	0.36 (16)	0.21 (26)	0.42 (16)
$-\overset{+}{N}H_2$– (H, R)	−0.08 (32)	−0.14 (28)	0.09 (9)
–NHC(=O)R	−0.26 (46)	0.00 (44)	0.21 (20)
–N=NY[c]	−0.53 (31)	−0.19 (37)	−0.06 (9)
$-NO_2$	−0.78 (208)	−0.27 (131)	−0.34 (70)
–Cl	−0.10 (263)	−0.07 (202)	0.03 (70)
–Br	−0.24 (108)	−0.02 (72)	−0.01 (41)
–I	−0.38 (44)	0.20 (22)	−0.05 (16)
$-SO_3$– (H, M)[e]	−0.34 (37)	0.00 (28)	0.04 (23)
$-SO_2NH$– (H, R)	−0.45 (28)	−0.21 (23)	−0.22 (6)

[a] A negative sign indicates a downfield shift. [b] The number of entries for this substituent orientation in the set of simultaneous equations used to calculate these constants is given in parentheses. [c] Y is an unsaturated moiety conjugated to the main group double bond. [d] This can be a substituted phenyl ring, but substituents ortho to the bond joining the rings must be absent (see text). [e] M can be an alkali metal or an ammonium ion.

of estimate for the shifts of 1629 aromatic protons included in the regression analysis is δ 0.09 and almost 98% of the predicted shifts using these shift constants are within δ ±0.20 of the experimental shifts. None of the measured shifts differed by more than δ 0.31 absolute from the predicted shift.

These new substituent shift constants for DMSO-d_6 solutions are significantly different from those compiled for use with "inert" solvents by Jackman and Sternhell. Table II compares the constants of some common substituents for the two different media. The greatest differences are usually observed for the more polar substituents. There is no consistency of direction in the change of the constant with change of solvent medium.

TABLE II
COMPARISON OF SUBSTITUENT SHIFT CONSTANTS IN DMSO AND INERT SOLVENTS

Substituent	Orientation	S (DMSO)	S (inert solvent)[a]	Δ[b]
$-CH_3$	o	0.18	0.17	0.01
	m	0.07	0.09	−0.02
	p	0.18	0.18	0.00
-CRRR	o	−0.03	−0.04	0.01
	m	0.05	0.10	−0.05
	p	0.15	0.24	−0.09
-OH	o	0.53	0.50	0.03
	m	0.14	0.14	0.00
	p	0.58	0.40	0.18
$-NH_2$	o	0.72	0.75	−0.03
	m	0.27	0.24	0.03
	p	0.84	0.63	0.21
$-NO_2$	o	−0.78	−0.95	0.17
	m	−0.27	−0.17	0.10
	p	−0.34	−0.33	−0.01
-Cl	o	−0.10	−0.02	−0.08
	m	−0.07	−0.06	−0.01
	p	0.03	0.04	−0.01
-Br	o	−0.24	−0.22	−0.02
	m	−0.02	0.13	−0.15
	p	−0.01	0.03	−0.04
$-C\equiv N$	o	−0.49	−0.27	−0.22
	m	−0.24	−0.11	−0.13
	p	−0.32	−0.30	−0.02

[a] See ref 1. [b] $\Delta = S$ (DMSO) − S (inert solvent).

The molecules of DMSO have a pyramidal structure with the sulfur atom at one apex[4] and there is a large charge separation along the oxygen–sulfur bond giving this molecule a large permanent dipole moment.[5] Consequently, when benzene derivatives are dissolved in DMSO-d_6 strong collision complexes are formed, possibly by a dipole–dipole interaction, with polarizable substituents[6] or the π electrons of the ring. As a result the electronic configuration of the solute is modified and the inductive, resonance, and through-space (field) effects of the substituents differ from those observed for the same solutes in nonpolar solvents. In addition, the effective size of a substituent is increased in such complexes and thus any steric interactions between the substituent and the remainder of the molecule are changed. It has been shown that in dilute DMSO solutions of phenol and aniline derivatives intermolecular solute–solute hydrogen bonding is absent and intramolecular bonding is markedly decreased,[7] since the –OH and –NH groups of the solute are almost exclusively bonded to the DMSO molecules. In view of these considerations, it is hardly surprising that the previously published substituent constants, derived from measurements in relatively nonpolar solvents where strong solute–solvent complex formation is less likely, yield predicted chemical shifts with large deviations from the experimental chemical shifts measured in DMSO-d_6 solutions.

In the calculation of the substituent constants listed in Table I, it was assumed that the effect of each substituent on a ring proton was independent of all other substituents and that the actual chemical shift was solely an additive function of the nature and orientation of all the ring substituents. These are the same assumptions made for the derivation of the substituent constants quoted by Jackman and Sternhell. This is a simplistic view which ignores possible steric interactions between substituents, particularly adjacent substituents. Additional phenomena, such as residual intramolecular hydrogen bonding, resonance interaction between substituents through the π-bond network, changes in solute–solvent ratio in the complexed species, etc., can also increase or decrease the chemical shifts of ring protons. In a given compound several of these may be operating simultaneously. Their net effect is usually small and no attempt has been made, except as noted below, to correct the constants listed in Table I for these phenomena. Application of such corrections would require prior knowledge of the structure of the compound, and a major purpose of this work was to obtain substituent shift constants which would aid in the identification of unknown structures. The relatively small standard error of estimate for predicted chemical shifts calculated from the substituent shift constants of Table I justifies this approach.

Preliminary calculations of the shift constants showed that two steric effects on ring proton shifts in multiply substituted benzene derivatives were too great to be ignored. The first of these was observed in biphenyl compounds; the second, in *N*-alkyl- and *N*,*N*-dialkylaniline derivatives.

When biphenyls have one or more substituents ortho to the bond joining the rings, the two rings may no longer be coplanar. In twisted biphenyls the resonance interaction between the rings is decreased and the protons of one ring are more shielded by the field effect of the ring current of the other ring. The magnitude of these changes is a function of the dihedral angle between the two rings and the largest changes are noted for ring protons ortho to the bond joining the rings. Therefore chemical shift data from biphenyl derivatives with substituents ortho to the bond joining the rings were not included in the computation of the substituent constants of Table I. The listed constants should be applied with caution in making structural determinations for unknown biphenyl derivatives.

Ring protons ortho and para to the amino group in *N*,*N*-dialkylanilines having a second substituent adjacent to the amino group are significantly deshielded as compared to *N*,*N*-dialkylanilines without an ortho substituent. Similar deshielding is also observed for

(4) Y. A. Kolesnick and V. V. Kozlow, *Russ. Chem. Rev.*, **37**, 519 (1968).
(5) D. Martin, A. Weise, and H. Niclas, *Angew. Chem., Int. Ed. Engl.*, **6**, 318 (1967).
(6) P. Weiner and E. Malinowski, *J. Phys. Chem.*, **75**, 3971 (1971).
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protons para to the alkylamino group in *N*-alkylanilines with substituents in both the 2 and 6 positions. In these derivatives substituent crowding forces the alkylamino groups out of the plane of the ring and the resonance contribution of the alkylamino group to the shielding of ortho and para protons is decreased. Shielding of protons meta to these alkylamino groups is not greatly altered. The chemical shift data from compounds containing these hindered alkylamino groups was segregated and used to compute the substituent constants for "hindered –NHR, NRR" given in Table I.

The substituent shift constants obtained in this study for DMSO solutions have proven to be very useful in identifying or confirming the structures of benzene derivatives and for making preliminary assignments of shifts in computer analyses of spectra. It must be emphasized that they reflect the average effect of a complexed substituent upon the ring protons and for a given compound calculated and observed shifts can differ. Even so, they yield closer estimations of the chemical shifts to be expected when the polar solvent DMSO-d_6 is employed for examination of compounds difficultly soluble in the usual nonpolar solvent. Comparison of scattered data in the literature on chemical shifts of benzene derivatives examined in acetone, also a highly polar solvent with some properties similar to that of DMSO, have indicated that the new substituent shift constants can sometimes yield predicted shifts which are closer to the measured values than the previously available constants for nonpolar solvents. The utility of the new values for qualitative assessment of substituent effects on chemical shifts of ring protons in condensed aromatic and heterocyclic compounds which are seldom appreciably soluble in nonpolar solvents is obvious.

Experimental Section

The compounds of known structure employed in this study were obtained by purchase from chemical supply houses or were synthesized in the laboratories of American Cyanamid Co. The samples were of high purity as evidenced by the absence of extraneous signals in their nmr spectra and were used without further purification. The spectra were obtained in DMSO-d_6 solutions containing less than 10% solute (w/v) with 1% sodium 3-trimethylsilylpropane-1-sulfonate (DSS) added as the internal standard. The deuterated DMSO (99.5% isotopic purity) was purchased from commercial suppliers and dried and stored over Linde Type 4A Molecular Sieves.

Spectra were measured on either a Varian A-60 spectrometer with the charts calibrated using a standard $CHCl_3$–TMS reference sample or on a Varian HA100-D spectrometer with calibration by means of the V-4315A frequency counter. Solution temperatures were maintained at 32–34°. A number of compounds were examined on both spectrometers; the chemical shifts abstracted from these spectra agreed within ±0.02 ppm. The observed shifts for the protons in the compounds used in this study ranged from δ 5.70 to 9.18 *vs.* DSS.

The unsubstituted benzene singlet signal determined from repetitive measurements on 5–10% (w/v) solutions in DMSO-d_6 at 34° was 737.6 ± 0.4 Hz downfield from the DSS signal. Therefore, a value of 7.38 was taken for δ_B in this work.[8]

The second-order aromatic signal patterns usually obtained were analyzed either by the algebraic methods described by Garbisch[9] or by the use of the iterative computer program LAOCOON-3.[10]

Assuming that the effect of a substituent depends only on its orientation with respect to the proton under consideration and that the effects of other protons regardless of their orientation are zero, an equation of the following type was written for each proton included in this study.

$$\delta_B - \delta_{exp} = \sum_{i,j} n_{i,j} S_{i,j} \qquad (2)$$

δ_{exp} is the observed shift *vs.* DSS of an aromatic proton in DMSO-d_6 solution. The coefficients, n, could have the values of 0, 1, or 2 depending on the number of substituents of a given type in the relevant orientation. The indices, i and j, define the nature and orientation of the substituent having the shift constant S. For example, the equations written for the protons of 3-nitro-4-cyanotoluene were

$$\text{H-2}\quad 7.38 - 8.24 = -0.86 = S_{o,CH_3} + S_{o,NO_2} + S_{m,CN} \qquad (3a)$$

$$\text{H-5}\quad 7.38 - 8.04 = -0.66 = S_{m,CH_3} + S_{m,NO_2} + S_{o,CN} \qquad (3b)$$

$$\text{H-6}\quad 7.38 - 7.84 = -0.46 = S_{o,CH_3} + S_{p,NO_2} + S_{m,CN} \qquad (3c)$$

In this manner 1629 equations involving constants for 29 different substituents were obtained. Simultaneous solution of these equations resulted in the 87 shift constants listed in Table I.

Acknowledgment.—I wish to thank Mrs. Christine Wilson, who prepared a number of the spectra used in this study, and Kenneth Burkhardt, Thomas Murphy, and Michael Miller, who materially aided in the necessary computer programming.

(8) δ_B is 7.41 when TMS is used as the internal standard.
(9) E. W. Garbisch, Jr., *J. Chem. Educ.*, **45**, 311, 402 (1968).
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The Effect of Substitution on the Photoreduction of Some Hindered Benzophenones[1]

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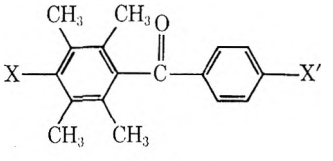
The photoreduction of 2,3,5,6-tetramethylbenzophenone (**1a**) and several of its 4 and 4′ (Cl, Br, OCH_3) derivatives with 2-propanol has been investigated. The products formed and the quantum yields for the disappearance of ketone, ϕ_B, depend on both the nature of the substituent and its position (4 or 4′). Substitution in the 4 position has little effect on ϕ_B while substitution in the 4′ position increases ϕ_B substantially relative to **1a**. Product analysis indicates that attack of a dimethylhydroxymethyl radical on the 4′ position of the hindered ketone leading to the formation of 1-(durylhydroxymethylene)-4-(dimethylhydroxymethyl)-2,5-cyclohexadiene (**10**) as an intermediate is an important step in the photochemistry of the ketones investigated.

In recent years the effect of substitution on the efficiency of the photoreduction of aromatic ketones has been the subject of several investigations.[2-5] The nature of this effect has been found to depend on the nature of the lowest triplet state of the molecule. Generally, aromatic ketones with lowest lying n-π^* states exhibit normal, efficient photoreduction by alcohols while those with lowest lying or closely lying π-π^* states show reduced reactivity. One problem which is encountered in the interpretation of these substituent effects is that most groups show both a resonance and an inductive effect simultaneously. Consequently the degree of involvement of each of these effects in the excited state is difficult to determine.

In this study, the photoreduction of 2,3,5,6-tetramethylbenzophenone and several of its 4 and 4′ derivatives **1a**–**g** with 2-propanol was investigated.



1a–g

1	X	X′
a	H	H
b	Br	H
c	Cl	H
d	OCH_3	H
e	H	Br
f	H	Cl
g	H	OCH_3

This series was chosen for several reasons, foremost among which is the fact that methyl substituents in both the 2 and the 6 positions inhibit the coplanarity of the duryl ring with the carbonyl group. The phenyl ring, however, can attain coplanarity without severe steric interactions. One anticipates that a substituent in the 4′position would interact with the carbonyl group both by resonance and induction while a substituent in the 4 position would interact primarily through induction. This assumption was supported by the uv spectra of these compounds which were identical for the derivatives substituted in the 4 position (**1a**–**d**), but experienced bathochromic shifts for those substituted in the 4′ position (**1e**–**g**). By comparing the effect on the efficiency of photoreduction of a substituent in the 4 position with the same substituent in the 4′ position, it was felt that a clearer picture of substituent interaction in the photoreduction process could be obtained.

(1) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 27 to Sept 1, 1972.
(2) J. N. Pitts, Jr., H. W. Johnson, and T. Kuwana, *J. Phys. Chem.* **66**, 2456 (1962).
(3) A. Becket and G. Porter, *Trans. Faraday Soc.*, **59**, 2051 (1963).
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Results and Discussion

Quantum yields (ϕ_B) relative to **1a** based on the disappearance of ketone were determined and are presented in Table I. Though the variations observed are

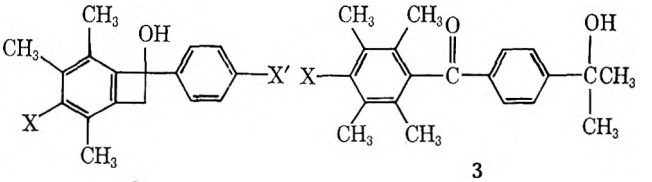
TABLE I
RELATIVE QUANTUM YIELDS OF DISAPPEARANCE OF 4- OR 4′-SUBSTITUTED 2,3,5,6-TETRAMETHYLBENZOPHENONES[a]

Ketone	ϕ_B
1a[b]	1.0
1b	0.5
1c	1.2
1d	1.2
1e	2.2
1f	4.3
1g	2.2

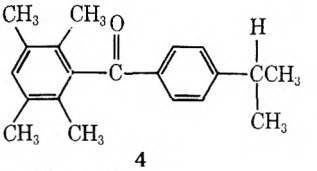
[a] All ketones are 0.01 *M* in 2.0 *M* 2-propanol–benzene. [b] Absolute quantum yield, 0.04.

difficult to interpret on the basis of known structure–reactivity relationships, two trends are evident. Substituents in the 4 position have only a slight effect on the quantum yields, while those in the 4′ position produce a marked increase in ϕ_B for each substituent.

Product analysis was accomplished using both preparative thin layer and column chromatography. Four



2 **3**



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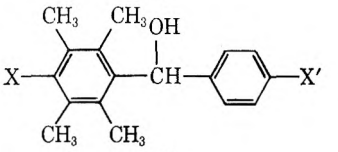


5

classes of compounds were isolated and assigned structures **2**, **3**, **4**, and **5** based on elemental analysis and ir

and nmr spectroscopy. It is noteworthy that no pinacols were detected in any of these reactions.

The nature of the substituent and its position on the ring have a profound influence on both the products formed and their yields. Product analyses and other pertinent data for the ketones studied are presented in Table II.

TABLE II
PRODUCTS FORMED IN THE PHOTOREDUCTION OF 2,3,5,6-TETRAMETHYLBENZOPHENONE AND ITS 4- AND 4′-SUBSTITUTED DERIVATIVES[a]

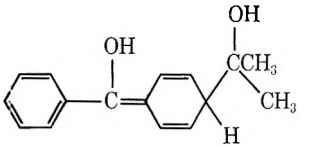
Ketone	Irradn period, hr	% ketone recovd[c]	% products 1a	2	3	4	5
1a	24	41.5		30	15		54
1b	40	56	59				
1c[b]	18.5	3.8		31			10
1d	18.5	62		5	11		84
1e	12	33	14	<1		14	<1
1f	2.5	61.5		26.5		38	
1g	12	1.8		70			21

[a] Irradiated solutions contained 0.5 g of ketone in 200 ml of 2.0 *M* 2-propanol–benzene. [b] The principal product in this reaction was an alkyl duryl ketone which has not yet been identified. [c] Based on total material isolated from column chromatography.

Benzocyclobutanol formation was observed in all cases except for the brominated derivatives **1b** and **1e**. In the case of **1b**, debromination is the only major primary photochemical process. Benzhydrols were formed in all cases except for the bromo compounds **1b** and **1e** and the 4′-chloro derivative **1f**. In the case of **1e** and **1f**, the two most reactive of the compounds studied, the lack of benzhydrol formation is compensated for by the formation of the isopropyl derivative (**4**), which is formed only in these two cases. The 4′-dimethylmethylol compound (**3**) was formed in detectable amounts only in the photoreduction of **1a** and **1d**.

The significance of these results becomes clear if one considers the problems that have existed in determining the mechanism of photoreduction. Though the photoreduction of benzophenone by alcohols has been known and studied for many years, the exact mechanism is still the subject of some controversy. Much of this controversy stems from attempts to explain the significance of the yellow color which develops during the photoreduction of carefully degassed solutions.[6-8] The origin of this color has been found to be a long-lived intermediate, the nature of which has remained in doubt for nearly 15 years.

Recently, enol structure **6** was proposed for this intermediate by several independent workers.[9-11] Still more recently, Weiner questioned the intermediacy of this structure in the photoreduction process.[12] Much of the problem arises from the fact that direct confirmation of this structure by product isolation or trapping has not been possible.[13] In the present study, product analysis clearly implicates an enol structure like **6** as an intermediate.



6

The results of our work in conjunction with those published[11] earlier support the following mechanism for the photoreduction of **1a–g** in 2-propanol.

Steps 1 and 2 are similar to those previously proposed for benzophenone.[2,6,8] In the present work a quenching study using **1a** and piperylene gave a linear Stern–Volmer plot from which the apparent triplet lifetime, τ (0.54×10^{-7} sec), and the rate constant for hydrogen abstraction, k_r ($7.39 \times 2\ M \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$), were obtained. At 0.03 *M* piperylene concentration all reactions of **1a** were quenched.

The reaction in step 3 explains the formation of product types **3** and **4** and is analogous to the mechanism proposed for benzophenone.[11] The isolation of **3** provides direct evidence for the intermediacy of a structure such as **10** in the photoreactions of the hindered benzophenones. This intermediate may subsequently undergo either reaction 7, 8, or 9 depending on the substituent in the 4′ position. When either –H or $-OCH_3$ is in this position (except **1b**) the dark reaction, step 7, is the preferred route producing two ketyl radicals, **7**, and acetone in a manner proposed by Filipescu.[11] The ketyl radicals would then undergo disproportionation, step 10, yielding the benzhydrol, **5**, and starting ketone. Disproportionation rather than combination has been shown to be the preferred reaction between ketyl radicals produced by sterically hindered ketones.[14] Upon the admission of air at the conclusion of the photolysis, the intermediate **10** reacts with atmospheric oxygen to produce **3** (step 8).

When either –Cl or –Br is in the 4′ position (**1e** and **1f**), **10** undergoes two successive elimination reactions to yield **4**, presumably by way of **11**. This reaction is apparently possible because of the relatively weak C–X bond in the intermediate and does not occur with either –H or $-OCH_3$ in the 4′ position.

Further evidence for steps 7–10 is provided by the

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(8) H. L. J. Bäckström, K. L. Appelgren, and R. J. V. Niklassen, *Acta Chem. Scand.*, **19**, 1555 (1965).

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(10) D. C. Neckers, "Mechanistic Organic Photochemistry," Rheinhold, New York, N. Y., 1967, p 171.

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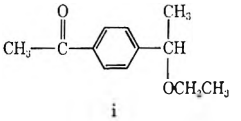
(13) A product having the structure i has been reported as being formed



i

in the photoreduction of acetophenone in ethyl ether: B. D. Charlland, *Can. J. Chem.*, **47**, 687 (1969).

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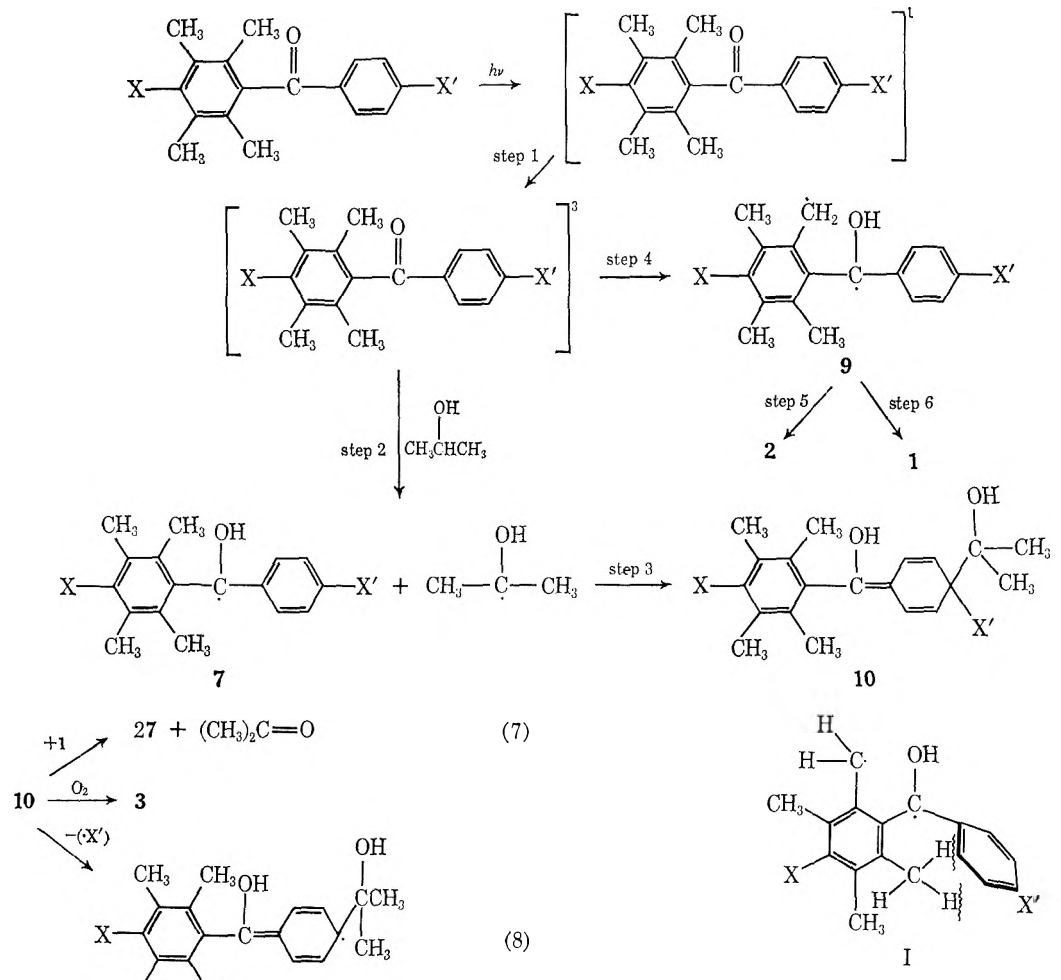


I

fact that irradiation of **3** (X = H) in 2 *M* 2-propanol in benzene produces **4** (eq 11 and 12). This shows that **3**

$$\mathbf{3} \xrightarrow{h\nu} \mathbf{3}^* \quad (11)$$

$$\mathbf{3}^* + CH_3CHCH_3 \longrightarrow \mathbf{11} \xrightarrow{-(OH)} \mathbf{4} \quad (12)$$

is not produced during the photolysis of **1a** but only after the admission of air since **4** was not detected with those ketones in which X′ = H (**1a**) or CH_3O (**1d**).

The photoenol formed in step 4 is similar to that reported in the photoreduction of 2-alkylbenzophenone[3,15,16] and 2,4,6-trialkylphenyl ketones.[17,18] An examination of molecular models shows that considerable steric interaction should be expected between the methyl group in the 6 position and the phenyl ring as shown in I.

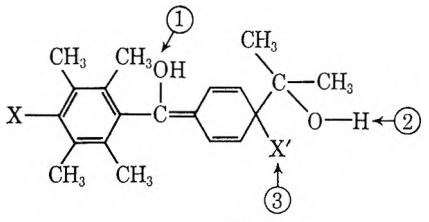
Such interactions are not present in systems substituted only in the 2 position where a reversible enolization process is the favored reaction.[15] In the present case, however, a cyclization process leading to the formation of benzocyclobutanols (step 5) would relieve this crowding.

In the absence of phosphorescence data no definite conclusions can be made regarding the type of excited states involved. The results obtained in this study, however, allow for considerable speculation. Consider the methoxyl-substituted compounds **1d** and **1g**. In the case of **1g**, the methoxyl group can become conjugated with the carbonyl group thereby lowering the $\pi-\pi^*$ state. Since the major product in this instance was the cyclobutanol compound **2**, it may be tentatively concluded that the $^3[\pi-\pi^*]$ state is the photoreactive state involved. In contrast to this the methoxyl group in **1d** should exert an inductive effect on the system, thereby lowering the $n-\pi^*$ state relative to the $\pi-\pi^*$ state.[19] Since, with **1d**, the photoreduction yields mainly benzhydrol, **5**, the $^3[n-\pi^*]$ state must be involved in the reduction and the $^3[\pi-\pi^*]$ state in cyclobutanol formation.

Though the stereochemistry of the ketones investigated in this study differs significantly from that of benzophenone, it is not unreasonable to assume that the photochemical processes occurring in the two systems are the same. Whether the formation of intermediate **10** is due to unique steric factors involving the carbonyl group or whether all benzophenone photoreductions proceed by way of a similar intermediate cannot be determined directly from this work. If one assumes, however, that intermediates such as **10** are common to all benzophenone photoreductions, then, using stereo-

(15) N. C. Yang and C. Rivas, *J. Amer. Chem. Soc.*, **83**, 2213 (1961).
(16) E. F. Zwicker, L. I. Grossweiner, and N. C. Yang, *J. Amer. Chem. Soc.*, **85**, 2671 (1963).
(17) T. Matsuura and Y. Kitaura, *Tetrahedron*, **25**, 4487 (1969).
(18) Y. Kitaura and T. Matsuura, *Tetrahedron*, **27**, 1597 (1971).
(19) Y. Ogata, K. Takagi, and Y. Fujii, *J. Org. Chem.*, **37**, 4026 (1972).

chemistry as the main criterion of difference, the results obtained can be applied to the photoreduction of aryl ketones in general. There appear to be three critical centers on the intermediate, **10** (arrows), which determine the course of the dark reaction.



10

As Filipescu, *et al.*, suggest, reaction could occur at ② through hydrogen abstraction by ketone.[11] This leads to benzopinacol in the case of benzophenone and to a benzhydrol in the case of hindered ketones. In the case of **1a–g**, however, owing to steric hindrance about the carbonyl group, this reaction is substantially suppressed.

When oxygen is introduced, a fast reaction occurs at ① in benzophenone and, because of hindrance, at ①, or ③ in the case of **1a**. When reaction occurs at ① and ② starting ketone is produced while reaction at ③ results in 4′ substitution. Further work is in progress on other hindered ketones and we hope to report these results in a subsequent paper.

Summary.—The photoreduction of several 4- or 4′-substituted duryl phenyl ketones yields at least four different classes of compounds indicated by structures **2–5**. The dimethylhydroxymethyl radical attacks the 4′ position of aryl ketones in a manner suggested by Filipescu and Minn.[11] If the substituent in the 4′ position is either –Cl or –Br, elimination of the halogen occurs, followed by elimination of –OH, yielding the 4′ isopropyl derivative **4**. The substituent and its position on the ring, 4 or 4′, has a profound influence on the nature of the products formed.

Experimental Section

Melting points are uncorrected and were determined on a Mel-Temp apparatus. The nmr spectra were recorded on a Joelco Model C-60HL spectrometer at 60 MHz using tetramethylsilane as an internal standard. Ir spectra were determined on a Perkin-Elmer Model 700 spectrophotometer, and uv spectra were measured on a Cary Model 15 spectrophotometer. The microanalyses were performed by Micro Analysis, Inc., Wilmington, Del. All solvents used in the photolysis studies were spectroscopic grade and were used as received. Benzene was obtained from Matheson Coleman and Bell and the 2-propanol from Fisher Scientific Co. The benzophenone and benzyhydrol used in the quantum yield determinations were recrystallized four times from petroleum ether (bp 60–80°) prior to use.

Synthesis of the Substituted Benzophenones.—The 4- and 4′-substituted derivatives were prepared by the Friedel–Crafts acylation of either durene or substituted durene with the appropriate benzoyl chloride according to the general method of Fuson.[20] The structure of the ketones prepared in this manner were confirmed by ir and nmr spectroscopy and either by a comparison with literature melting points or by elemental analysis.[21] Pertinent data for new compounds is listed in Table III.

TABLE III

1	Mp, °C	% yield[a]	Analyses, %
c	122–124	55	Calcd for $C_{17}H_{17}ClO$: C, 74.84; H, 6.29; Cl, 13.00. Found: C, 74.57; H, 6.37; Cl, 12.78.
d	153.5–154.5	74	Calcd for $C_{18}H_{20}O_2$: C, 80.55; H, 7.52. Found: C, 80.58; H, 7.58.
f	170.0–171.5	90	Calcd for $C_{17}H_{17}ClO$: C, 74.84; H, 6.29; Cl, 13.00. Found: C, 74.97; H, 6.33; Cl, 13.08.

[a] Based on Friedel–Crafts reaction.

Quantum Yield Determinations.—Quantum yields were measured using solutions of 0.01 *M* ketone and 2.0 *M* 2-propanol in benzene sealed under vacuum in 13-mm-o.d. Pyrex tubes after a minimum of five freeze–thaw cycles at a vacuum of <0.01 mm. Samples were irradiated in parallel using a Rayonet Model MGR-500 merry-go-round at 30 ± 1° using a filter solution of nickel sulfate and cobalt sulfate[22] to isolate the 3130-Å light from a Hanovia Type A 550-W lamp. The quantum yield of duryl phenyl ketone was determined using benzophenone benzhydrol actinometry.[23] Duryl phenyl ketone was in turn used as the standard for determination of the quantum yields of the substituted derivatives. Samples were analyzed for disappearance of ketone by observing the decrease in band intensity of the uv absorption spectra of diluted solutions of the isolated ketones after irradiation. The ketones were isolated from the reaction by thin layer chromatography and compared to nonirradiated samples treated in an analogous manner. Absorbancies were determined using an average of five wavelengths to measure the concentrations before and after irradiation.

Photolysis of 1a in 2 *M* 2-Propanol in Benzene.—A solution of duryl phenyl ketone (0.500 g) in 200 ml of 2 *M* 2-propanol in benzene was irradiated for 24 hr with the 3000-Å lamps. The solution was yellow at the end of the irradiation period. Evaporation of the solvent under reduced pressure gave a yellow oil. The oil was dissolved in petroleum ether–benzene (1:1) and chromatographed on a silica gel column (30 g). Elution with petroleum ether–benzene (1:5) gave 0.182 g of unreacted duryl phenyl ketone. Further elution gave 0.139 g of the hydrol derivative (**5a**) of duryl phenyl ketone and 0.078 g of a colorless oil. An ir spectrum of **5a** was virtually superimposable on that of the alcohol formed by the chemical reduction of duryl phenyl ketone with sodium. The naphthylurethane derivative of **5a** had mp 178–179.5° (lit.[20] 177–178.5°). The ir spectrum (neat) of **5a** showed peaks at 3350 (OH), 1010 and 1030 (C–O) cm^{-1}. The nmr spectrum ($CDCl_3$) showed the following bands: δ 7.25 (s, 5, Ar), 6.96 (s, 1, Ar), 6.40 (s, 1, CHOH), 2.20 (s, 3, CH_3), 2.10 (s, 3, CH_3).

The colorless oil was identified as the benzocyclobutanol derivative **2a**: ir 3350 (OH) and 1060 (C–O) cm^{-1}; nmr ($CDCl_3$) δ 6.99 (s, 5, Ar), 6.60 (s, 1, Ar), 3.10 (s, 2, CH_3), 2.64 (s, 1, OH), 2.02 (s, 3, CH_3), 1.98 (s, 3, CH_3), 1.80 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.49; H, 7.57.

Further elution with chloroform–ether (9:1) gave 0.039 g **3** (X = H) as an oil with a yellow tint which crystallized upon standing. Recrystallization from benzene–petroleum ether gave a white solid: mp 127–128°; ir 3375 (OH), 1660 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 7.57 (AB quartet, J = 9 Hz, 4, Ar), 6.95 (s, 1, Ar), 2.12 (s, 6, CH_3), 1.86 (s, 6, CH_3), 1.47 (s, 6, CH_3).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.03; H, 8.17. Found: C, 81.29; H, 8.17.

Photolysis of 1b in 2 *M* 2-Propanol in Benzene.—A 0.028 *M* solution (100 ml) in **1b** in 2 *M* 2-propanol was irradiated for 40 hr with the 3000-Å lamps. The solution was slightly yellow at the end of the irradiation. Evaporation of solvent under reduced pressure gave a light yellow oil. The oil was dissolved in hexane–benzene (1:1) and chromatographed on a column of 40 g of silica gel. Elution with benzene first gave 0.317 g of unreacted ketone followed by 0.146 g of duryl phenyl ketone, identified by a comparison of its ir spectrum with that of an authentic sample. Further elution with chloroform gave 0.039 g of a clear oil which appeared to be a mixture of durylphenylcarbinol (**5a**) and the

(20) R. C. Fuson, B. C. McKusick and J. Mills, *J. Org. Chem.*, **11**, 60 (1946).

(21) Known compounds were synthesized by procedures described in the references that follow: **1a** and **1b**, R. C. Fuson and B. C. McKusick, *J. Amer. Chem. Soc.*, **65**, 60 (1943); **1e**, R. C. Fuson, W. S. Friedlander, and G. W. Parshall, *J. Amer. Chem. Soc.*, **76**, 5119 (1954); **1g**, R. C. Fuson, W. D. Emmons, and G. W. Parshall, *J. Amer. Chem. Soc.*, **76**, 5467 (1954).

(22) P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.*, **88**, 1245 (1966).

(23) W. M. Moore and M. Ketchum, *J. Org. Chem.*, **11**, 60 (1946).

cyclobutanol derivative (2a) of duryl phenyl ketone as shown by ir spectroscopy.

Photolysis of 1e in 2 *M* 2-Propanol in Benzene.—A solution of 0.500 g of 1e in 200 ml of 2 *M* 2-propanol in benzene was irradiated for 12 hr with the 3000-Å lamps. The solution was dark yellow at the end of the photolysis. Evaporation of solvent under reduced pressure gave a brown oil which was dissolved in benzene–petroleum ether (1:1) and chromatographed on a silica gel (30 g) column. Elution with benzene–petroleum ether (1:3) gave 0.163 g of unchanged 1e, identified by comparison of its ir spectrum with that of an authentic sample. Elution with benzene–petroleum ether (5:1) gave 0.094 g of a 1:1 mixture of duryl phenyl ketone and 4, determined by ir and nmr spectroscopy. Further elution with benzene gave 0.026 g of products arising from the photolysis of 1a.

Photolysis of 1c in 2 *M* 2-Propanol in Benzene.—Irradiation of 0.500 g of 1c in 200 ml of 2 *M* 2-propanol in benzene for 18.5 hr produced a very slight yellow color in the solution. Evaporation of the solvent under reduced pressure gave an oil with a light yellow tint. The oil was dissolved in benzene–petroleum ether (1:1) and chromatographed on a 30-g column of silica gel. Elution with benzene–petroleum ether (5:1) gave 0.013 g of starting ketone identified by a comparison of its ir spectrum with that of an original sample. Further elution with benzene–petroleum ether (5:1) gave a mixture of 0.140 g of two hydroxyl-containing compounds as evidenced by their ir spectrum. Preparative tlc in benzene afforded the isolation of two white solids. The compound with the larger R_f value was identified as the hydrol derivative **5c**: ir (KBr) 3350 (OH), 1020 (C–O) cm^{-1}; nmr ($CDCl_3$) δ 7.17 (s, 5, Ar), 6.34 (s, 1, CHOH), 2.32 (s, 3, CH_3), 2.14 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{19}ClO$: C, 74.29; H, 6.98; Cl, 12.90. Found: C, 74.28; H, 6.73; Cl, 13.04.

The compound with the lower R_f value was identified as the benzocyclobutanol derivative **2c**: ir 3325 (OH), 1460, 1150, 1065 (C–O) cm^{-1}; nmr ($CDCl_3$) δ 7.28 (s, 5, Ar), 3.36 (s, 2, CH_2), 2.70 (s, 1, OH), 2.28 (s, 3, CH_3), 2.18 (s, 3, CH_3), 2.02 (s, 3, CH_3).

Further elution with chloroform–ethyl ether (20:1) gave 0.065 g of a yellow oil. Its ir showed major absorptions at 3425 (w), 2925, 1690 (br), 1460, and 765 cm^{-1}. Tlc showed the presence of at least four components. The colored oil was not further investigated. Further elution with chloroform–ether (10:1) gave 0.130 g of an unidentified white solid. An ir spectrum (KBr) showed major absorptions at 3400, 2925, 1680 (C=O), 1450, 1380, 1120, and 1000 cm^{-1}. The nmr spectrum ($CDCl_3$) showed a well resolved quartet at δ 3.43 (J = 6 Hz) and a triplet at 1.2 (J = 6 Hz). Additional CH_3 peaks are present at δ 2.3 (6 H), 207 (6 H), and 1.13 (6 H). Most significant, however, was the fact that no bands appeared in the aromatic region.

Photolysis of 1f in 2 *M* 2-Propanol in Benzene.—A solution of 0.500 g of 1f in 200 ml of 2 *M* 2-propanol in benzene was irradiated for a period of 2.5 hr with the 3000-Å lamps. The solution became very yellow within the first few minutes of irradiation and was dark yellow at the end of the photolysis. Evaporation of the solvent under reduced pressure gave a yellow oil. The oil was dissolved in benzene–petroleum ether (2:1) and chromatographed on a column of silica gel (30 g). Elution with benzene–petroleum ether (3:1) gave 0.295 g of unreacted 1f which was identified by comparison of its ir spectrum with one of an authentic sample. Further elution with benzene–petroleum ether (5:1) gave 0.070 g of white solid, mp 107–108°, identified as structure **4**: ir (KBr) 1660 (C=O), 1600, 1250, 1190, cm^{-1}; nmr ($CDCl_3$) δ 7.34 (AB q, J = 8 Hz, 4, Ar), 6.88 (s, 1, Ar), 2.88 (septet, J = 7 Hz, 1, Ar), 2.17 (s, 6, CH_3), 1.93 (s, 6, CH_3), 1.28 (s, 3, CH_3), 1.17 (s, 3, CH_3).

Anal. Calcd for $C_{20}H_{24}O$: C, 85.65; H, 8.64. Found: C, 85.75; H, 8.57.

Further elution with benzene–petroleum ether (5:1) gave 0.049 g of a white solid, mp 98.5–99.5°, which was identified as the benzocyclobutanol derivative **2f**: ir (KBr) 3500 (OH), 1490, 1195, 1100 cm^{-1}; nmr ($CDCl_3$) δ 7.06 (s, 4, Ar), 6.72 (s, 1, Ar), 3.24 (s, 2, CH_2), 2.50 (s, 1, OH), 2.12 (s, 3, CH_3), 2.08 (s, 3, CH_3), 1.90 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28; Cl, 13.00. Found: C, 75.14; H, 6.36; Cl, 12.21.

Photolysis of 1g in 2 *M* 2-Propanol.—A solution of 0.500 g of 1g in 200 ml of 2 *M* 2-propanol in benzene was irradiated for 12 hr with the 3000-Å lamps. The solution was very slightly yellow at the end of the irradiation period. Evaporation of the solvent under reduced pressure gave a light yellow oil which was dissolved in benzene–petroleum ether (5:1) and chromatographed on a silica gel (30 g) column. Elution with benzene–petroleum ether (5:1) gave 0.009 g of starting ketone which was identified by comparison of its ir spectrum with that of an authentic sample. Further elution with chloroform gave 0.109 g of a white solid, mp 116–117.5°, which was identified as the hydrol derivative **5g**: ir (KBr) 3500 (OH), 1040 cm^{-1}; nmr ($CDCl_3$) δ 7.21 (s, 1, Ar), 6.88 (AB q, J = 9 Hz, 4, Ar), 6.32 (s, 1, CHOH), 3.75 (s, 3, OCH_3), 2.22 (s, 6, CH_3), 2.12 (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.94; H, 8.22. Found: C, 79.84; H, 8.15.

Further elution with chloroform gave 0.343 g of a white solid, mp 113–114°, which was determined to be the benzocyclobutanol derivative **2g**: ir (KBr) 3500 (OH), 1170, 1040 cm^{-1} nmr ($CDCl_3$) δ 7.11 (AB q, J = 9 Hz, 4, Ar), 6.94 (s, 1, Ar), 3.77 (s, 3, OCH_3), 3.35 (s, 2, CH_2), 2.22 (s, 3, CH_3), 2.15 (s, 3, CH_3), 2.04 (s, 3, CH_3).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.55; H, 7.53. Found: C, 80.55; H, 7.73.

Photolysis of 1d in 2 *M* 2-Propanol in Benzene.—A solution of 0.500 g of 1d in 200 ml of 2 *M* 2-propanol in benzene was irradiated for 18.5 hr. The solution was slightly yellow at the conclusion of the photolysis. Work-up of the reaction mixture as usual gave a light yellow oil which was dissolved in a small amount of benzene–petroleum ether (1:5) and chromatographed on a 30 g column of silica gel. Elution with benzene afforded 0.290 g of unchanged ketone. Elution with chloroform gave 0.149 g of a white solid, mp 101–102°, which was identified as the hydrol derivative **5d**: ir (KBr) at 3525 (OH), 1100, 1010 cm^{-1}; nmr ($CDCl_3$) δ 7.18 (s, 5, Ar), 6.34 (s, 1, CHOH), 3.60 (s, 3, OCH_3), 2.56 (s, 1, OH), 2.15 (s, 6, CH_3), 2.10 (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.94; H, 8.22. Found: C, 79.98; H, 8.11.

Further elution with chloroform–ether (9:1) gave 0.009 g of a clear oil. An ir spectrum (neat) of this material showed major absorptions at 3400 (OH), 1450, 1110, 775, and 715 cm^{-1}. Owing to the extremely low yield of this product, further analysis was not undertaken, although it appears, solely on the basis of the ir spectrum, that this substance is most likely the benzocyclobutanol derivative **2d**.

Elution with chloroform–ether (5:1) afforded 0.019 g of a clear oil. Tlc showed that this was a single product: ir (neat) 3425 (OH), 1660, 1330, 1230, 1110, 770 cm^{-1}; nmr ($CDCl_3$) δ 7.75 (AB q, J = 8 Hz, 4, Ar), 3.72 (s, 3, OCH_3), 2.20 (s, 6, CH_3), 2.13 (s, 6, CH_3), 1.60 (s, 6, CH_3). This information indicates that this compound has structure **3d**.

Registry No.—**1a**, 4885-14-7; **1b**, 40910-02-9; **1c**, 40910-03-0; **1d**, 40910-04-1; **1e**, 40910-05-2; **1f**, 40910-06-3; **1g**, 40910-07-4; **2a**, 40910-08-5; **2c**, 19020-69-0; **2d**, 40910-10-9; **2f**, 40910-11-0; **2g**, 40910-12-1; **3a**, 40910-13-2; **3d**, 40910-14-3; **4a**, 40910-15-4; **5a**, 40940-77-0; **5c**, 40910-16-5; **5d**, 40910-17-6; **5g**, 40910-18-7.

Reagents for Photoaffinity Labeling of Estrogen Binding Proteins. Synthesis of Some Azide and Diazo Derivatives of Estradiol, Estrone, and Hexestrol

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Fourteen estrogen derivatives bearing a photosensitive functional group have been synthesized for use as photoaffinity labels for estrogen binding proteins: diazoacetate derivatives of 17β-estradiol and estrone, 16-diazoestrone, and 3-diazo-2-ketopropyl ether and ortho azide derivatives of estradiol, estrone, and hexestrol. All of these compounds are reasonably stable and easily purifiable. Attempts to introduce a diazo function at B-ring positions 6 and 7 of the estrogens have been unsuccessful: the 6-diazo derivative is thermally labile and the 6-keto-7-diazo derivative fails to form. This is presumably due to the hindrance at position 7, as the corresponding position (2) in 7-hydroxy-1-tetralone is easily functionalized.

There are a number of interesting interactions between hormonal steroids and binding sites on proteins. Enzymes involved in steroidogenesis and steroid metabolism display affinity for their steroid substrates,[1] and the activity of certain other enzymes is affected in an allosteric fashion by steroid ligands.[2] Circulatory transport of steroids is assisted by binding to serum albumin and to several globulins.[3] Perhaps the most interesting interactions involve the binding shown by certain proteins present in steroid hormone target tissues. This binding is stereospecific and of very high affinity, and it has been demonstrated for estrogens,[4] androgens,[5] progestins,[4] and corticosteroids[6] in a number of different target tissues. In some cases, early biochemical events resulting from hormone administration have been correlated with steroid binding and subcellular movement of the steroid–protein complex.

The characterization of these target tissue binding proteins, often termed "receptors," has been a challenging task. Their low concentrations and often their thermal lability make purification difficult, and the fact that they are labeled only by virtue of their ability to complex a labeled steroid in a noncovalent fashion places severe limits on the types of investigations that can be carried out. In most studies, the availability of a radiolabel attached in a covalent fashion to these proteins would be of great advantage.

We have undertaken a study of the covalent labeling of the estrogen binding protein found in immature rat uterus, using the photoaffinity labeling technique. In this report we describe the synthesis of several derivatives of estrone (**5**), estradiol (**1**), and hexestrol (**44**)[7] that bear photosensitive diazocarbonyl or azide groups and have the potential to act as photoaffinity labeling reagents. The binding affinity of these compounds for the uterine estrogen binding protein has been determined by competitive assay and will be reported elsewhere.[8] Studies on their effectiveness as selective labeling reagents for this protein are currently in progress.

Results and Discussion

A number of reports have described the synthesis of electrophilic steroid derivatives for affinity labeling of steroid binding sites.[9-12] Some labeling studies involving pure enzymes have been successful, but those investigations directed at the high-affinity binding proteins from target tissues have given unsatisfactory results.[13]

Considerations of the heterogeneity of readily available preparations of the rat uterine estrogen binding protein led us to choose the technique of photoaffinity labeling over the conventional affinity labeling based on alkylation or acylation.[14,15] Although the technique of photoaffinity labeling[15b] was introduced more than a decade ago, it has not been used to study steroid binding sites, and other applications have been rather sporadic.[16] Most investigations have utilized the diazocarbonyl function, originally introduced by Westheimer,[17] as the group through which covalent attachment is to take place under photolytic conditions.

(1) (a) U. Westphal, "Steroid Protein Interactions," Springer-Verlag, West Berlin, 1971, Chapter 16; (b) R. B. Clayton, "Methods in Enzymology," Vol. 15, Academic Press, New York, N. Y., 1969, Section 5.

(2) A. W. Douville and J. C. Warren, *Biochemistry*, **7**, 4052 (1968), and references cited therein.

(3) (a) Reference 1a, Chapters 6–8, 10–13; (b) E. Milgrom, P. Allouch, M. Atger, and E-E. Baulieu, *J. Biol. Chem.*, **248**, 1106 (1973); (c) P. L. Corvol, A. Chrambach, D. Rodbard, and C. W. Bardin, *ibid.*, **246**, 3435 (1971).

(4) E. V. Jensen and E. R. DeSombre, *Annu. Rev. Biochem.*, **41**, 203 (1972).

(5) S. Liao and S. Fang, *Vitamins Hormones*, **27**, 17 (1969).

(6) M. Beato and P. Fiegelson, *J. Biol. Chem.*, **247**, 7890 (1972).

(7) Common names used in this paper are estradiol = 1,3,5(10)-estratriene-3,17β-diol; estrone = 3-hydroxy-1,3,5(10)-estratriene-17-one; hexestrol = *meso*-3,4-bis(4′-hydroxyphenyl)hexane.

(8) J. A. Katzenellenbogen, H. J. Johnson, Jr., and H. N. Myers, *Biochemistry*, in press.

(9) C. Liarakos and M. May, *Endocrinology*, **84**, 1247 (1969).

(10) (a) A. J. Solo and J. O. Gardner, *Steroids*, **11**, 37 (1968); (b) A. J. Solo and J. O. Gardner, *J. Med. Chem.*, **14**, 222 (1971).

(11) (a) C-C. Chin and J. C. Warren, *J. Biol. Chem.*, **243**, 5056 (1968); (b) T. G. Muldoon and J. C. Warren, *ibid.*, **244**, 5430 (1969); (c) C-C. Chin and J. C. Warren, *Biochemistry*, **9**, 1917 (1970); (d) M. Ganguly and J. C. Warren, *J. Biol. Chem.*, **246**, 3646 (1971); (e) F. Sweet, F. Arias, and J. C. Warren, *ibid.*, **247**, 3424 (1972); (f) C-C. Chin and J. C. Warren, *Biochemistry*, **11**, 2720 (1972).

(12) J. Kallos and K. P. Shaw, *Proc. Nat. Acad. Sci. U. S.*, **68**, 916 (1971).

(13) 4-Mercuriestradiol appears to react with a sulfhydryl group in the binding site of the estradiol binding protein from rat uterus (ref 11b). However, the mercury–sulfur link is quite labile, so that detailed characterization of this protein derivative is difficult.

(14) (a) H. Kiefer, J. Lindstrom, E. S. Lennox, and S. J. Singer, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1688 (1970); (b) a detailed discussion of this point is given in ref 8.

(15) (a) For recent reviews affinity labeling, see S. J. Singer, *Advan. Protein Chem.*, **22**, 1 (1967), and E. Shaw, *Physiol. Rev.*, **50**, 244 (1970); (b) for a recent review of photoaffinity labeling, see J. R. Knowles, *Accounts Chem. Res.*, **5**, 155 (1972).

(16) Recent examples include (a) D. T. Browne, S. S. Hixson, and F. H. Westheimer, *J. Biol. Chem.*, **246**, 4477 (1971); (b) C. Hexter and F. H. Westheimer, *ibid.*, **246**, 3928, 3934 (1971); (c) C. A. Converse and F. F. Richards, *Biochemistry*, **8**, 4431 (1969); (d) D. J. Brunswick and B. S. Cooperman, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1801 (1971); (e) J. Frank and R. Schwyzer, *Experientia*, **26**, 1207 (1970); (f) P. G. Waser, A. Hofmann, and W. Hopff, *ibid.*, **26**, 1342 (1970).

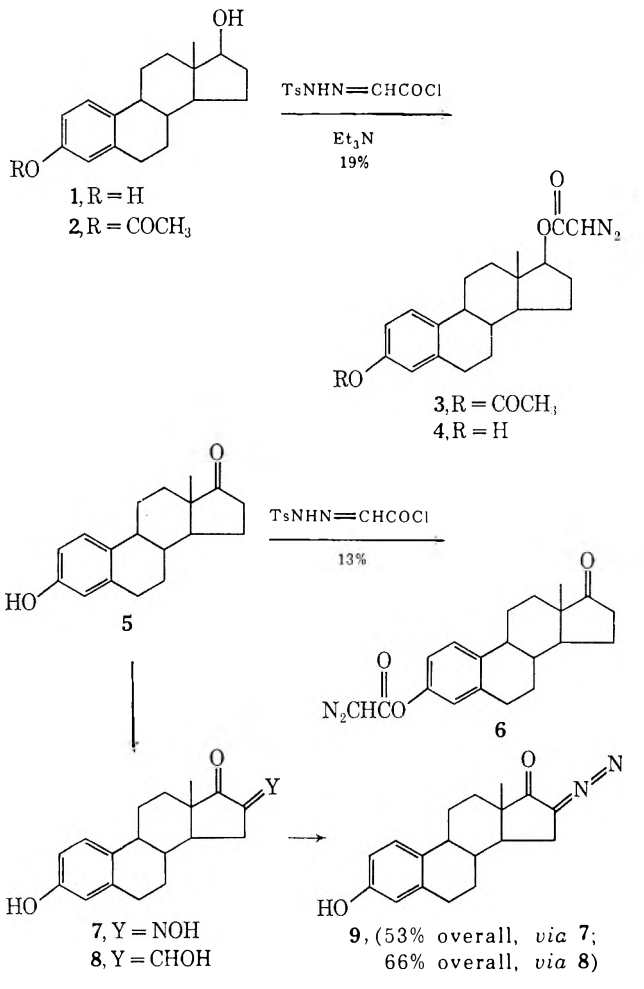
(17) A. Singh, E. R. Thornton, and F. H. Westheimer, *J. Biol. Chem.*, **237**, PC 3006 (1962).

More recently, the use of aryl azides has been described.[14a,15b,18]

Ideally, the inclusion of a photosensitive attaching function into the architecture of the steroidal ligand should result in a minimum disruption in the binding between steroid and protein. However, because so little is known about the nature of the binding site of the rat uterine protein we are interested in, we have chosen to restrict our initial efforts to relatively simple estrogen derivatives. The compounds we have prepared are functionalized at the chemically most accessible positions, the two hydroxyl groups, the positions ortho to the phenolic hydroxyl, and the positions α to the 17-keto group in estrone, and they bear one of the two known photoattaching functions. We have also investigated the synthesis of certain B-ring derivatives.

Diazo Compounds.—The preparation of estrone 3-diazoacetate (**6**) and estradiol 17-diazoacetate (**4**) is outlined in Scheme I. Treatment of estradiol (**1**) with

SCHEME I



1 equiv of the acid chloride of glyoxylic acid tosylhydrazone[19] allows the isolation of the 17-diazoacetate derivative **4** in 19% yield after purification.[20] None of the 3-diazoacetate or the 3,17-bis diazoacetate of estradiol was found. The apparent selectivity of this reagent for the 17 hydroxyl, rather than the phenolic hydroxyl, is curious, as most reported acylations occur preferentially at position 3.[21]

In order to establish the position of acylation rigorously, the 17-diazoacetate **4** was prepared *via* the well-characterized estradiol 3-acetate **2**.[22] The product obtained after potassium carbonate–methanol hydrolysis of the 3-acetate–17-diazoacetate **3** was identical in all respects with the product prepared by direct acylation of estradiol. The nmr spectrum of **4** (pyridine-d_5) further confirms the position of the diazoacetate: the 17α proton in **4** resonates as a triplet at δ 4.85, a position characteristic of 17β-acetates; the corresponding proton in 17β-estradiol resonates at δ 4.00.

Estrone 3-diazoacetate (**6**) was prepared directly from estrone by treatment with the tosylhydrazone of glyoxylic acid chloride. The diazo esters **4** and **6** are highly crystalline and are readily recrystallized from benzene or methanol. They are quite light sensitive since exposure to laboratory illumination at 25° results in some decomposition within 24 hr.

The diazo ketone D-ring derivative, 16-diazoestrone **9**, was prepared by two different routes (Scheme I). Nitrosation of estrone[23] gave 16-oximoestrone **7**, which, upon chloramine oxidation,[24] gave **9** in 53% overall yield from estrone. Alternatively 16-hydroxymethyleneestrone,[25] obtained by condensation of estrone with ethyl formate, was treated with tosyl azide and triethylamine[26] to give **9** in 66% yield overall from **5**. The diazo ketone **9** is a yellow, highly crystalline solid that is quite thermally stable. It can be repeatedly recrystallized from acetone and, in the crystalline state, can be stored for several months at room temperature, under normal laboratory illumination, without noticeable degradation.

In order to avoid problems that might arise from having a hydrolyzable ester function between the site of attachment and the position of radiolabel (generally, steroid positions 6 and 7), as in the diazoacetate derivatives **4** and **6**, three ether-linked diazo ketone derivatives (**12**, **17**, and **23**) were synthesized (Scheme II).

Treatment of estrone with excess ethyl bromoacetate in ethanolic sodium ethoxide gave the oxyacetic ester **10** in high yield. Hydrolysis with potassium hydroxide in ethanol was quantitative and gave the corresponding acid which was converted into the acid chloride with thionyl chloride and treated with excess diazomethane to give the diazo ketone **12** in 79% yield. This compound is a yellow crystalline solid that recrystallizes well from acetone and is quite thermally stable. Recrystallization from ethanol, however, causes some decomposition.

(18) (a) G. W. J. Fleet, J. R. Knowles, and R. R. Porter, *Biochem. J.*, **128**, 499 (1972); (b) R. Schwyzer and M. Coviezel, *Helv. Chim. Acta*, **54**, 1395 (1971); (c) M. B. Perry and L. L. W. Heung, *Can. J. Biochem.*, **50**, 510 (1972).

(19) (a) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 53 (1968); (b) H. O. House, F. J. Santer, and C. J. Blankley, *Org. Syn.*, **49**, 22 (1969).

(20) Although higher yields of diazoacetates have been obtained using this reagent in aliphatic systems (ref 19), alteration in reaction conditions and reagent stoichiometry failed to increase the yield of **4**.

(21) G. E. Abraham and P. K. Grover in "Principles of Competitive Protein Binding Assays," D. Odell and W. H. Daughaday, Ed., Lippincott, Philadelphia, Pa., 1971, p 140. We have also found that treatment of estradiol with 2 equiv of bromoacetyl bromide in tetrahydrofuran at 0° with no base present gives the 17β-bromoacetate (crude yield 95%; twice recrystallized, 66%).

(22) O. O. Orazi and R. A. Corral, *J. Amer. Chem. Soc.*, **91**, 2162 (1969).

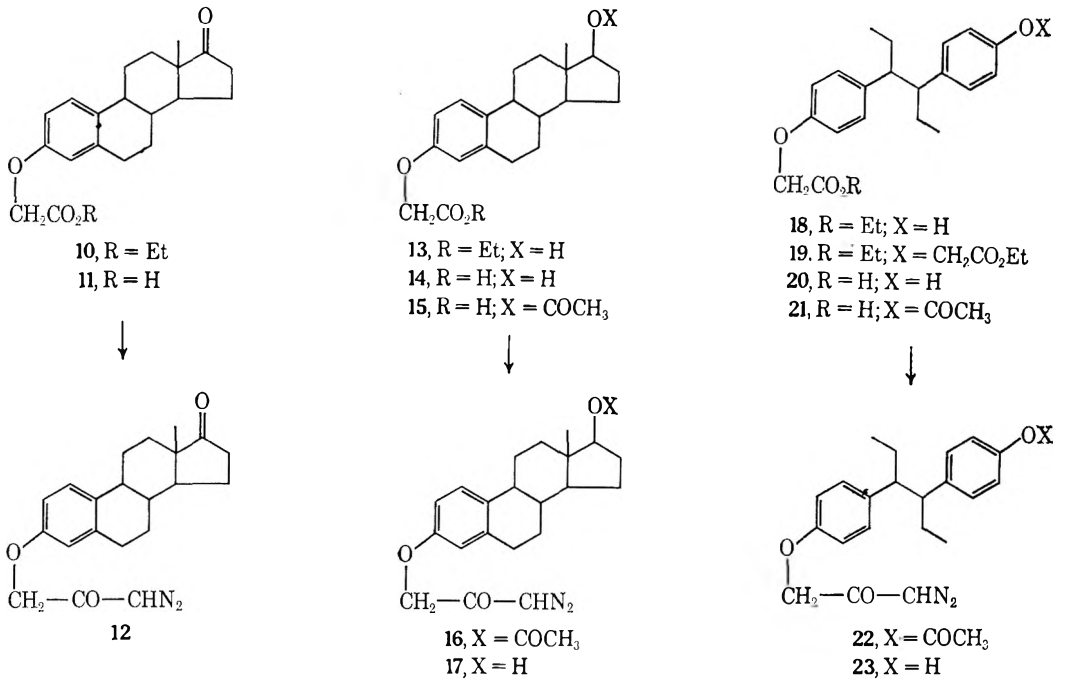
(23) M. N. Huffman and H. H. Darby, *J. Amer. Chem. Soc.*, **66**, 150 (1944).

(24) M. P. Cava and B. R. Vogt, *J. Org. Chem.*, **30**, 3775 (1965).

(25) R. O. Clinton, *Chem. Abstr.*, **70**, P4412*d* (1969).

(26) M. Regitz and J. Ruter, *Chem. Ber.*, **101**, 1263 (1968).

SCHEME II



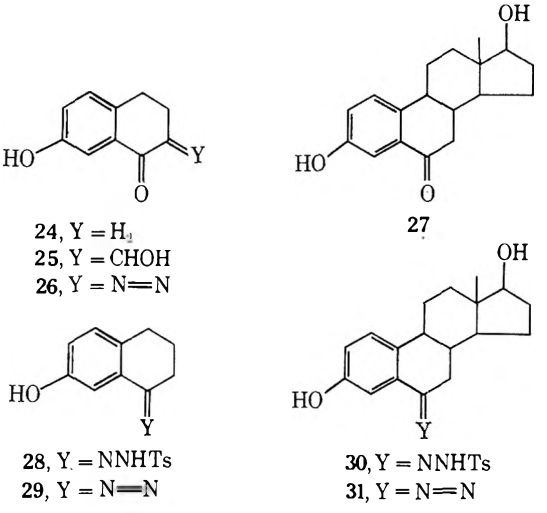
Synthesis of the corresponding diazo ketones in the estradiol and hexestrol series required selective reaction and protection of the two hydroxyl functions. Reaction of estradiol with excess ethyl bromoacetate was highly selective; only traces of the bisalkylated material could be detected by tlc after complete consumption of the starting estradiol. However, with hexestrol **44**, the equal reactivity of the two hydroxyl functions demanded more selective conditions. Reaction with a limited excess of ethyl bromoacetate and base for short time periods allowed the isolation of the monoalkylated hexestrol **18** in 44% yield, along with starting material (19%) and bis ester **19** (19%). The monoesters in both series were carried through an analogous series of steps: hydrolysis with potassium hydroxide in ethanol, protection of the free hydroxyl by acetylation with acetic anhydride–pyridine, conversion into the acid chloride with thionyl chloride, and reaction with excess diazomethane to give the protected diazo ketones **16** and **22**, respectively. With potassium carbonate, deacetylation of the hexestrol derivative was rapid, but the more hindered estradiol derivative required longer hydrolysis time. Hydrolysis with potassium hydroxide was less satisfactory.

The diazo ketones **17** and **23** are both yellow solids that can be readily recrystallized. They are somewhat less stable than the estrone derivative (**12**) but can be stored without decomposition at −20°.

All the diazo derivatives we have prepared show prominent molecular ions in their 70-eV mass spectra, a characteristic diazo stretching band in the infrared (2250–2050 cm^{-1}), and strong ultraviolet absorption at 250–280 nm (with a weak band or tail in the region 350–400 nm).

Several attempts were made to introduce photosensitive functional groups into positions 6 and 7 of the steroid (Scheme III). Due to the tedious and inefficient procedure involved in the preparation of 6-ketoestradiol (**27**),[27,28] 7-hydroxytetralone (**24**) was used as a model system. As done previously in the preparation of **9** (Scheme I), the diazo ketone **26** could be conveniently prepared *via* the hydroxymethylene derivative **25**. Nitrosation of this system also proceeded smoothly. However, despite numerous attempts, both nitrosation and condensation with ethyl formate failed completely in the steroid system (**27**). In each case, starting material could be recovered from the reaction mixtures in high yield. Construction of a space filling model attests to the greater steric hindrance of position 7 in **27** than the corresponding position in the tetralone system (**24**).

SCHEME III



The possibility of introducing a diazo function directly into position 6 of the steroid was also investigated (Scheme III). The tosylhydrazone derivatives in both the steroid (**30**) and the model tetralin system (**28**) were decomposed with sodium methoxide in pyridine.[29] Direct assay of the reaction mixture during

(27) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940).

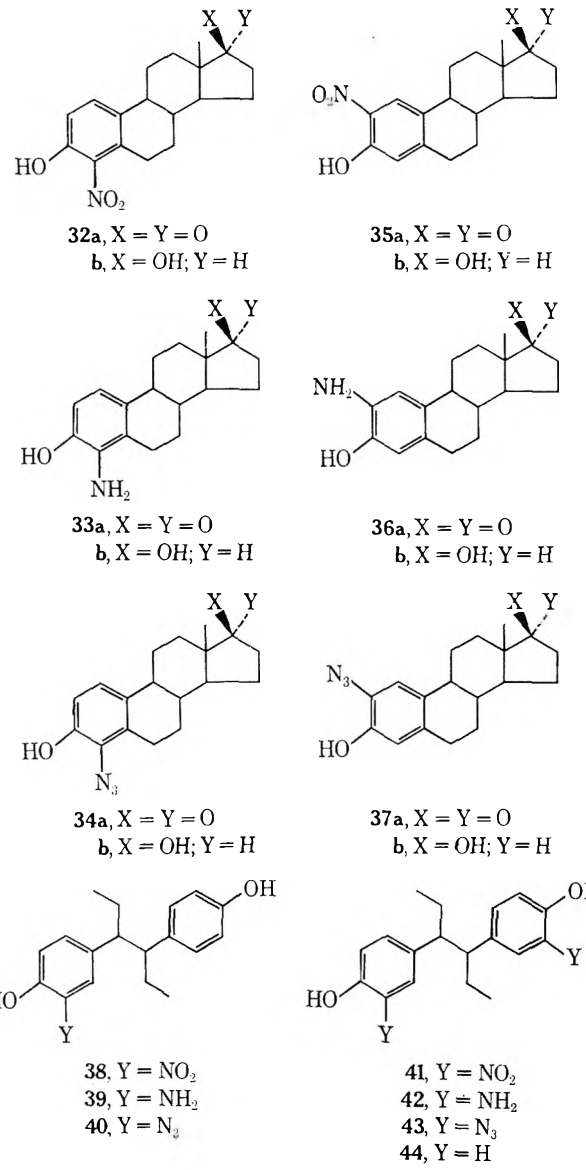
(28) P. D. G. Dean, D. Exley, and M. W. Johnson, *Steroids*, **18**, 593 (1971).

(29) D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963).

the initial phase of the reaction showed an ir band at 2240 cm^{-1}, characteristic of the desired diazo derivatives **29** and **31**. However, in both cases these derivatives proved to be thermally unstable; the deep red color of the reaction mixture (also characteristic of aryl-substituted diazomethanes[29,30]) soon faded, and no diazo products could be isolated.

Azides.—The azide derivatives **34a** and **b**, **37a** and **b**, **40**, and **43** were prepared by standard techniques (Scheme IV). Nitration of estrone **5** with 1 equiv of

SCHEME IV



nitric acid in glacial acetic acid gave a 1:1 mixture of the 2- and 4-nitroestrones **35a** and **32a**.[11c,31] These isomers could be separated readily by column chromatography and were isolated in 39 and 32% yield, respectively. Reduction with hydrogen over a palladium catalyst,[11c] or more conveniently using sodium dithionite,[32] furnished the amino compounds **33a** and **36a** in greater than 80% yield. As direct nitration of estradiol produced a complex mixture of products from which the desired nitroestradiols **32b** and **35b** could be obtained only with great difficulty, entry into the estradiol series was achieved through the nitro estrones. Sodium borohydride reduced the ketone in preference to the aryl nitro group, permitting the conversion of **32a** into **32b** and **35a** into **35b**. Alternatively, reduction of the amino estrones **33a** and **36a** with lithium aluminum hydride gave the amino estradiols **33b** and **36b** directly. The β orientation of the 17-hydroxyl in **32b** and **35b** was confirmed by 220-MHz nmr (in DMSO-d_6). Both compounds show a sharp singlet for the 18-methyl group at δ 0.68. The 18-methyl in 17β-estradiol also resonates at this position, but in the 17α epimer it is shifted to δ 0.62.[33,34]

Final transformation of the four amino estrogens **33a** and **33b** and **36a** and **36b** to the corresponding azides was achieved by diazotization with sodium nitrite in hydrochloric acid, followed by treatment with sodium azide.[35]

The same sequence of reactions was used to convert hexestrol into the 3-azide and the 3,3′-bisazide derivatives **40** and **43**. The initial nitration products **38** and **41** could be separated by careful column chromatography, and the identity of **41** as the symmetrical dinitration product was confirmed by its nmr and mass spectra.

All of the azides prepared are tan solids with ultraviolet absorption bands near 250 and 300 nm. They exhibit a characteristic azide stretch in the infrared (2120 cm^{-1}) and have weak, but detectable, molecular ions in their 70-eV mass spectra. Upon standing at room temperature, under normal laboratory light, all the azides show some decomposition; however, they may be stored for long periods of time at −20° without decomposition.

Conclusions

The photoaffinity labeling reagents that we have prepared should be widely applicable to the study of estrogen binding sites. The effect that structural modification of the steroidal ligand (resulting from embodiment of the photoattaching function) has on the binding affinity and the selectivity with which these compounds are capable of labeling binding sites are questions that must be answered individually in each system studied.[8]

Our particular interest is in labeling the estrogen binding protein of rat uterus. As pure preparations of this protein are not readily available, high binding affinity is crucial for high labeling selectivity. We have determined the binding affinity of these compounds for this protein by competitive assay. Certain ones display high affinity for the binding protein, and preliminary investigations indicate that they may indeed be capable of labeling the estrogen binding site.[8]

Experimental Section

The following chemicals were obtained from the sources indicated: estrone and 17β-estradiol (G. D. Searle; Steraloids) and

(30) B. Eistert, M. Regitz, G. Heck, and H. Schwall in "Houben-Weyl," Vol X/4, 4th ed., E. Muller, Ed., G. Thieme Verlag, Stuttgart, 1968, p 468.
(31) A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959).
(32) S. Kraychy, *J. Amer. Chem. Soc.*, **81**, 1702 (1959).
(33) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 242.
(34) In most of the nmr spectra run in DMSO-d_6, the resonance due to the 17α hydrogen, which generally falls at δ 3.7 (6, J = 7 Hz), was obscured by broad signals due to water absorbed by the samples.
(35) E. Noetling and O. Michael, *Chem. Ber.*, **26**, 86 (1893).

hexestrol (Mann). Ethanol-free chloroform was obtained by passing chloroform reagent over alumina. Diazomethane was freshly prepared as alcohol-free ethereal solution from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich) using preparation II as given. Spectroscopic data were obtained on the instruments listed: ir (Perkin-Elmer 237), nmr (Varian A-60, HA-100, or HR 220), mass spectra (Varian-MAT CH-5 and 731), uv (Cary-White 15), and molecular rotation (Bendix NPL polarimeter). Microanalysis was performed by the microanalytical service of the University of Illinois.

A standard procedure for product isolation was used in all reactions: exhaustive extraction with a solvent, drying over an anhydrous salt, filtration, and evaporation of solvent under reduced pressure on a rotary evaporator. In each procedure, the extraction solvent and drying agent used are given in parentheses.

Analytical thin layer chromatography (tlc) was performed either on Eastman Chromatosheets 6060 or Brinkmann F-254 glass-backed plates. The following solvent systems were often used: system A, chloroform–ether (97:3); system B, benzene–ethyl acetate–chloroform (5:1:5); system C, benzene–ethyl acetate–acetic acid (90:10:0.5); system D, ether–hexane (1:1). The R_f values for estrone, estradiol, and hexestrol on Eastman Chromatosheets in these system follow (respectively): A, 0.45, 0.33, 0.25; B, 0.35, 0.22, 0.23; C, 0.43, 0.32, 0.41; D, 0.14, 0.10, 0.23.

Estradiol 3-Acetate (2).—A solution of 400 mg (1.47 mmol) of estradiol (1) and 357 mg (1.9 mmol) of 3-acetyl-1,5,5-trimethylhydantoin[22] in 8 ml of THF was refluxed under nitrogen for 31 hr. After the solution was allowed to cool, the solvent was removed under reduced pressure, and water was added. Product isolation (EtOAc; $MgSO_4$) gave 360 mg of a pale yellow oil which was purified by preparative tlc (R_f 0.4, system A). Recrystallization from ethyl acetate–hexane furnished 280 mg (60%) of pure white product (2), mp 139–140° (lit.[22] mp 136–139°).

Estradiol 3-Acetate 17-Diazoacetate (3).—A solution of 246 mg (0.95 mmol) of glyoxylic acid chloride *p*-toluenesulfonylhydrazone and 100 mg (0.316 mmol) of estradiol 3-acetate (2) in 10 ml of ethyl acetate was treated dropwise at 0° with 95 mg (0.95 mmol) of triethylamine in 1 ml of ethyl acetate. An additional 190 mg of triethylamine was added, and the reaction mixture was stirred at 0° for another hour. After the solution was filtered to separate triethylamine hydrochloride, dilute sodium bicarbonate was added. Product isolation (EtOAc; $MgSO_4$) gave a pale yellow liquid which after preparative tlc (R_f 0.70, system A) yielded 40 mg (32%) of product **3** as an oil that failed to crystallize: ir ($CHCl_3$) 2120 (C=N=N), 1750 (C=O, acetyl), and 1680 cm^{-1} (C=O, diazo ester); nmr ($CDCl_3$) δ 0.8 (s, 3 H), 2.4 (s, 3 H), 4.7 (s, 1 H), 6.8–7.7 (m, 3 H).

Anal. Calcd for $C_{22}H_{26}N_2O_4$: mol wt, 382.1891. Found: mol wt (high-resolution mass spectrum), 382.1893.

Estradiol 17-Diazoacetate (4) [from Estradiol (1)].—A solution of 384 mg (1.47 mmol) of glyoxylic acid chloride *p*-toluenesulfonylhydrazone and 405 mg (1.48 mmol) of estradiol (1) in 10 ml of ethyl acetate was treated dropwise at 0° with 154 mg (1.52 mmol) of redistilled triethylamine in 2 ml of ethyl acetate. After 0.5 hr, an additional 225 mg (2.22 mmol) of triethylamine was added, and the resulting solution was stirred at room temperature for 1 hr. The reaction mixture was filtered to separate 180 mg of triethylamine hydrochloride, and the solvent was removed under reduced pressure. The crude diazoacetate was purified by preparative tlc (R_f 0.63, system A) to yield 95 mg (19%) of a yellow solid. Recrystallization from methanol gave pure estradiol 17-diazoacetate (4): mp 172–182° dec; ir (KBr) 2120 (C=N=N) and 1655 cm^{-1} (C=O, diazo ester); uv (EtOH) λ_{max} 246 (ϵ 1600), 283 (23,400); nmr ($CDCl_3$) δ 0.78 (s, 3 H, $-CH_3$), 1.0–3.1 (m, 15 H), 4.75 (t, 1 H), 4.80 (s, 1 H, N=CH), 6.5–7.2 (m, 3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 340 (M^+, 89) 312 (1), 270 (3), 239 (2), 211 (4), 159 (100).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.29; H, 7.13; N, 8.21.

Estradiol 17-Diazoacetate (4) (from 3).—A solution of 40 mg (0.105 mmol) of estradiol 3-acetate 17-diazoacetate (3) in 1 ml of methanol was mixed with 2 ml of methanolic potassium carbonate and stirred at room temperature. After 24 hr, water was added, and the product was isolated (ether; $MgSO_4$). The crude product was purified by preparative tlc (R_f 0.63, system A) to yield 20 mg (57%) of pure ester (4), spectroscopically and chromatographically identical with the ester 4 prepared directly from estradiol.

Estrone 3-Diazoacetate (6).—Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (400 mg, 1.54 mmol) in 5 ml of methylene chloride was treated dropwise at 0° with a solution of estrone (5) (400 mg, 1.48 mmol) and redistilled triethylamine (150 mg, 1.48 mmol) in 4 ml of methylene chloride–THF (1:1). After 0.5 hr, an additional 225 mg (2.22 mmol) of triethylamine was added, and the resulting solution was allowed to warm to room temperature and to stir for an additional hour. The reaction mixture was filtered to separate 100 mg of triethylamine hydrochloride, and the solvent was removed at 25° under reduced pressure. The crude product was purified by preparative tlc on alumina (chloroform, 2 developments) to yield 69 mg (13%) of a pale yellow solid. Recrystallization from benzene–petroleum ether gave estrone diazoacetate (6) as pale yellow prisms: mp 159–160°; uv (EtOH) λ_{max} 215 nm (ϵ 9200), 250 (17,350); ir (KBr) 2125 (C=N=N), 1637 (C=O, cyclopentyl), 1655 cm^{-1} (C=O, diazo ester); nmr ($CDCl_3$) δ 0.9 (s, 3 H, $-CH_3$), 1–3.0 (m, 15 H), 4.7 (s, 1 H, N=CH—), 6.8–7.5 (m, 3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 338 (M^+, 12), 270 (100), 213 (7), 186 (6), 160 (7), 159 (6), 146 (14), 115 (8), 91 (7), 69 (9), 55 (6), 28 (25).

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.80; H, 6.48; N, 8.35.

16-Oximoestrone (7).[23]—Estrone (22.2 mmol, 6.06 g) was stirred under nitrogen in 50 ml of freshly distilled *tert*-butyl alcohol for 10 min (dissolution incomplete). Potassium *tert*-butoxide (110 mmol, 12.0 g) was added, and stirring was continued for 30 min (dissolution complete). *n*-Butyl nitrite (35 mmol, 5 ml) was added *via* syringe, and the solution turned deep red, and then orange within a few minutes. A second portion of *n*-butyl nitrite (35 mmol, 5.0 ml) was added after 8 hr, and stirring was continued an additional 16 hr. The reaction mixture was quenched in 100 ml of ice and acidified with glacial acetic acid. The precipitate that formed was redissolved in THF–EtOAc (1:1), and product isolation ($MgSO_4$) gave a yellow solid that was triturated with three small portions of cold acetone to give 5.71 g (85%) of 16-oximo estrone as a off-white powder. This material was homogeneous by tlc (R_f 0.17, system B). Further purification by recrystallization from THF–hexane afforded white crystals: mp 238–239°; uv (EtOH) λ_{max} 280 nm (ϵ 2880), 232 (13,900); $[\alpha]^{24}D$ +87° (*c* 0.4416, THF); ir 3600–3000 (broad, OH), 1750 (C=O), 1650, 1510, 950 cm^{-1}; nmr (DMSO-d_6) δ 0.88 (s, 3 H), 6.3–7.1 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 299 (M^+, 99), 254 (100), 213 (46), 159 (55), 146 (21), 145 (22), 133 (56), 62 (19).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.10; H, 7.06; N, 4.86.

16-Hydroxymethylenestrone (8).[25]—Estrone (5) (5 g, 18.5 mmol) was dissolved in 25 ml of THF with warming on the steam bath, and 125 ml of dry benzene was added. Sodium hydride (13.1 g of a 57% dispersion in mineral oil, 315 mmol) was washed with three portions of dry benzene to remove the mineral oil and transferred as a slurry to the steroid solution with vigorous stirring. Five or six drops of absolute ethanol were added, and then the flask was placed under a nitrogen atmosphere. After stirring for 25 min, ethyl formate (20.2 g, 22.0 ml, 272 mmol) was added dropwise over a 30-min period. The reaction mixture was stirred vigorously at 25°, and the progress of the reaction was monitored periodically by tlc of an acidified aliquot. After 24 hr, the reaction vessel was cooled in ice, and 2 *N* HCl added cautiously (frothing) until the mixture was acidic. Product isolation (EtOAc, $MgSO_4$) gave 6.5 g of a solid. Tlc analysis (R_f 0.27, system B) showed a small amount of contaminating estrone that could be removed by chromatography on silica gel, but the product became discolored by this procedure. Recrystallization from acetone was inefficient, but gave chromatographically homogeneous material, mp 229–231° (lit.[25] 229–232°). As the next product (16-diazo estrone 9) crystallized readily, the crude product was used without further purification: $[\alpha]^{24}D$ +144° (*c* 0.357, THF); ir (KBr) 3400 (broad, OH), 1720 (C=O), 1640 cm^{-1}; nmr (DMSO-d_6) δ 0.82 (s, 3 H), 2.73 (br t), 6.4–7.3 (3 H, aromatic), 7.43 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 298 (M^+, 100), 214 (17), 213 (59), 160 (24), 159 (38), 146 (33), 133 (26).

16-Diazoestrone (9) [(from 16-Hydroxymethyleneestrone (8)].—The crude 16-hydroxymethylenestrone (8) (5.9 g, 20.4 mmol) was dissolved in 50 ml of THF and 400 ml of methylene chloride and 12 ml (71.4 mmol) of triethylamine were added. After

flushing the flask with nitrogen, 10.5 ml (52.4 mmol) of tosyl azide dissolved in 30 ml of methylene chloride was added over a 10-min period. After stirring at 25° for 2–3 hr, product isolation (THF–EtOAc; $MgSO_4$) gave the yellow, crystalline solid which was freed from excess tosyl azide by trituration with benzene and ether. The yellow, crystalline product (3.9 g, 66%) was homogeneous by tlc analysis (R_f 0.44, system B). Recrystallization of 500 mg from acetone gave 386 mg of analytically pure material: mp 215–217° dec; uv (EtOH) λ_{max} 251 nm (ϵ 3200), 282 (1130), 288 (1140), 305 (sh), 381 (ϵ 4); $[\alpha]^{24}D$ −38° (*c* 0.5136, THF); ir (KBr) 3470 (br), 2040 (s), 1665, 1640, 1600, 1575, 1495, 1460, 1445, 1320, 1250 cm^{-1}; nmr (DMSO-d_6) δ 0.95 (s, 3 H), 2.75 (m), 6.3–7.1 (3 H, aromatic), 8.92 (s, 1 H, OH); mass spectrum (70 eV) *m/e* (rel intensity) 296 (M^+, 100), 211 (22), 172 (25), 160 (23), 159 (56), 158 (23), 157 (31), 146 (22), 145 (27), 133 (40), 79 (21).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.87; H, 6.92; N, 9.25.

16-Diazoestrone (9) [(from 16-Oximoestrone (7)].—16-Oximoestrone (7) (135 mg, 0.45 mmol) was dissolved in 4 ml of THF and 0.5 ml of a 5 *N* sodium hydroxide solution, and 0.8 ml of a 28% ammonium hydroxide solution was added. A solution of sodium hypochlorite (1 ml, 5.25%, 1 mmol; Clorox) was added, and the reaction mixture was allowed to stir under nitrogen for 6 hr at 25°. Product isolation (EtOAc; $MgSO_4$) gave 100 mg of crude product. Preparative tlc (chloroform–ethanol 9:1, 2 developments; 8:2, 2 developments) furnished 83 mg (62%) of the yellow, crystalline product 9 that was identical in all respects with the material prepared by the preceding method.

3-*O*-Carbethoxymethylestrone (10).—Estrone (2 g, 7.4 mmol) was dissolved in 35 ml of ethanol and 10 ml of THF. Sodium ethoxide (11 mmol; 5.5 ml of 2 *M* solution in ethanol) and 3.7 g (3 ml, 22.2 mmol) of ethyl bromoacetate were added, and the reaction mixture was refluxed for 24 hr. An additional portion of sodium ethoxide and ethyl bromoacetate was added, and refluxing continued for 2 hr. After the reaction mixture was quenched in saturated NaCl solution, product isolation (EtOAc–THF; $MgSO_4$) gave 2.41 g of crude product. A small amount of contaminating ethyl bromoacetate was removed by trituration with hexane to give 2.39 g (91%) of a white crystalline solid that was homogeneous by tlc (R_f 0.58, system A). An analytical sample was prepared by recrystallization from acetone–hexane: mp 98–100°; $[\alpha]^{24}D$ +138° (*c* 0.5253, THF); ir ($CHCl_3$) 1755–1720 (s), 1605, 1575, 1495 cm^{-1}; nmr (DMSO-d_6) δ 0.83 (s, 3 H), 1.22 (t, J = 7 Hz, 3 H), 2.8 (br t), 4.16 (q, J = 7 Hz, 2 H), 4.67 (s, 2 H), 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 356 (M^+, 32), 136 (24), 121 (21), 109 (33), 107 (20), 95 (21), 93 (21), 81 (47), 69 (100).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.94; H, 7.90.

3-*O*-Carboxymethylestrone (11).—3-*O*-Carbethoxymethylestrone (10) (2.29 g, 7.1 mmol) was dissolved in 35 ml of ethanol and 8 ml of a 1 *M* potassium hydroxide solution (8 mmol) was added. The reaction mixture was stirred overnight at room temperature, the solvent evaporated, and the residual salt washed with ether. The washed residue was dissolved in water and acidified with 10% H_2SO_4. Product isolation (ether–THF; $MgSO_4$) gave 1.78 g of crude acid. Recrystallization from benzene–ethyl acetate gave 1.46 g (63%) of a white crystalline solid, mp 214–215°, (R_f 0.39, system C). An analytical sample was prepared by three recrystallizations from the same solvent system: $[\alpha]^{24}D$ +159° (*c* 0.4651, THF); ir (KBr) 3600–2200 (br OH), 1750 (C=O), 1620, 1510, 1250 cm^{-1}; nmr ($CDCl_3$) δ 0.92 (s, 3 H), 2.85 (br, t, 2 H), 4.63 (s, 2 H), 6.5–7.4 (3 H, aromatic), 7.8 (br s, 1 H, OH); mass spectrum (70 eV) *m/e* (rel intensity) 328 (M^+, 100), 243 (22), 204 (24), 115 (20), 97 (33), 92 (23), 91 (36).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.80; H, 7.27.

3-*O*-(3′-Diazo-2′-ketopropyl)estrone (12).—3-*O*-Carboxymethylestrone (11) (200 mg, 0.61 mmol) was dissolved in 12 ml of ethanol-free chloroform and 435 mg (0.262 ml, 3.66 mmol) of thionyl chloride and 0.003 ml of pyridine were added. After 18 hr at 25°, the solvent was evaporated at room temperature under vacuum, and excess thionyl chloride was removed by evaporation of two additional 5-ml portions of ethanol-free chloroform. The acid chloride in a small volume of chloroform was added to a large excess (*ca.* 6 mmol) of distilled diazomethane in ether at 0°. After 3 hr at 0° and 18 hr at 25°, half of the solvent was distilled off on the steam bath, and the solution remaining was filtered (Celite) and evaporated to give 258 mg of a yellow crystalline solid. Purification by preparative tlc (ether–hexane 1:3, 2 developments) gave 170 mg (79%) of a yellow crystalline solid (R_f 0.39, system D). An analytical sample was prepared by recrystallization from acetone: mp 156–158°; uvλ (EtOH) 272 nm (ϵ 7700); $[\alpha]^{24}D$ +125° (*c* 0.5058, THF); ir (KBr) 2120 (C=N=N), 1750 (C=O), 1650, 1510, 1380 cm^{-1}; nmr ($CDCl_3$) δ 0.92 (s, 3 H), 2.83 (2 H), 4.50 (s, 2 H), 5.75 (s, 1 H), 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 352 (M^+, 19), 326 (17), 324 (54), 296 (6), 270 (100), 238 (12), 226 (16), 213 (26), 199 (13).

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.21; H, 7.10; N, 7.82.

3-*O*-Carbethoxymethylestradiol (13).—Estradiol (2 g, 7.4 mmol) dissolved in 30 ml of absolute ethanol, 5.5 ml of a 2 *M* solution of sodium ethoxide in ethanol, and 2.45 ml (3.67 g, 22 mmol) of ethyl bromoacetate were allowed to react by the procedure used to prepare 3-*O*-carbethoxymethylestrone (10). Evaporation of excess ethyl bromoacetate (40°, 1 mm) gave 2.66 g of a yellow oil which was purified by column chromatography ($CHCl_3$ and $CHCl_3$–EtOH 97:3, as eluent). The chromatographically homogeneous fractions were pooled to give 2.43 g (85%) of a white solid, mp 88–90°. An analytical sample was prepared by recrystallization from hexane: $[\alpha]^{24}D$ +60° (*c* 0.6959, THF); ir (KBr) 3500 (OH), 1760 (C=O), 1500, 1220 cm^{-1}; nmr ($CDCl_3$) δ 0.75 (s, 3 H), 1.28 (t, J = 7 Hz, 3 H), 2.8 (br t, 2 H), 3.68 (t, J = 7 Hz, 1 H), 4.22 (q, J = 7 Hz, 2 H), 4.52 (s, 2 H), 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 358 (M^+, 100), 299 (10), 285 (6), 271 (15), 258 (16), 253 (21), 246 (10), 232 (11), 219 (7), 159 (23).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.47; H, 8.22.

3-*O*-Carboxymethylestradiol (14).—3-*O*-Carbethoxymethylestradiol (13) (2.43 g, 5.5 mmol) was dissolved in 35 ml of ethanol, and 6 ml of 1 *M* aqueous potassium hydroxide solution was added. Reaction and product isolation as described for 3-*O*-carboxymethylestrone gave 1.93 g of crude product. After recrystallization from ethyl acetate, 1.64 g (91%) of a white crystalline solid was obtained. An analytical sample was prepared by three recrystallizations from toluene–ethyl acetate: mp 214–215°; $[\alpha]^{24}D$ +50° (*c* 0.5998, THF); ir (KBr) 3600–2200 (broad, OH), 1735 (C=O), 1610, 1500, 1220 cm^{-1}; nmr (DMSO-d_6) δ 0.67 (s, 3 H), 2.75 (br t), 3.54 (t, J = 6 Hz, 1 H), 4.57 (s, 2 H), 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 330 (M^+, 100), 271 (30), 253 (13), 230 (21), 218 (23), 204 (18), 159 (17), 157 (15), 114 (17).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.39; H, 7.92.

3-*O*-Carboxymethylestradiol 17-Acetate (15).—3-*O*-Carboxymethylestradiol (14) (1.64 g, 5.0 mmol) was dissolved in 12 ml of pyridine and 4 ml (40 mmol) of acetic anhydride was added. After stirring at 25° for 18 hr, water was added and the product extracted with ethyl acetate. The extracts were washed with 10% sulfuric acid, dried ($MgSO_4$), and evaporated to give 1.75 g (94%) of crude acetate. Recrystallization from benzene gave 1.13 g (61%) of a white, crystalline solid that was chromatographically homogeneous (R_f 0.48, system C). An analytical sample was recrystallized three times from ethyl acetate–hexane: mp 195–197°; $[\alpha]^{24}D$ +56° (*c* 0.422, THF); ir (KBr) 3600–2200 (broad, OH), 1770 (ester C=O), 1750 (acid C=O), 1510, 1250 cm^{-1}; nmr (DMSO-d_6)[34] δ 0.80 (s, 3 H), 2.00 (s, 3 H), 2.75 (br t), 4.57 (s, 2 H), 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 372 (M^+, 100), 271 (16), 253 (20), 230 (22), 217 (18), 204 (16), 191 (13), 158 (17), 145 (13), 115 (13), 81 (17), 77 (28).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.14; H, 7.53.

3-*O*-(3′-Diazo-2′-ketopropyl)estradiol 17-Acetate (16).—3-*O*-Carboxymethylestradiol 17-acetate (15) (120 mg, 0.32 mmol) was dissolved in 10 ml of ethanol-free chloroform and treated with 0.15 ml (357 mg, 3.0 mmol) of thionyl chloride. Three drops of pyridine were added, and the reaction mixture was stirred at 50° for 5 hr. Reaction according to the procedure used in the preparation of the corresponding estrone derivative 12 gave 132 mg of a solid, which contained a small amount of 3-carboxymethylestradiol 17-acetate (tlc analysis). Purification by preparative tlc (ether–hexane, 1:3, 1 development; 1:1, 2 developments) gave 45 mg (35%) of a pale yellow solid that was chromatographically homogeneous (R_f 0.55, system D) and analytically pure: mp 97° dec; uv λ_{max} (EtOH) 2700 nm (ϵ

9480); $[\alpha]^{24}D$ +24° (*c* 0.6800, THF); ir (KBr) 2140 (C=N=N), 1750 (broad C=O), 1650, 1510, 1380, 1260 cm^{-1}; nmr ($CDCl_3$) δ 0.83 (s, 3 H), 2.04 (s, 3 H), 2.8 (br t, 2 H), 4.48 (s, 2 H), 4.70 (t, J = 8 Hz, 1 H), 5.73 (s, 1 H) 6.5–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 396 (M^+, 3), 368 (3), 326 (3), 314 (5), 213 (2), 172 (3), 160 (5), 147 (4), 133 (4), 55 (12), 43 (21), 28 (100).

Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.68, H, 7.06; N, 7.17.

3-*O*-(3′-Diazo-2′-ketopropyl)estradiol (17).—Diazoketopropylestradiol acetate (16) (252 mg, 0.64 mmol) was dissolved in 75 ml of methanol–THF (2:1) and 440 mg (3.8 mmol) of potassium carbonate in 10 ml of methanol was added. After stirring 22 hr at 25°, the crude product was isolated (EtOAc, $MgSO_4$). Purification by preparative tlc (system A, 2 developments) gave 108 mg (48%) of a pale yellowc rystalline solid: mp 150° dec; uv λ_{max} (EtOH) 273 nm (ε 8000); $[\alpha]^{24}D$ −12° (*c* 0.3374, THF); ir (KBr) 3500 (OH), 2120 (C=N=N), 1650 (C=O), 1510, 1380, 1260 cm^{-1}; nmr ($CDCl_3$) δ 0.8 (s, 3 H), 3.7 (t, 1 H), 4.5 (s, 2 H), 5.7 (s, 1 H), 6.6–7.3 (3 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 354 (M^+, 2), 326 (3), 272 (11), 213 (4), 160 (5), 159 (5), 43 (100).

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.90; H, 7.26; N, 7.78.

4-*O*-Carbethoxymethylhexestrol (18).—Hexestrol (6.5 g, 24.1 mmol) was dissolved in 200 ml of absolute ethanol, and 14.5 ml of a 2 *M* solution of sodium ethoxide in ethanol was added, followed by 8.1 ml (12.1 g, 72.3 mmol) of ethyl bromoacetate. After 0.5 hr at 25°, tlc analysis (product R_f 0.43, system A) indicated that dialkylated product (19) was beginning to form. Saturated sodium chloride solution (100 ml) was added, and product isolation (THF–ether; $MgSO_4$) gave a pale yellow oil which was chromatographed on a column of silica gel, eluting with chloroform–ethanol (99:1). Fractions containing 4-*O*-carbethoxymethylhexestrol (18) were pooled and the solvent was removed to yield 3.7 g (43.5%) of a white solid. Recrystallization from benzene gave plates: mp 134–136°; ir (KBr) 3440 (OH), 1740 (ester C=O), 1220 cm^{-1} (O–C); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.2 (m, 7 H), 2.5 (m, 2 H), 4.2 (q, 2 H), 4.7 (s, 2 H), 6.6–7.1 (m, 8 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 263 (2), 223 (2), 222 (16), 221 (100), 219 (10), 193 (10), 147 (20), 135 (30).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.25; H, 7.92.

4,4′-*O*-Bis(carbethoxymethyl)hexestrol (19).—Fractions containing the product 19 were pooled and solvent was removed to yield 2.0 g (18.6%) of a white solid. Recrystallization from benzene gave plates: mp 110–112°; ir (KBr) 1760 (ester C=O), 1230 cm^{-1} (O–C); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.3 (m, 10 H), 2.5 (m, 2 H), 4.1 (q, 4 H), 4.7 (s, 4 H), 6.8–7.2 (m, 8 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 442 (M^+, 8), 369 (14), 223 (39), 222 (100), 221 (84), 207 (10), 206 (14).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.82; H, 7.96.

4-*O*-Carboxymethylhexestrol (20).—4-*O*-Carbethoxymethylhexestrol (18) (3.0 g, 8.45 mmol) was dissolved in 60 ml of absolute ethanol, and 10 ml of 1 *M* aqueous potassium hydroxide solution was added. Reaction and product isolation according to the procedure for 3-*O*-carboxymethylestrone (11) gave 2.68 g (98%) of a white solid. Recrystallization from benzene gave white crystals: mp 137–140°; ir (KBr) 3400 (OH), 1750 (C=O), 1230 cm^{-1} (O–CH_2); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.2 (m, 4 H), 2.5 (m, 2 H), 4.6 (s, 2 H), 6.8–7.2 (m, 8 H, aromatic), 7.35 (s, 1 H, phenolic OH); mass spectrum (70 eV) *m/e* (rel intensity) 328 (M^+, 1), 193 (100), 165 (42), 147 (48), 134 (42).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.93; H, 7.38.

4-*O*-Carboxymethylhexestrol 4′-Acetate (21).—4-*O*-Carboxymethylhexestrol (20) (1.4 g, 4.26 mmol) was dissolved in 16 ml of pyridine, and 3.94 ml (4.26 g, 42.6 mmol) of acetic anhydride was added. Reaction and product isolation according to the procedure for 3-*O*-carboxymethylestradiol 17-acetate (15) gave after recrystallization from benzene 1.5 g (95%) of a fine white powder: mp 125–127°; ir (KBr) 1770 (acid C=O), 1730 s (ester C=O), 1220 cm^{-1} (O–C); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.2 (m, 4 H), 2.3 (s, 3 H), 2.5 (m, 2 H), 4.6 (s, 2 H), 6.8–7.4 (m, 8 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 370 (M^+, 1), 221 (2), 193 (100), 164 (10), 147 (13), 135 (26), 107 (20), 91 (60).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.44; H, 6.94.

4-*O*-(3′-Diazo-2′-ketopropyl)hexestrol 4′-Acetate (22).—Carboxymethylhexestrol acetate (21) (1.5 g, 4.05 mmol) was dissolved in 25 ml of ethanol-free chloroform and treated with 2.9 ml (4.8 g, 40.5 mmol) of thionyl chloride. One drop of pyridine was added. Reaction and product isolation according to the procedure used in the preparation of 3-*O*-(3′-diazo-2′-ketopropyl)-estradiol 17-acetate (16) gave 1.56 g of a brown solid. Purification by preparative tlc (system A, 2 developments) gave after recrystallization from benzene 320 mg (20%) of a pale yellow crystalline solid: mp 122° dec; uv λ_{max} (EtOH) 268 nm (ε 9350); ir (KBr) 2120 (C=N=N), 1760 (ester C=O), 1635 cm^{-1} (ketone C=O); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.3 (m, 4 H), 2.2 (s, 3 H), 2.5 (m, 2 H), 4.6 (s, 2 H), 6.2 (s, 1 H), 6.8–7.2 (m, 8 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 394 (M^+, 4), 221 (22), 217 (100), 207 (59), 189 (45), 147 (44), 136 (52).

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.90: H, 6.38; N, 7.19.

4-*O*-(3′-Diazo-2′-ketopropyl)hexestrol (23).—Diazoketopropylhexestrol acetate (160 mg, 0.405 mmol) was dissolved in 10 ml of methanol, and 2 ml of saturated potassium carbonate solution was added. Reaction and product isolation according to the procedure for 3-*O*-(3′-diazo-2′-ketopropyl)estradiol (17) gave 92 mg (64%) of a pale yellow solid, after purification by preparative tlc ($CHCl_3$, 2 developments): mp 92° dec; uv λ_{max} (EtOH) 274 nm (ε 9920); ir (KBr) 3400 (OH), 2120 (C=N=N), 1620 cm^{-1} (ketone C=O); nmr (DMSO-d_6) δ 0.5 (t, 6 H), 1.3 (m, 4 H), 2.5 (m, 2 H), 4.6 (s, 2 H), 6.2 (s, 1 H), 6.8–7.2 (m, 8 H, aromatic), 9.1 (s, 1 H, OH); mass spectrum (70 eV) *m/e* (rel intensity) 352 (M^+, 4), 271 (14), 270 (64), 216 (67), 191 (44), 165 (37), 137 (33), 136 (100).

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.83; H, 6.99; N, 7.80.

4-Nitroesterone (32a) and 2-Nitroestrone (35a).[11c,31]—Estrone (5 g, 18.5 mmol) was dissolved in boiling glacial acetic acid. The solution was allowed to cool to 70°, and 1.17 ml of concentrated nitric acid was added in one portion (color change, yellow to deep orange). A precipitate formed as the reaction medium was cooled to room temperature, and after 24 hr it was collected by filtration, washed with cold glacial acetic acid, and dried *in vacuo*, to give 1.84 g (32%) 4-nitroestrone (32a), mp 250° dec. An analytical sample, obtained after one recrystallization from aqueous acetic acid, melted with decomposition above 270° (lit.[31] 270–280° dec): $[\alpha]^{24}D$ +286° (*c* 0.59, THF); ir (KBr) 3450 (OH), 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.80 (s, 3 H), 1.20–2.40 (15 H), 7.00 (AB quartet, 2 H), 10.3 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 315 (M^+, 35), 298 (14), 181 (15), 169 (15), 131 (24), 119 (25), 97 (21), 69 (100), 41 (17), 28 (12).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.23; H, 6.88; N, 4.28.

The filtrate was poured into 350 ml of distilled water to precipitate the remaining nitro derivatives and the yellow solid (3.67 g) was collected and dried *in vacuo*. It was dissolved in benzene and purified by column chromatography. Elution with benzene yielded, after recrystallization from 80% ethanol, 2.29 g (40%) of 2-nitroestrone (35a): mp 183–185° (lit.[31] 183.5–184°); $[\alpha]^{24}D$ +190° (*c* 0.6135, $CHCl_3$); ir (KBr), 3440 (OH), 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.82 (s, 3 H), 1.20–2.40 (15 H), 6.80 (s, 1 H), 7.73 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 315 (M^+, 100), 271 (51), 259 (29), 258 (49), 217 (33), 205 (25), 97 (23), 55 (23), 41 (30), 28 (33).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.40; H, 6.65; N, 4.55.

4-Nitroestradiol (32b).—A solution of 315 mg (1.0 mmol) of 4-nitroestrone (32a) in 25 ml of dry THF was added dropwise to a stirred solution of 608 mg (16.0 mmol) of sodium borohydride in 20 ml of dry THF, 4 ml of 1 *N* sodium hydroxide, and 3 ml of distilled water. The resulting mixture was refluxed for 6 hr, after which time the alkaline reaction mixture was acidified with 1 *N* hydrochloric acid. Product isolation (ether; Na_2SO_4) gave 135 mg (43%) 4-nitroestradiol (32b) after two crystallizations from ethanol: mp 210° dec; $[\alpha]^{24}D$ +210° (*c* 0.5515, THF); ir (KBr) 3600–3000 (broad OH), 1525, 1365 cm^{-1} (C–NO); nmr (DMSO-d_6, 220 MHz)[34] δ 0.68 (s, 3 H), 4.62 (s, 1 H, C-17 OH), 7.12 (AB quartet, 2 H), 10.55 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 317 (M^+, 25), 300 (26), 258 (25), 128 (27),

115 (34), 107 (23), 95 (26), 93 (26), 91 (29), 81 (30), 79 (25), 77 (32), 67 (25).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.78; H, 7.18; N, 4.30.

4-Aminoestrone (33a).—To a refluxing solution of 4-nitroestrone (**32a**) (196 mg, 0.62 mmol) in 50 ml of acetone, 10 ml of water, and 5 ml of 1 *N* sodium hydroxide was added 1.0 g of sodium dithionite. The red reaction mixture was stirred under reflux for 30 min; then 700 mg of sodium dithionite was added. Small portions of 1 *N* sodium hydroxide were added periodically to maintain alkalinity. After another 30 min, a final 300-mg portion of sodium dithionite was added, the reaction mixture was cooled briefly, and acetone was removed under reduced pressure. The alkaline solution was neutralized with 10% acetic acid and allowed to stand at 0° for 2 hr. The white precipitate collected by filtration under nitrogen was washed with water and dried *in vacuo* to yield 171 mg (96%) of 4-aminoestrone (**33a**): mp 254° dec. Recrystallization from methanol–benzene gave 150 mg (88%) of **33a**: mp 260–261° dec (lit.[33] 260–262°); $[\alpha]^{24}D$ +171° (*c* 0.4974, THF); ir (KBr) 3600–3100 cm^{-1} (broad OH and NH); mass spectrum (70 eV) *m/e* (rel intensity) 285 (M^+, 100).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.66; H, 8.12; N, 4.99.

4-Aminoestradiol (33b).—To a round-bottom flask containing 175 mg (5 mmol) of lithium aluminum hydride in 25 ml of dry THF was added 285 mg (1 mmol) of 4-aminoestrone (**33a**) in 20 ml of dry THF. The reaction mixture was stirred at 25° for 2 hr, and excess $LiAlH_4$ was then destroyed by dropwise addition of water, followed by an equal volume of saturated ammonium chloride. Product isolation (ether; Na_2SO_4) gave 182 mg (63%) 4-aminoestradiol after recrystallization from aqueous methanol. An analytical sample was obtained by three recrystallizations from aqueous methanol: mp 260° dec; $[\alpha]^{24}D$ +37° (*c* 0.22, THF); ir (KBr) 3680–3000 (broad OH, NH), 1610 cm^{-1} (phenyl); mass spectrum (70 eV) *m/e* (rel intensity) 287 (M^+, 100), 122 (16).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.92; H, 8.67; N, 4.77.

4-Azidoestrone (34a).—A solution of 4-aminoestrone (**33a**) (200 mg, 0.52 mmol) in 10 ml of acetone and 5 ml of 2 *N* hydrochloric acid was cooled to 0° and diazotized with 49 mg of sodium nitrite in 2 ml of water. After 30 min the cold solution of diazonium salt was added to a tenfold excess (455 mg, 0.70 mmol) of sodium azide in 10 ml of water. The solution was overlayed with 100 ml of ether and stirred for about 30 min. Product isolation (ether; Na_2SO_4) gave crude material which was purified by preparative tlc (ether). The chromatogram was protected from light during development and subsequent product isolation. Recrystallization from methanol–benzene gave 124 mg (57%) 4-azidoestrone (**34a**) as straw-colored needles: mp 135° dec; uv λ_{max} (EtOH) 258 nm (ϵ 8350), 289 (4930); $[\alpha]^{24}D$ +167° (*c* 0.192, EtOH); ir (KBr) 3300 (broad OH), 2120 (N_3), 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 311 (M^+, 2), 285 (100), 283 (18), 187 (13), 161 (17), 131 (14), 122 (30), 115 (16), 97 (14), 91 (14), 77 (17), 41 (21).

Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.22; H, 6.84; N, 13.45.

4-Azidoestradiol (34b).—4-Aminoestradiol (**33b**) (110 mg, 0.39 mmol) in 5 ml of 2 N hydrochloric acid and 10 ml of acetone was diazotized with 27 mg of sodium nitrite and treated with tenfold excess sodium azide according to the procedure used in the preparation of 4-azidoestrone (**34a**). Preparative tlc of the crude azide (ether) gave 72 mg (59%) of 4-azidoestradiol (**34b**) after recrystallization from aqueous acetone: mp 140° dec; uv λ_{max} (EtOH) 257 nm (ϵ 6290), 292 (3130); $[\alpha]^{24}D$ +82° (*c* 0.7788, EtOH); ir (KBr) 3500–3100 (OH), 2120 cm^{-1} (N_3); mass spectrum (70 eV) *m/e* (rel intensity) 313 (M^+, 0.4), 288 (22), 287 (100), 286 (13), 285 (49), 187 (11), 175 (14), 174 (10), 162 (11), 161 (10), 160 (11), 122 (22).

Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.07; H, 7.28; N, 13.48.

2-Nitroestradiol (35b).—2-Nitroestrone (**35a**) (315 mg, 1 mmol) was reduced with sodium borohydride by the same procedure used in the preparation of 4-nitroestradiol (**32b**). Recrystallization of the crude product from aqueous ethanol gave 182 mg (58%) of **35b**, mp 168–172°. An analytical sample was recrystallized another two times from aqueous ethanol: mp 169–171°; $[\alpha]^{24}D$ +164° (*c* 0.5121, $CHCl_3$); ir (KBr) 3600–3280 (broad OH), 1540, 1310 (C–NO_2), but absence of C=O near 1700 cm^{-1}; nmr (DMSO-d_6, 220 MHz)[34] δ 0.68 (s, 3 H), 0.91–2.75 (16 H), 4.55 (s, C-17 OH), 6.82 (s, 1 H), 7.73 (s, 1 H), 10.46 (broad s, phenolic OH); mass spectrum (70 eV) *m/e* (rel intensity) 317 (M^+, 56), 259 (21), 258 (100), 205 (59), 71 (24), 57 (36), 43 (20), 28 (22).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.37; H, 7.31; N, 4.27.

2-Aminoestrone (36a).—2-Nitroestrone (**35a**) (500 mg, 1.59 mmol) in 150 ml of acetone, 30 ml of water, and 20 ml of 1 *N* sodium hydroxide was reduced with 1.38 g of sodium dithionite by the same procedure used in the preparation of 4-aminoestrone (**33a**); the additional portion of dithionite added was 276 mg. After recrystallization from aqueous methanol, 396 mg (87%) 2-aminoestrone (**36a**), mp 210° dec, was obtained. An analytical sample was recrystallized twice from aqueous methanol: mp 220° dec (lit.[35] 220° dec); $[\alpha]^{24}D$ 208° (*c* 0.558, THF); ir (KBr) 3100–2600 (broad, OH and NH_2 stretch), 1725 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 286 (24), 285 (M^+, 100), 161 (11), 135 (14), 122 (23), 32 (15), 28 (63).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12, N, 4.91. Found: C, 75.52; H, 7.90; N, 4.93.

2-Aminoestradiol (36b).—Reduction of 300 mg (1.06 mmol) of 2-aminoestrone (**36a**) in 15 ml of THF with 163 mg (4.64 mmol) of $LiAlH_4$ in 40 ml of THF was accomplished by the same procedure used in the preparation of 4-aminoestradiol (**33b**). Recrystallization of the crude product from methanol–benzene gave 128 mg (42%) of 2-aminoestradiol (**36b**), mp 198–200°. An analytical sample was prepared by an additional recrystallization from methanol–benzene: mp 200–201°; $[\alpha]^{24}D$ +122° (*c* 0.1100, THF); ir (KBr) 3580–3000 (very broad, OH, NH), 1610 cm^{-1} (phenyl); mass spectrum (70 eV) *m/e* (rel intensity) 287 (M^+, 100), 135 (15), 122 (30), 78 (45), 77 (14), 28 (15).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.06; H, 8.56; N, 5.06.

2-Azidoestrone (37a).—A solution of 2-aminoestrone (260 mg, 0.92 mmol) in 5 ml of 2 *N* hydrochloric acid and 10 ml of acetone was diazotized at 0° with 68 mg of sodium nitrite in 2 ml of distilled water by the same procedure used to prepare 4-azidoestrone (**34a**). Recrystallization of the crude product from aqueous methanol gave 230 mg (81%) 2-azidoestrone (**37a**): mp 140–150° dec; uv λ_{max} (EtOH) 253 nm (ϵ 7200), 300 (5390); $[\alpha]^{24}D$ +191° (*c* 0.9062, EtOH); ir (KBr) 3420 (broad OH), 2130 (N_3), 1730 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.81 (s, 3 H), 1.20–2.40 (15 H), 6.56 (s, 1 H), 6.73 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 311 (M^+, 2), 285 (100), 283 (21), 172 (17), 161 (13), 160 (10), 135 (10), 122 (25), 58 (13), 43 (46).

Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.29; H, 6.63; 13.34.

2-Azidoestradiol (37b).—A solution of 2-aminoestradiol (**36b**) (60 mg, 9.21 mmol) in 3 ml of 2 *N* hydrochloric acid and 6 ml of acetone was diazotized with 14.4 mg of sodium nitrite in 1 ml of water by the same procedure used in the preparation of 4-azidoestradiol (**34b**). The crude azide was purified by preparative tlc using ether–hexane (1:3) as developing solvent, to give 25 mg (38%) of 2-azidoestradiol (**37b**) as tan crystals from THF–hexane: mp 140° dec; uv λ_{max} (EtOH) 254 nm (ϵ 7650), 301 (5600); $[\alpha]^{24}D$ +135° (*c* 0.8118, EtOH), ir (KBr) 3560–3400 (broad OH), 2120 cm^{-1} (N_3); mass spectrum (70 eV) *m/e* (rel intensity) 313 (M^+, 0.6), 287 (3), 28 (100).

Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 68.82; H, 7.26; N, 13.29.

3-Nitrohexestrol (38) and 3,3′-Dinitrohexestrol (41).—Hexestrol (6.0 g, 19 mmol) was dissolved in 250 ml of glacial acetic acid at its boiling point. When the solution had cooled to 70°, 1.5 ml of concentrated nitric acid was added dropwise. The resulting orange reaction mixture was cooled to 25° and allowed to stand overnight. A yellow precipitate which formed in the reaction medium was collected, and the filtrate was neutralized with sodium bicarbonate. Product isolation (ether; Na_2SO_4) from the aqueous solution gave an orange residue. Purification of the products of nitration was accomplished by careful column chromatography. The residue from the filtrate was dissolved in THF and adsorbed onto a small amount of silica gel. The THF was removed under vacuum, and the coated silica gel was placed on top of a silica gel column (100:1 silica gel–compound). Elution with 30% benzene in hexane gave a yellow product (dinitrohexestrol 41) which recrystallized from ethanol as bright yellow flakes (182 mg): mp 240° dec; ir (KBr) 3440 (OH), 1535, 1320 cm^{-1} (C–NO_2); nmr (220 MHz, DMSO-d_6) δ 0.52 (t, 6 H), 1.23–

1.46 (m, 4 H), 7.34 (q, 2 H), 7.78 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 360 (M^+, 6), 285 (23), 181 (100), 180 (90), 153 (68), 152 (100), 106 (100), 58 (91), 79 (71), 78 (37), 77 (98), 65 (36), 55 (26), 51 (26), 41 (48), 39 (24), 28 (37), 27 (26).

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.95; H, 5.56; N, 7.53.

Elution of the column with 70% benzene in hexane and finally benzene gave 1.85 g of another yellow solid (3-nitrohexestrol **38**) which could be recrystallized from aqueous ethanol only with difficulty: mp 139–142°; ir (KBr) 3520–3300 (OH), 1540, 1320 cm^{-1} (C–NO_2); nmr ($CDCl_3$) δ 0.58 (t, 6 H), 1.10–1.65 (m, 4 H), 2.40–2.70 (m, 2 H), 4.93 (broad s, 1 H), 6.68–7.91 (m, 7 H, aromatic), 10.40 (sharp s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 315 (M^+, 1), 136 (12), 135 (100), 107 (37).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.75; H, 6.50; N, 4.27.

Chromatographic purification of the solid which had separated from the reaction medium gave an additional 765 mg 3,3′-dinitrohexestrol, mp 240° dec, after recrystallization from aqueous ethanol. The combined yields of the products were 3-nitrohexestrol (**38**), 1.85 g (30%), and 3,3′-dinitrohexestrol (**41**), 947 mg (14%).

3-Aminohexestrol (39).—3-Nitrohexestrol (**38**) (315 mg, 1 mmol) in 40 ml of acetone, 20 ml of water, and 10 ml of 1 *N* sodium hydroxide was reduced with 1 g of sodium dithionite by the same procedure used in the preparation of 4-aminoestrone (**33a**); a final portion of 174 mg of dithionite was added. Recrystallization of the crude precipitate from aqueous methanol gave 263 mg (92%) of 3-aminohexestrol: mp 200–202° dec; ir (KBr) 3600–3100 (OH, NH), 1610 cm^{-1} (C=C, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 285 (M^+, 18), 151 (18), 150 (100), 135 (24), 133 (14), 107 (14).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.80; H, 8.14; N, 4.87.

3-Azidohexestrol (40).—3-Aminohexestrol (**39**) (200 mg, 0.7 mmol) in 5 ml of 1 *N* hydrochloric acid and 15 ml of acetone was diazotized with 49 mg of sodium nitrite in 2 ml of water according to the procedure used in the preparation of 4-azidoestrone (**34a**). After purification of the crude product by preparative tlc (5% MeOH in $CHCl_3$, protect from light), recrystallization from aqueous methanol gave 150 mg (69%) 3-azidohexestrol (**40**): mp 145° dec; uv λ_{max} (EtOH) 250 nm (ε 6930), 288 (4850), 297 (4550); ir (KBr) 3440 (broad OH), 2130 (N_3), 1600, and 1610 cm^{-1} (phenyl); mass spectrum (70 eV) *m/e* (rel intensity) 311 (M^+, 6), 150 (27), 136 (12), 135 (99), 134 (14), 107 (39), 28 (100).

Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.30; H, 6.86; N, 13.56.

3,3′-Diaminohexestrol (42).—3,3′-Dinitrohexestrol (**41**) (360 mg, 1 mmol) in 40 ml of acetone, 20 ml of distilled water, and 10 ml of 1 *N* sodium hydroxide was reduced with 1.74 g of sodium dithionite by the same procedure used in the preparation of 4-aminoestrone (**33a**); a final portion of 174 mg of dithionite was added. The crude precipitate was recrystallized from aqueous methanol, giving 224 mg (75%) of 3,3′-diaminohexestrol (**42**): mp 240° dec; ir (KBr) 3600–3100 (broad OH, NH), 1600 cm^{-1} (phenyl); mass spectrum (70 eV), *m/e* (rel intensity) 300 (M^+, 18), 151 (33), 150 (100), 133 (17), 122 (13).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.71; H, 8.10; N, 9.39.

3,3′-Diazidohexestrol (43).—A solution of 3,3′-diaminohexestrol (**42**) in 10 ml of acetone and 5 ml of 2 *N* hydrochloric acid was cooled to 0°, diazotized with 34.5 mg of sodium nitrite in 2 ml of distilled water, and treated with a tenfold excess (325 mg, 5.0 mmol) of sodium azide in 10 ml of distilled water, according to the procedure used in preparing 4-azidoestrone (**34a**). The crude product was purified by preparative tlc (chloroform; protect from light during development) and recrystallization from aqueous ethanol, giving 55 mg (31%) of 3,3′-diazidohexestrol (**43**): mp 115° dec; uv λ_{max} (EtOH) 297 nm (ε 9430), 244 (14,400); ir (KBr) 3420 (OH), 2130 (N_3), 1600 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 352 (M^+, 4), 176 (23), 28 (100).

Anal. Calcd for $C_{18}H_{20}N_6O_2$: C, 61.35; H, 5.72; N, 23.82. Found: C, 61.07; H, 5.71; N, 23.53.

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Registry No.—**1**, 50-28-2; **2**, 3434-88-6; **3**, 41164-27-6; **4**, 41164-28-7; **5**, 53-16-7; **6**, 41164-29-8; **7**, 6038-23-9; **8**, 3460-92-2; **9**, 41164-31-2; **10**, 41164-32-3; **11**, 1428-66-6; **12**, 41164-34-5; **13**, 41164-35-6; **14**, 41164-36-7; **15**, 41164-37-8; **16**, 41164-38-9; **17**, 41164-39-0; **18**, 41172-42-3; **19**, 6325-61-7; **20**, 6737-97-9; **21**, 41172-45-6; **22**, 41172-46-7; **23**, 41172-47-8; **32a**, 5976-74-9; **32b**, 6936-94-3; **33a**, 14984-42-0; **33b**, 6301-88-8; **34a**, 41164-44-7; **34b**, 41164-45-8; **35a**, 5976-73-8; **35b**, 6298-51-7; **36a**, 14984-43-1; **36b**, 6301-87-7; **37a**, 41164-50-5; **37b**, 41259-43-2; **38**, 41172-48-9; **39**, 41172-49-0; **40**, 41172-50-3; **41**, 41172-51-4; **42**, 41172-52-5; **43**, 41172-53-6; **44**, 5635-50-7; glyoxylic acid chloride *p*-toluenesulfonylhydrazone, 14661-69-9; potassium *tert*-butoxide, 865-47-4; thionyl chloride, 7719-09-7; piperidine, 110-86-1; ethyl bromoacetate, 105-36-2; acetic anhydride, 108-24-7; potassium carbonate, 584-08-7; sodium ethoxide, 141-52-6.

The Catalytic Hydrogenation of Substituted 4-Chromanones and 4-Chromanols

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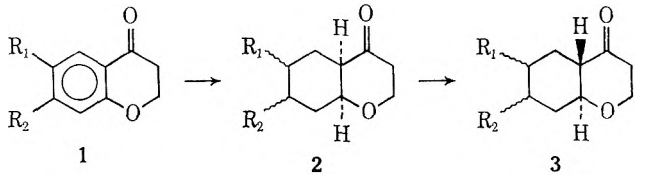
The catalytic hydrogenation over ruthenium of 6- and 7-carbomethoxy-4-chromanone, 6-methyl-4-chromanone, 6-carbomethoxy-4-chromanol, and the ethylene ketal of 6-carbomethoxy-4-chromanone has been attempted. Conditions were found for the ketones leading to perhydro alcohols as the major products. Electron-donating ring substituents appear to minimize significantly any competing hydrogenolyses.

The catalytic hydrogenation of the aromatic rings of 4-chromanones, while not reported in the literature,[1] provides an attractive route for the preparation of analogs of *cis*- and *trans*-decalin containing an oxygen atom as one of the ring constituents[2] (Scheme I).

SCHEME I



1 2 3

a, $R_1 = CO_2CH_3$; $R_2 = H$

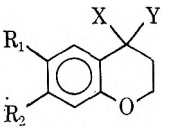
b, $R_1 = CH_3$; $R_2 = H$

c, $R_1 = H$; $R_2 = CO_2CH_3$

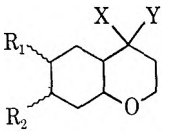
The major difficulty lay in the choice of catalyst and reaction conditions, so as to minimize hydrogenolysis of either the benzylic carbonyl groups[1,3] (as such or in a reduced form) or the phenolic carbon–oxygen bond,[4] and suggested primary emphasis on ruthenium catalysts.

The desired starting materials, **1a–c**, were prepared by literature methods[5,6] and exhibited the expected spectral properties.[7] To evaluate the optimum benzylic functionality, 6-carbomethoxy-4-chromanone (**1a**) was reduced with sodium borohydride to the 6-carbomethoxy-4-chromanols (**4**) and also converted to the ethylene ketal **5**.

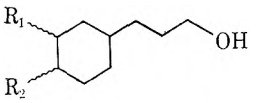
Preliminary experiments using ruthenium catalysts in 80% aqueous ethanol for the hydrogenation of 6-carbomethoxy-4-chromanone (**1a**) led to complete hydrogenolysis of the benzylic carbon–oxygen bond and extensive reduction of the aromatic ring. The hydrogenolysis products 6-carbomethoxychroman (**6**) and saturated material with gross structure **7** (R = CH_2CH_3) were obtained in a 1:2 ratio, and evidence was obtained that **6** was converted to **7** under the reaction conditions. Hydrogenation of **1a** in 90% aqueous methanol over 5% ruthenium on charcoal at 100° and 1950 psig for 20 hr proved satisfactory for extensive aromatic ring hydrogenation with less hydrogenolysis. Chromatography of 800 mg of crude reaction mixture permitted isolation of 290 mg of a mixture of perhydro alcohols[8] **8**, 260 mg of hydrogenated and benzylically hydrogenolyzed **7** (R = CH_3), and 160 mg of hydrogenated and benzylically and phenolically hydrogenolyzed **9**. Under these reaction conditions, ring



4, $R_1 = CO_2CH_3$; $R_2 = Y = H$; $X = OH$
5, $R_1 = CO_2CH_3$; $R_2 = H$; $XY = -O(CH_2)_2O-$
6, $R_1 = CO_2CH_3$; $R_2 = X = Y = H$
10, $R_1 = CO_2CH_3$; $R_2 = Y = H$; $X = OCH_3$
13, $R_1 = CH_3$; $R_2 = X = Y = H$
14, $R_2 = CO_2CH_3$; $R_1 = X = Y = H$
18, $R_2 = CO_2CH_3$; $R_1 = Y = H$; $X = OH$



7, $R_1 = CO_2R$; $R_2 = X = Y = H$
8, $R_1 = CO_2CH_3$; $R_2 = Y = H$; $X = OH$
11, $R_1 = CO_2CH_3$; $R_2 = Y = H$; $X = OCH_3$
12, $R_1 = CH_3$; $R_2 = Y = H$; $X = OH$
15, $R_2 = CO_2CH_3$; $R_1 = X = Y = H$
16, $R_2 = CO_2CH_3$; $R_1 = Y = H$; $X = OH$



9, $R_1 = CO_2CH_3$; $R_2 = H$
17, $R_1 = H$; $R_2 = CO_2CH_3$

(1) (a) For results of Raney nickel hydrogenations of 7-methoxy- and 7-hydroxy-4-chromanone, see R. T. Blickenstaff and I. Y. C. Tao, *Tetrahedron*, **24**, 2495 (1968), and P. Naylor, G. R. Ramage, and P. Schofield, *J. Chem. Soc.*, 1190 (1958). (b) For the results of hydrogenations of 4-chromenones, see R. Mozingo and H. Adkins, *J. Amer. Chem. Soc.*, **60**, 669 (1938). (c) For typical results on hydrogenation of flavones, see M. Suzuki and T. Oda, *Nippon Kagaku Zasshi*, **89**, 878 (1968) [*Chem. Abstr.*, **70**, 57575*r* (1969)]; S. Fujise, *et al.*, *Nippon Kagaku Zasshi*, **84**, 81 (1963) [*Chem. Abstr.*, **60**, 5445*a* (1964)]; S. Mitsui, *et al.*, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **72**, 339 (1951) [*Chem. Abstr.*, **46**, 8102*i* (1952)].

(2) The stereochemical designations at the bridgeheads in the perhydro products obtained in this work are arbitrarily chosen to reflect the cis or trans relationships and are not meant to imply absolute configurations.

(3) (a) W. John, P. Günther, and M. Schmeil, *Ber.*, **71**, 2637 (1938); (b) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp 81–84, 110–111, and 135.

(4) Reference 3b, pp 72–73.

(5) J. Lichtenberger and R. Geyer, *Bull. Soc. Chim. Fr.*, 282 (1963).

(6) J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr*, 325 (1958).

(7) The melting point of 6-carbomethoxy-4-chromanone (**1a**), 72.5–74.5°, was significantly different from the value of 130° reported previously.[5] However, elemental analyses, spectral data, and the method of preparation confirm the assigned structure.

(8) After Jones oxidation[9] gas chromatographic analysis suggested the presence of three ketones. Based on the known preference[10] for cis addition in catalytic hydrogenations and on small-scale equilibration studies[11] involving the ketones, it appears reasonable to assign cis ring fusions (**2a**) to the major isomers.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, pp 142–144.

(10) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 350–353; J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, pp 591–596.

(11) G. Schwartzkopf, unpublished observations.

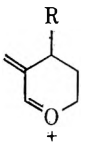
hydrogenation was essentially complete and benzylic hydrogenolysis amounted to ~60%.

Reduction of alcohol **4** in 90% aqueous methanol over ruthenium resulted in slower ring reduction and almost quantitative benzylic hydrogenolysis. Products obtained were aromatic ester **6** (50–60% yield), saturated ester **7** (R = CH_3; 30–40% yield), and <10% each of the methyl ethers of the starting alcohol (**10**) and the reduced alcohol (**11**). Ketal **5** was found to be unstable on refluxing in 90% aqueous methanol for 19 hr, producing 30–40% ketone **1a**. Addition of sodium bicarbonate prevented this hydrolysis. However, reduction of the ketal in aqueous methanol containing sodium bicarbonate over ruthenium did not lead to reaction of any kind. Based on these results, keto systems (**1**) were used exclusively in subsequent experiments.

Two questions remained to be investigated. The first was whether the carbomethoxy group exerted a significant influence through electron withdrawal. Hydrogenation of 1.0 g of 6-methyl-4-chromanone (**1b**) in 90% aqueous methanol over ruthenium produced a mixture of at least six components. The two major components, constituting ~65% of vacuum-distilled material (540 mg), were isolated by preparative vapor phase chromatography[12] and identified as isomeric saturated alcohols (**12**). A minor component appeared to be 6-methylchroman (**13**) from mass spectral evidence.

The second question was whether the carbomethoxy group exerted a significant influence by virtue of being para to the chroman oxygen function. Hydrogenation of 7-carbomethoxy-4-chromanone (**1c**) in aqueous methanol over ruthenium produced 830 mg of an oil which was subjected to column chromatography. The three products isolated were 140 mg of 7-carbomethoxychroman (**14**), 190 mg of hydrogenolyzed saturated ester **15**, and 360 mg of an isomeric mixture of the desired saturated alcohols[13] **16**. Approximately 80 mg of impure hydrogenated and benzylically and phenolically hydrogenolyzed **17** was also obtained, but resisted separation from 7-carbomethoxy-4-chromanol (**18**). These products correspond to ~80% aromatic ring hydrogenation with ~50% benzylic hydrogenolysis and are similar enough to those obtained from 6-carbomethoxy-4-chromanone (**1a**) to suggest that the only substituent-effect difference in the 6- and 7-carbomethoxy-4-chromanone hydrogenations is a slight increase in the hydrogenolysis of the phenolic carbon–oxygen bond when the carbomethoxy group is in the 6 position.

In obtaining mass spectra of the various reaction products, we have uncovered a useful feature in the spectra of all of the saturated bicyclic compounds (**7**, **11**, **12**, and **15**) except the carbomethoxy alcohols (**8** and **16**). In these compounds, the base peak at 70 eV corresponds to a fragment of gross structure **19** irrespective of the nature of the substituent R in position 4 and of the nature or position of substituents in the other ring. The generality of this behavior in related heterocyclic systems[14] and the actual structure of such fragments remain to be explored.



19

In summary, catalytic hydrogenation conditions have been established for the reduction of 6- and 7-substituted chromanones so that the major components obtained will be the perhydro alcohols. Electron-donating ring substituents appear to minimize significantly any competing hydrogenolyses. However, the limited range of substituents studied suggests caution in the application of these results.

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using solutions in deuteriochloroform. Ir spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Mass spectral analyses were obtained at 70 eV. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany.

6-Carbomethoxy-4-chromanone (**1a**).—This compound was prepared from *p*-cresol in 27% overall yield by the method of Lichtenberger and Geyer[6] and was obtained from hexane as a pale orange solid: mp 72.5–74.5° (lit.[5] mp 130°); ir (Nujol) 1710 cm^{-1} (C=O); nmr δ 8.21 (d, 1, *J* = 2 Hz, H-5), 7.98 (dd, 1, *J* = 2, 8 Hz, H-7), 6.73 (d, 1, *J* = 8 Hz, H-8), 4.55 (t, 2, *J* = 6 Hz, OCH_2CH_2), 3.88 (s, 3, OCH_3), 2.80 (t, 2, *J* = 6 Hz, CH_2-CH_2C=O).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.72; H, 4.80.

6-Methyl-4-chromanone (**1b**).—This compound was prepared from 2-carboxyethyl *p*-tolyl ether in 30% yield by the method of Colonge and Guyot:[6] mp 28–32° (lit.[6] mp 34°); ir (Nujol) 1690 cm^{-1} (C=O); nmr δ 7.69 (d, 1, *J* = 2 Hz, H-5), 7.31 (dd, 1, *J* = 2, 9 Hz, H-7), 6.88 (d, 1, *J* = 9 Hz, H-8), 4.51 (t, 2, *J* = 6.5 Hz, OCH_2CH_2), 2.77 (t, 2, *J* = 6.5 Hz, CH_2CH_2C=O), 2.30 (s, 3, CH_3).

7-Carbomethoxy-4-chromanone (**1c**).—This compound was prepared from *m*-cresol in 4.5% overall yield by the method of Lichtenberger and Geyer[5] and was obtained from methanol as white crystals: mp 108–109° (lit.[4] mp 103°); ir (Nujol) 1685 (ketone C=O), 1720 cm^{-1} (ester C=O); nmr δ 7.93 (d, 1, *J* = 8 Hz, H-5), 7.61 (d, 1, *J* = 2 Hz, H-8), 7.60 (dd, 1, *J* = 2, 8 Hz, H-6), 4.69 (t, 2, *J* = 6 Hz, OCH_2CH_2), 3.93 (s, 3, OCH_3), 2.83 (t, 2, *J* = 6 Hz, CH_2CH_2C=O).

6-Carbomethoxy-4-chromanol (**4**). A stirred solution of 2.06 g (10.0 mmol) of **1a** in 25 ml of moist methanol was treated with 380 mg (10.0 mmol) of sodium borohydride in several portions over a few minutes at room temperature. After 1 hr the stirred solution was treated with 2.3 ml of glacial acetic acid and concentrated. The residue was treated with saturated $NaHCO_3$ solution and then extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and the solvent evaporated, giving 2.1 g (100%) of an oil: ir (neat) 3440 (OH), 1720 cm^{-1} (C=O); nmr δ 8.04 (d, 1, *J* = 2 Hz, H-5), 7.81 (dd, 1, *J* = 2, 9 Hz, H-7), 6.83 (d, 1, *J* = 9 Hz, H-8), 4.79 (t, 1, *J* = 4 Hz, H-4), 4.30 (m, 2, OCH_2CH_2), 3.83 (s, 3, OCH_3), 3.33 (br s, 1, OH), 2.00 (m, 2, CH_2CH_2CHOH). This crude material was directly hydrogenated without further purification.

Ethylene Ketal of 6-Carbomethoxy-4-chromanone (**5**).—A stirred mixture of 2.06 g (10.0 mmol) of **1a**, 2.2 ml (40.0 mmol) of ethylene glycol, 200 mg of *p*-toluenesulfonic acid, and 20 ml of benzene was refluxed under a water separator for 31 hr. The cooled mixture was poured onto 50 ml of saturated $NaHCO_3$ solution containing 50 g of ice and then extracted with ether.

(12) Extreme difficulty was encountered in trapping products.

(13) Upon Jones oxidation,[9] gas chromatographic analysis with a variety of column substrates did not suggest the presence of more than one component. This presumably cis isomer (**2c**) was converted on equilibration[11] to a different and presumably trans isomer.

(14) For an example in the decahydroquinoline series, see V. G. Zaikin, N. S. Wulfson, V. I. Zaretskii, A. A. Bakaev, A. A. Akhrem, L. I. Ukhova, and N. F. Uskova, *Org. Mass Spectrom.*, **2**, 1257 (1969).

The ethereal extract was washed with water and dried (Na_2SO_4). Evaporation gave 2.9 g of an oil. Chromatography on silica gel (Baker) using benzene–chloroform gave a clean mixture (9:1) of ketal **5** and **1a** (owing to deketalization during chromatography). Recrystallization of this mixture from methanol gave 780 mg (31%) of **5**: mp 81–84°; ir (Nujol) 1700 cm^{-1} (C=O); nmr δ 8.09 (d, 1, J = 2 Hz, H-5), 7.85 (dd, 1, J = 2, 9 Hz, H-7), 6.81 (d, 1, J = 9 Hz, H-8), 4.50–4.00 (m, 6), 3.87 (s, 3, OCH_3), 2.10 (t, 2, J = 6 Hz, CH_2CH_2C).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.21; H, 5.59.

General Hydrogenation Procedure in Aqueous Methanol.—Solutions of chromans in 30 ml/g of 90% aqueous methanol were hydrogenated for 18–20 hr in a stirred stainless steel autoclave at 1700–2100 psig at 100–110° using 200–300 mg/g of 5% ruthenium on carbon. The catalysts were removed by filtration and the filtrates concentrated. The moist residues were extracted with CH_2Cl_2, and the extracts washed with water, dried ($MgSO_4$), and concentrated.

Hydrogenation of 1a.—The general procedure was used for the hydrogenation of 1.00 g (4.85 mmol) of **1a**. Chromatography on silica gel (Woelm) of the 800 mg of crude product obtained gave 260 mg (27%) of 6-carbomethoxyhexahydrochroman (**7**, R = CH_3) in the 5% ethyl acetate–methylene chloride fractions as an oil: ir (neat) 1740 cm^{-1} (C=O); nmr δ 4.20–3.20 (m, 3, $CHOCH_2$), 3.68 (s, 3, OCH_3); mass spectrum m/e (rel intensity) 198 (7), 167 (8), 166 (8), 139 (3), 138 (10), 97 (100).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.85; H, 9.05.

The 20% ethyl acetate–methylene chloride fractions contained 160 mg (17%) of methyl 3-(3-hydroxypropyl)cyclohexanecarboxylate (**9**) as an oil: ir (neat) 3420 (OH), 1740 cm^{-1} (C=O); nmr δ 3.68 (s, 3, OCH_3), 3.64 (t, 2, J = 6 Hz, CH_2CH_2OH), 1.87 (s, 1, OH); mass spectrum m/e (rel intensity) 200 (0.7), 182 (3), 169 (3), 154 (3), 141 (17), 81 (100), 59 (12), 31 (17).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.07. Found: C, 66.11; H, 10.06.

The ethyl acetate fractions contained 290 mg (28%) of a mixture of 6-carbomethoxy-4-hexahydrochromanol isomers (**8**) as an oil: ir (neat) 3420 (OH), 1735 cm^{-1} (C=O); nmr δ 3.68 (s, OCH_3), 2.45 (s, OH); mass spectrum m/e (rel intensity) 214 (4), 213 (3), 197 (8), 196 (36), 113 (32), 81 (100), 80 (100), 57 (54).

Hydrogenation of 4.—The general procedure was used for the hydrogenation of 1.9 g (9.12 mmol) of **4**. Chromatography on silica gel (Woelm) of the 1.60 g of crude product obtained gave 740 mg (42%) of **6**, 410 mg (23%) of **7** (R = CH_3), and 390 mg of mixtures of **7** (R = CH_3), **10**, and **11** (18:14:1).

6-Carbomethoxychroman (**6**) was an oil: ir (neat) 1715 cm^{-1} (C=O); nmr δ 7.71 (m, 2, H-5 and -7), 6.80 (d, 1, J = 9 Hz, H-8), 4.20 (t, 2, J = 5 Hz, OCH_2CH_2), 3.86 (s, 3, OCH_3), 2.79 (t, 2, J = 6 Hz, CH_2CH_2Ar), 1.99 (m, 2, $CH_2CH_2CH_2$).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68,70; H, 6.19.

6-Carbomethoxyhexahydrochroman (**7**, R = CH_3) was identified by its nmr spectrum and elemental analysis, in agreement with material previously obtained (see above).

The mixtures of **7** (R = CH_3), **10**, and **11** were resolved by gas chromatography–mass spectra and examination of the mixture nmr spectra. 6-Carbomethoxy-4-methoxychroman (**10**): nmr δ 7.89 (m, H-5 and -7), 6.83 (d, J = 9 Hz, H-8), 4.59 (t, J = 6, H-4), 4.28 (m, OCH_2CH_2), 3.88 (s, CO_2CH_3), 3.40 (s, OCH_3), 2.08 (m, $CH_2CH_2CHCOCH_3$); mass spectrum m/e (rel intensity) 222 (65), 191 (100), 163 (27). 6-Carbomethoxy-4-methoxyhexahydrochroman (**11**): mass spectrum m/e (rel intensity) 228 (4), 197 (18), 127 (100).

Hydrogenation of 1a in Aqueous Ethanol.—A solution of 1.00 g (4.85 mmol) of **1a** in 20 ml of 80% aqueous ethanol was hydrogenated for 23 hr at 1600 psig at 100° using 150 mg of 5% ruthenium on carbon. The catalyst was removed by filtration and the filtrate concentrated. The moist residue was extracted with ether and the ethereal extract dried ($MgSO_4$). Evaporation gave 830 mg of an oil. This was directly subjected to a Jones oxidation,[8] producing 550 mg of an oil. The oil was partially separated using preparative thin layer chromatography on silica gel plates. This gave 70 mg (8%) of impure **6**, identified by its nmr and mass spectrum, and 310 mg (30%) of 6-carbethoxyhexahydrochroman (**7**, R = C_2H_5) as a crude oil: nmr δ 4.10 (quartet, J = 7 Hz, OCH_2CH_3), 3.68 (m, OCH_2CH_2), 1.25 (t, J = 7 Hz, OCH_2CH_3); mass spectrum m/e (rel intensity) 212 (28), 167 (84), 139 (44), 138 (100), 97 (100).

Hydrogenation of 1b.—The general procedure was used for the hydrogenation of 1.00 g (6.16 mmol) of **1b**. Vacuum distillation of the crude product gave 540 mg of an oil: bp 90–160° (3 mm). Gas chromatography indicated six components. Mass spectra allowed identification of a minor component, 6-methylchroman (**13**): mass spectrum m/e (rel intensity) 148 (10), 147 (100).

The two major components (amounting to >65% of the distillate) were collected by preparative gas chromatography. Both appeared to be isomers of 6-methyl-4-hexahydrochromanol (**12**). Collection gave 10 mg of the first component: mass spectrum m/e (rel intensity) 170 (28), 169 (13), 153 (17), 152 (99), 113 (100), 57 (70).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55, H, 10.65. Found: C, 70.73; H, 10.61.

Also obtained was 30 mg of the second component: ir (neat) 3340 cm^{-1} (OH); nmr δ 3.69 (m, OCH_2CH_2), 1.72 (s, OH), 0.96 (m, CH_3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.67; H, 10.79.

Hydrogenation of 1c.—The general procedure was used for the hydrogenation of 1.00 g (4.85 mmol) of **1c**. Chromatography on silica gel (Woelm) of the 830 mg of crude product obtained gave 140 mg 7-carbomethoxychroman (**14**) in the 1% ethyl acetate–methylene chloride fraction as an oil: ir (neat) 1720 cm^{-1} (C=O); nmr δ 7.54 (m, 2, H-6 and -8), 7.09 (d, 1, J = 9 Hz, H-5), 4.19 (t, 2, J = 5 Hz, OCH_2CH_2), 3.87 (s, 3, OCH_3), 2.81 (t, 2, J = 6 Hz, CH_2CH_2Ar), 2.01 (m, 2, $CH_2CH_2CH_2$).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.78; H, 6.40.

The 10% ethyl acetate–methylene chloride fractions contained 190 mg (20%) of 7-carbomethoxyhexahydrochroman (**15**) as an oil: ir (neat) 1735 cm^{-1} (C=O); nmr δ 4.00 to 3.60 (m, 3, $CHOCH_2$), 3.68 (s, 3, OCH_3); mass spectrum m/e (rel intensity) 198 (8), 167 (14), 139 (13), 138 (35), 97 (100).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15; Found: C, 66.75; H, 9.26.

The 20% ethyl acetate–methylene chloride fractions contained 160 mg of a mixture of **17** and **18** (3:1) with a trace of **15** present. The mixture was resolved by gas chromatography–mass spectra and examination of the mixture nmr spectrum. 7-Carbomethoxy-4-chromanol (**18**): nmr δ 7.48 (m, Ar H), 4.75 (t, J = 5 Hz, H-4), 4.24 (t, J = 5 Hz, OCH_2CH_2), 3.84 (s, OCH_3); mass spectrum m/e (rel intensity) 208 (67), 207 (8), 190 (8), 177 (25), 149 (100). Methyl 4-(3-hydroxypropyl)-cyclohexanecarboxylate (**17**): nmr δ 3.68 (s, OCH_3), 3.55 (t, J = 6 Hz, CH_2CH_2OH), 2.23 (s, OH); mass spectrum m/e (rel intensity) 200 (3), 182 (12), 169 (13), 154 (7), 141 (38), 81 (100), 59 (30), 45 (10), 31 (33).

The ethyl acetate fractions contained 360 mg (35%) of a mixture of 7-carbomethoxy-4-hexahydrochromanol isomers (**16**) as an oil: ir (neat) 3420 (OH), 1730 cm^{-1} (C=O); nmr δ 3.68 (s, OCH_3), 2.01 (s, OH); mass spectrum m/e (rel intensity) 214 (0.6), 196 (7), 113 (9), 57 (59), 41 (100).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.82; H, 8.66.

Acknowledgments.—We wish to thank Dr. Robert L. Augustine for his suggestions and Mr. Regis Pellet for the mass spectra. One of us (G. S.) wishes to express appreciation to Merck and Co. for financial assistance.

Registry No.—**1a**, 41118-19-8; **1b**, 39513-75-2; **1c**, 41118-21-2; **4**, 41118-22-3; **5**, 41118-23-4; **6**, 41118-24-5; **7** (R = CH_3), 41118-25-6; **7** (R = C_2H_5), 41118-26-7; **8**, 41118-27-8; **9**, 41118-28-9; **10**, 41118-29-0; **11**, 41118-30-3; **12**, 41174-27-0; **13**, 3722-74-5; **14**, 41118-24-5; **15**, 41118-33-6; **16**, 41118-34-7; **17**, 41118-35-8; **18**, 41118-36-9.

Reactions of Cyclopentadienylidenetriphenylphosphorane (Phosphafulvene)

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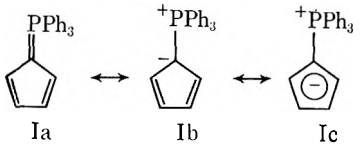
Attempts have been made to carry out the reactions of cyclopentadienylidenetriphenylphosphorane (phosphafulvene, I) with a number of dienophiles and electrophiles. From its reaction behavior toward the reagents, I has been found not to exhibit chemical properties expected for ylene and ordinary ylide compounds, but to have aromatic character in the cyclopentadienyl ring. The reactivity and the reaction position are discussed in terms of the results obtained from Hückel MO calculations.

The system investigated in this study is the dipolar mesomeric system, cyclopentadienylidenetriphenylphosphorane (I), whose skeleton is constructed of a cyclopentadienyl ring and an exocyclic phosphorus atom. This type of molecule is reminiscent of the carbon analog, fulvene. The dipole moment of dimethylfulvene is reported as only 1.44 D,[1] indicating that the nonpolar covalent structure dominantly contributes to its ground state. Actually, fulvenes act as both dienes and dienophiles in the Diels–Alder reaction, although some electrophilic substitutions of I are reported to occur.[2] On the other hand, since I shows a considerably large dipole moment of 7.0 D,[3] dipolar structures (Ib, Ic) other than covalent structure (Ia) might be important in the resonance hybrid of I.



Ia Ib Ic

Ramirez, *et al.*,[3] who first synthesized I, suggested its aromatic character from the experimental result[4] that diazo coupling took place on the cyclopentadienyl ring of I. They also described roughly equal contributions of ylene (Ia) and negative-charge delocalized ylide (Ic) structures, because its observed dipole moment (7.0 D)[3,5] corresponds to just the average value between the calculated moment 0.0 D for Ia and 14.0 D for Ic. In this prediction, however, only the π moment is taken into account, but the σ moment in the opposite direction is not. This situation prompted us to elucidate further the electronic structure of I. This could allow a better understanding of the nature of the d orbitals of I. In the first place, the electronic spectrum of cyclopentadienylidenetri-*n*-propylphosphorane (II), which was recently synthesized in order to simplify the spectrum, was measured in our laboratory and the observed intramolecular charge-transfer absorption band was theoretically treated by the semiempirical "molecules in molecule method."[6] Consequently, it was concluded that the polar ylide structure (Ib or Ic) dominantly contributes to the resonance hybrid of II in the ground state. As a next step, the reaction behavior of I toward a variety of reagents were studied. First, the reactions of I with dienophiles such as dialkyl acetylenedicarboxylate, tetracyanoethylene, and maleimide, and subsequently the reactions of I with various electrophiles, benzaldehyde and dichlorocarbene, were attempted. Here we wish to report the reaction behavior of I toward these reagents which are in marked contrast with those of fulvene. The reactivity of I is discussed in terms of the ionization potentials calculated by Hückel MO theory, and the reaction position predicted from electron transfer theory,[7] superdelocalizabilities,[8] and localization energies[9] are compared with the experimental results.

Results and Discussion

Reaction with Dienophiles.—The investigation of reaction behavior of I with dienophiles is interesting in comparison with those of fulvene, and also useful for determining whether I behaves as the ylene (Ia) or ylide (Ib, Ic). The reaction of I with electron-deficient unsaturated compounds such as dialkyl acetylenedicarboxylate, tetracyanoethylene,[10] and maleimide, which are known to be reactive dienophile as well as weak electrophile, was attempted. The reaction procedures and the spectral data of the products III, IV, and V (Figure 1) were described in our previous communication.[11] All the products were Michael addition reaction products by electrophilic attack on the cyclopentadienyl ring in I. No evidence for the Diels–Alder reaction was obtained. Even in the reaction of I with good dienophiles such as norbornadiene and 1,2-diphenylcyclopropene, Diels–Alder reaction did not take place.

Reactions with Electrophiles.—As mentioned above, since the reaction behavior of I with the dienophiles strongly supported the electron-rich 5C 6π aromatic character of the cyclopentadienyl ring of I, the reactions of I with several electrophiles have been carried out. The reaction products are summarized in Figure 1.

Discussion of nitration, nitrosation, bromination, and Vilsmeier reactions including structure proof were described in our previous communication.[12] The exclusive formation of 2-substituted derivatives was chemically proved in the case of nitrosation reaction.[12]

(1) G. W. Wheland and D. E. Mann, *J. Chem. Phys.*, **17**, 264 (1969).
(2) J. H. Day, *Chem. Rev.*, **53**, 167 (1953).
(3) F. Ramirez and S. Levy, *J. Amer. Chem. Soc.*, **79**, 67 (1957).
(4) F. Ramirez and S. Levy, *J. Amer. Chem. Soc.*, **79**, 6167 (1957).
(5) The dipole moment of I in benzene solution at 25° was also measured in our laboratory. Since the calculated molar reflection which is used to evaluate the observed dipole moment is dependent on atomic refractions, the difference of the atomic refractions for the ylide and for the ylene structures might affect the observed dipole moment values. Our observed values for I are 6.89 and 6.87 for the ylide and the ylene structures, respectively, both of which are nearly identical and in good agreement with that obtained by Ramirez, *et al.*
(6) (a) Z. Yoshida, K. Iwata, and S. Yoneda, *Tetrahedron Lett.*, 1517 (1971); (b) K. Iwata, S. Yoneda, and Z. Yoshida, *J. Amer. Chem. Soc.*, **93**, 6745 (1971).
(7) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 563 (1954).
(8) K. Fukui, T Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jap.*, **27**, 423 (1954); *J. Chem. Phys.*, **27**, 1247 (1957).
(9) G. W. Wheland, *J. Amer.Chem. Soc.*, **64**, 900 (1940).
(10) E. Lord, P. Naan, and C. D. Hall, *J. Chem. Soc. B*, 213 (1971).
(11) Z. Yoshida, S. Yoneda, H. Hashimoto, and Y. Murata, *Tetrahedron Lett.*, 1527 (1971).
(12) Z. Yoshida, S. Yoneda, Y. Murata, and H. Hashimoto, *Tetrahedron Lett.*, 1523 (1971).

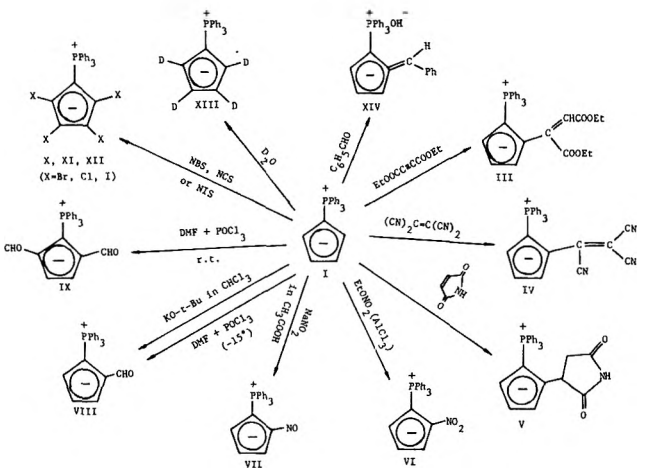


Figure 1.—Reactions of I with electrophiles and dienophiles.

The pmr data also supported the substitution of the 2 position. For instance, the pmr spectrum of the nitration reaction product (VI) showed three peaks of equal area centered at τ 2.85 (1 H), 2.90 (1 H), and 3.70 (1 H) besides the phenyl proton signal at τ 2.2–2.5 (15 H) as seen in Figure 2b. Among these three peaks (τ 2.85, 2.90, and 3.70), one peak at τ 3.70 is located within the signal due to the cyclopentadienyl ring protons of the parent compound (Figure 2a),[13] and the other two peaks shift downfield. This is readily interpreted if the nitro group is attached to the 2 position of I; *i.e.*, two electron-withdrawing substituents (phosphonium and nitro groups) should make the two protons at the 3 and 5 positions shift to lower field. Such interpretation might be applicable for III, IV, VII, and VIII.[16]

Tetrachloro and tetraiodo derivatives (XI and XII) were prepared by treatment of I with 4 mol of *N*-chloro- and *N*-iodosuccinimide at room temperature, respectively. It is noteworthy that the halogenation of I with even a small quantity of *N*-halosuccinimide exclusively afforded the tetrahalo derivatives.

Deuteration proceeded easily to give the tetradeuterio derivative (XIII), which was shown by the nmr spectrum. When deuterium oxide was added to a solution of I in deuteriochloroform, the multiplet at τ 3.4–3.8 corresponding to the cyclopentadienyl protons decreased gradually, and after 1 hr the signal was gone.

Reactions of I with Benzaldehyde.—The resonance structure (Ib), in which the negative charge is localized on the carbon adjacent to the phosphorus atom, is also considered to be important in the resonance hydrid of I. If Ib is important in the transition state, the reaction expected of phosphorus ylides might take place. The reaction of I with benzaldehyde in tetrahydrofuran at ice temperature as well as at room temperature was carried out; in both cases, only a wine-red crystalline product (XIV, 185° dec) was obtained. The elemental analysis ($C_{30}H_{25}OP$) did not correspond to the Wittig

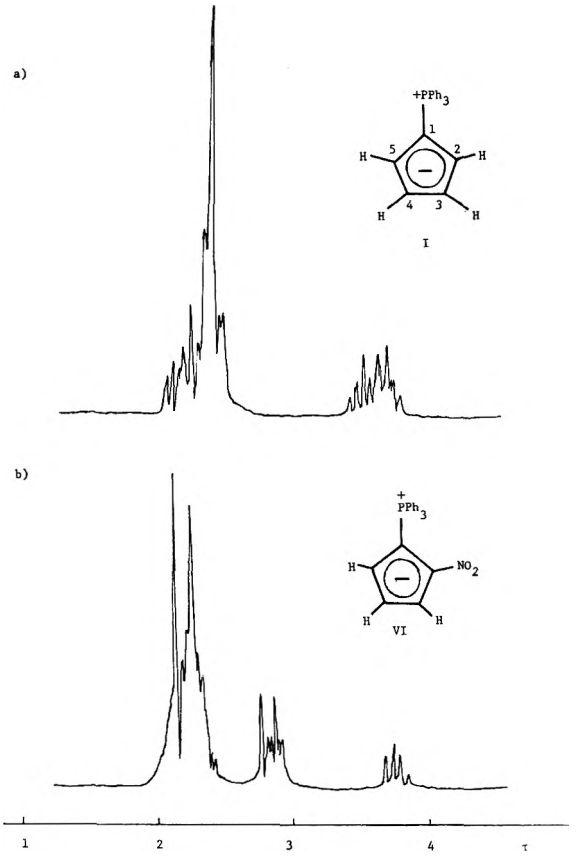
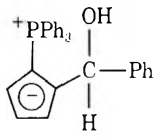


Figure 2.—The nmr spectra of I and VI.

reaction product (6-phenylfulvene) but to a compound represented as XIV. The nmr spectrum of XIV in



XIV

DMSO-d_6 showed a singlet at τ 1.5 (1 H, methine) and two multiplets at τ 1.8–3.0 (20 H, phenyl) and at 3.1–3.6 (3 H, cyclopentadienyl). The existence of OH was confirmed by the observation of ν_{OH} (3500 cm^{-1}) and the displacement of OH with BF_4^- by the addition of HBF_4 to XIV. These spectral data support the structure given above. No evidence of the Wittig reaction was obtained. This is rather surprising, because, even fluorenylidenetriphenylphosphorane which is the dibenzo derivative of I easily reacts with benzaldehyde to give triphenylphosphine oxide and benzalfluorene in excellent yield.[17] This striking aspect of I can be interpreted as the reflection of the minor contribution of the negative-charge localized structure Ib to the resonance hybrid. The negative charge is considered not to be concentrated at the carbon adjacent to the phosphorus atom, but to be delocalized over the cyclopentadienyl ring of I. The formation of XIV clearly indicates a large contribution of the charge-delocalized resonance structure Ic. The difference between the reaction behavior of I and that of fluorenylidenetriphenylphosphorane might be explained by comparing

(13) The signal due to the cyclopentadienyl ring protons is expected to be an AA'BB' pattern,[14] but it is very complicated[15] because of spin–spin coupling with phosphorus as shown in Figure 2a.

(14) In the pmr spectrum of dimethylsulfonium cyclopentadienylide, which is an analog of I, an AA'BB' pattern was observed: Z. Yoshida, S. Yoneda, and M. Hazama, *Chem. Commun.*, 716 (1971).

(15) The pmr spectrum of the cyclopentadienyl ring of I has been completely analyzed: W. B. Smith, W. H. Watson, and S. Chiranjeevi, *J. Amer. Chem. Soc.*, **89**, 1438 (1967).

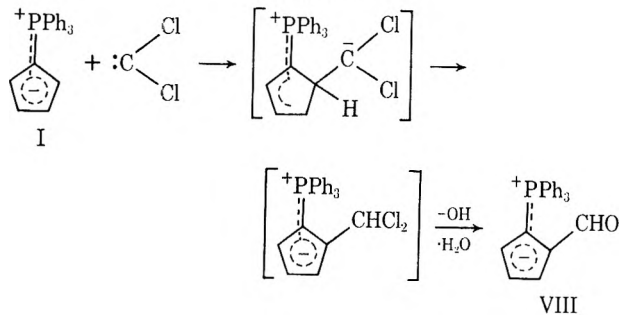
(16) These pmr data are in the Experimental Section.

(17) A. W. Johnson, *J. Org. Chem.*, **24**, 282 (1957).

the pK_a values of 4.69[18] for I with that of 7.5 for fluorenylidenetriphenylphosphorane.[19]

Reactions of I with Dichlorocarbene.—Treatment of I in chloroform with potassium *tert*-butoxide at 0° gave the monoformyl derivatives of I (VIII). This was confirmed by a mixture melting point (221–222°) method with an authentic sample prepared by the method previously described in this paper. No products other than VIII were detected on tlc of the reaction mixture. The reaction mechanism can reasonably be presented as shown in Scheme I. Again it should be noted that

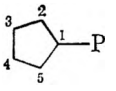
SCHEME I



the reaction behavior of I with the electrophilic dichlorocarbene is quite different from that of indenylidene- and fluorenylidenetriphenylphosphorane. In the latter cases, the reaction yielded triphenylphosphine and the corresponding olefins, *i.e.*, dichloromethyleneindene and -fluorene.[20] Consequently, it could be concluded that the negative-charge delocalized ylide structure (Ic) displays a more important role than the negative-charge localized one (Ib) in the reaction of I.

Hückel MO Treatment.—In the 6π-electron system (I) the Hückel MO calculation was carried out. The Coulomb integrals (α_P) and the resonance integrals (β_{C-P}) were taken as follows.

$$\alpha_P = \alpha + \delta_P\beta \quad (1)$$



Here the coefficient δ_P was estimated from the ionization potential[6] (I_P) of the 3d orbital of phosphorus atom by using eq 2. The other Coulomb integrals are given in

$$\delta_P = I_p - 7.2/3.0 = 2.06 - 7.2/3.0 = -1.71 \quad (2)$$

eq 3 and 4. The resonance integral for the C–P bond

$$\alpha_1 = \alpha - 0.1\beta \quad (3)$$

$$\alpha_2 = \alpha_3 = \alpha_4 = \alpha_5 = \alpha \quad (4)$$

is given in eq 5. The value of K_{C-P} was estimated by

$$\beta_{C-P} = K_{C-P}\beta \quad (5)$$

Jaffe's table[21] using effective nuclear charges for the 3d orbital ($Z_p = 1.39$).[22] The resonance integrals for all the C–C bonds are taken to be β. Solving the secular equation by using the above parameters, energy levels and wave functions were obtained (Table I).

(18) The pK_a values of I was determined by the potentiometric titration in 50 vol. % methanol solution.

(19) A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

(20) M. Okano, Y. Ito, and R. Oda, *Tetrahedron Lett.*, 6 (1964).

(21) H. H. Jaffe, *J. Chem. Phys.*, **21**, 258 (1953).

(22) D. W. J. Cruickshank and B. C. Webster, *J. Chem. Phys.*, **40**, 3733 (1964).

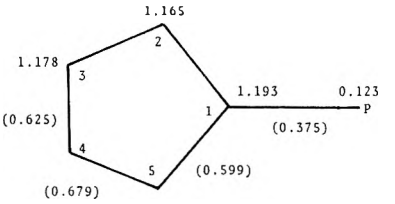


Figure 3.—The π-electron density and the π-bond order of I.

TABLE I

ENERGY LEVELS AND WAVE FUNCTIONS OF I

Energy level (β)	Wave function					
	P	1	2	3	4	5
−2.323	0.108	0.463	0.444	0.435	0.435	0.444
−1.618	0.223	0.618	0.151	−0.511	−0.511	0.151
−1.212	−0.000	−0.000	−0.602	−0.372	0.372	0.602
0.618	0.609	0.349	−0.459	0.207	0.207	−0.459
0.704	0.000	0.000	0.372	−0.602	0.602	−0.372
2.021	0.753	−0.531	0.263	−0.079	−0.079	0.263

The calculated ionization potential of -0.618β (8.60 eV) is an extremely small values. Therefore, the reaction of I with electrophilic reagents should easily take place. The molecular diagram of I is shown in the Figure 3. All the π-bond order values of 0.599 for the C_1–C_2 bond, 0.679 for the C_2–C_3 bond, and 0.625 for the C_3–C_4 bond are within the aromatic range (0.5–0.7) proposed by Streitwieser.[23] From the π-electron distribution, the π electron is shown to migrate from the cyclopentadienyl ring to phosphorus atom by only 0.123 which agrees with the prediction[6] that the ylide structure rather then the ylene structure is much important in the resonance hybrid of I. The remainder of the negative charge is delocalized almost homogeneously over the five-membered ring. The order of π-electron densities (q_r) is $q_1 > q_3 > q_2$. Therefore, electrophilic attack would be predicted to occur at the 1 position. However, the π-electron density is a reaction index in the unperturbed state of the molecule. More reliable reaction indices such as the superdelocalizabilities (S_E),[8] the localization energies (L_r),[9] and the free valences (F_r) of the reaction intermediate in electron-transfer theory[7] were evaluated and are given in Table II. The localization energy is the energy difference

TABLE II

REACTION INDICES OF I

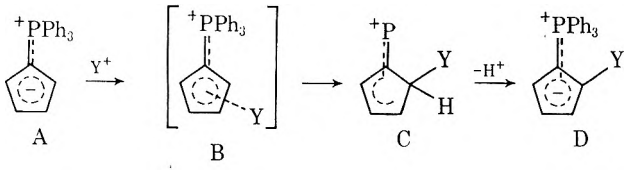
	q_r	f_r[a]	S_E	F_r	$L(-\beta)$
P	0.123	0.000	0.152		
C_1	1.193	0.000	1.297	0.159	2.215
C_2	1.165	0.724	1.431	0.678	2.016
C_3	1.178	0.276	1.377	0.513	2.062
C_4	1.178	0.276	1.377	0.513	2.062
C_5	1.165	0.724	1.431	0.678	2.016

[a] Frontier electron density.

between the ground state (A) and the intermediate state (C) in Scheme II. The free valences of the intermediate (B) is one of the good reaction indices in a system where electron transfer easily takes place. The discussion in terms of electron transfer theory has been already described in more detail in our previous publication.[12] As seen in the Table II, all the reaction

(23) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 172.

SCHEME II



indices which do not involve π-electron density indicate that the electrophilic attack should take place at the 2 or 5 position, in good agreement with the experimental results.

The fact that the reaction of I with most electrophilic reagents such as NO_2^+, NO^+, etc, gave monosubstituted or, at most, disubstituted derivatives of I (only the halogenation afford tetrasubstituted ones) can be rationalized by ionization potentials calculated from Hückel MO method. The calculated ionization potentials (E_{ho}, energy of the highest occupied MO) of several substituted derivatives are listed in Table III.

TABLE III
IONIZATION POTENTIALS OF THE DERIVATIVES OF I

Substituent	NO_2	NO	Cl	Br
Unsubstituted	0.618	0.618	0.618	0.618
5	0.694	0.697	0.577	0.582
2,5	0.721	0.742	0.540	0.550
2,3,5			0.522	0.535
2,3,4,5			0.511	0.526

In the case of attack by NO_2^+ or NO^+, the ionization potentials are shown to increase with increasing substitution. This indicates that the subsequent electrophilic substitution become difficult. On the other hand, the ionization potential decreases with halogen substitution and this accounts for the fact that the tetrahalo derivative is exclusively obtained in the halogenation.

Experimental Section

Spectra.—Ultraviolet spectra were taken on Hitachi EPS-3T photometer. Infrared spectra were recorded on a Hitachi grating infrared spectrophotometer Model-215. Nmr spectra were recorded on a Jeolco C-60H nmr spectrometer.

Cyclopentadienylidenetriphenylphosphorane (I).—I was prepared by the method of Ramirez[3] and had mp 230–231° (lit. 229–231°).

Triphenylphosphonium-α,β-carboethoxyvinylcyclopentadienylide (III).—To a stirred solution of 1.94 g (0.006 mol) of I in 30 ml of methylene chloride was added dropwise a solution of 1.0 g (0.006 mol) of diethyl acetylenedicarboxylate in methylene chloride at room temperature. The solution was yellow and immediately turned to reddish orange. The reaction mixture was allowed to stand for an additional 30 min at room temperature and poured with stirring into 50 ml of *n*-hexane. The yellow precipitate which deposited was collected by filtration, washed with ethanol, and recrystallized from methylene chloride–ethanol to afford III as yellow crystals in almost quantitative yield: mp 224–225°; ir (KBr) $\nu_{C=O}$ 1687, 1725 cm^{-1}; uv max (MeOH) 225 mμ (log ϵ 4.56), 269 (4.04), 394 (4.23); nmr ($CDCl_3$) τ 2.1–2.6 (m, 1.5 H, phenyl), 3.2, 3.7, 4.0 (each m, 1 H, cyclopentadienyl), 5.28 (s, 1 H, vinyl), 5.10 (q, 2 H, methylene), 6.15 (q, 2 H, methylene), 8.15 (t, 3 H, methyl), 9.05 (t, 3 H, methyl).

Anal. Calcd for $C_{31}H_{29}O_4P$: C, 74.98; H, 5.88. Found: C, 74.88; H, 6.04.

Triphenylphosphonium-2-tricyanovinylcyclopentadienylide (IV).—To a suspension of 2.55 g (0.0098 mol) of I in tetrahydrofuran (60 ml) was added at 10° a solution of 1.0 g (0.0098 mol) of tetracyanoethylene in tetrahydrofuran (10 ml). The reaction mixture immediately turned orange and gradually become reddish orange. The reaction mixture was allowed to stir for 3 hr at the same temperature, concentrated by evaporation, and chromatographed on alumina using methylene chloride as the eluent. The solvent was removed under reduced pressure from the reddish orange colored eluate, and the residue was recrystallized from chloroform–*n*-hexane to afford IV as reddish orange crystals in 40% yield: mp 218–219°; ir (KBr) $\nu_{C=N}$ 2220 cm^{-1}; uv max (MeOH) 223 mμ (log ϵ 4.55), 267 (4.02), 462 (4.63); nmr ($CDCl_3$) τ 2.1–2.6 (m, 16 H, phenyl and cyclopentadienyl), 3.2 (m, 1 H, cyclopentadienyl), 3.7 (m, 1 H, cyclopentadienyl).

Anal. Calcd for $C_{23}H_{18}N_3P$: C, 78.67; H, 4.24; N, 9.82. Found: C, 78.30; H, 4.54; N, 9.83.

The above reaction in the presence of triethylamine gave IV in quantitative yield.

Preparation of V.—A solution of 2.0 g (0.0061 mol) of I and 0.3 g (0.0031 mol) of maleimide in dioxane (40 ml) was refluxed for 15 hr and chromatographed over cellulose powder using benzene as the eluent. Solvent was removed from the eluate, and the residue was repeatedly recrystallized from methanol–benzene to give V in 50% yield: mp 195–196°; ir (KBr) $\nu_{C=O}$ 1700, 1770 cm^{-1}; uv max (methylene chloride) 269 mμ (log ϵ 4.04), 295 (3.83), 475 (1.30); nmr ($CDCl_3$) τ 1.7 (s, 1 H, NH), 2.0~2.6 (m, 1.5 H, phenyl), 3.5–3.8 (m, 3 H, cyclopentadienyl), 5.85 (t, J = 6.8 Hz, 1 H, methyne), 6.90 (d, J = 6.8 Hz, 2 H, methylene).

Anal. Calcd for $C_{27}H_{22}NO_2P$: C, 79.61; H, 5.65. Found: C, 79.52; H, 5.43.

Reaction of I with Norbornadiene (or 1,2-Diphenylcyclopropene).—Following the procedure employed in the preparation of III, IV, and V, the reaction of I with norbornadiene (or 1,2-diphenylcyclopropene) was carried out. After work-up of the mixture, I was quantitatively recovered.

Triphenylphosphonium-2-nitrocyclopentadienylide.—To a stirred solution of 1.0 g (0.0031 mol) of I in 30 ml of chloroform was added 2.0 g of aluminum chloride and 0.56 g (0.0061 mol) of ethyl nitrate at room temperature under nitrogen atmosphere, and the mixture was stirred for 3 hr at 40°. The reaction mixture was chromatographed on alumina using methylene chloride as an eluent, the solvent was removed from the eluate, and the residue was recrystallized from methylene chloride–ethanol to yield triphenylphosphonium-2-nitrocyclopentadienylide (VI) in 80% yield: mp 243–44°; ir (KBr) $\nu_{as\text{-}NO_2}$ 1465 cm^{-1}, $\nu_{s\text{-}NO_2}$ 1382 cm^{-1}; uv max (acetonitrile) 222 mμ (log ϵ 4.59), 266 (3.78), 372 (4.33); nmr ($CDCl_3$) τ 2.2–2.6 (m, 15 H, phenyl), 2.85 (m, 1 H, cyclopentadienyl), 2.90 (m, 1 H, cyclopentadienyl), 3.7 (m, 1 H, cyclopentadienyl).

Anal. Calcd for $C_{23}H_{18}O_2NP$: C, 74.39; H, 4.89; N, 3.78. Found: C, 74.22; H, 5.11; N, 3.50.

Triphenylphosphonium-2-nitrosocyclopentadienylide.—To a solution of 1.0 g (0.0031 mol) of I in acetic acid was added dropwise aqueous sodium nitrite (0.214 g, 0.0031 mol) for 10 min at 0–5°. After stirring an additional 20 min at the same temperature, the reaction mixture was neutralized with aqueous sodium hydroxide at 0°. A green precipitate deposited, which was separated by filtration, washed several times with water, and chromatographed on alumina to give triphenylphosphonium-2-nitrosocyclopentadienylide (VII) in almost quantitative yield as dark green crystals: mp 210° dec; uv max (MeOH) 268 mμ (log ϵ 3.67), 360 (3.94); nmr ($CDCl_3$) τ 2.3–2.8 (m, 15 H phenyl), 3.0 (m, 1 H, cyclopentadienyl), 3.5 (m, 1 H, cyclopentadienyl), 3.8 (m, 1 H, cyclopentadienyl).

Anal. Calcd for $C_{23}H_{18}ONP$: C, 77.75; H, 5.35, N, 3.94, P, 8.72. Found: C, 77.60; H, 5.32, N, 3.88, P 8.74.

The position of substitution was confirmed as follows. To a mixture of aniline (1 ml) and glacial acetic acid (3 ml) was added dropwise a solution of 1.0 g of VII in ethanol at room temperature. After stirring for 12 hr at 90–100°, the reaction mixture was poured into water, and the brown precipitate that separated was filtered and chromatographed on silica gel to give orange crystals: mp 238–240°; uv max (EtOH) 220 mμ (log ϵ 4.70), 4.55 (4.25). This compound was identified as triphenylphosphonium-2-phenylazocyclopentadienylide[4] by a mixture melting point method, its uv spectrum, and R_f value.

Triphenylphosphonium-2-formylcyclopentadienylide (VIII).—The Vilsmeier reagent was prepared as follows. To 40 ml (0.52 mol) of *N*,*N*-dimethylformamide was added 16.1 ml (0.18 mol) of phosphorus oxychloride at −15 to −10° under nitrogen atmosphere, and the mixture was kept at the same temperature for 10

min. To this solution, 26.1 g (0.080 mol) of I was slowly added maintaining the temperature at −15 to −10°. The mixture was allowed to stand until room temperature. The reddish orange reaction mixture was poured into ice–water, and the precipitate was collected and chromatographed on alumina to give an orange solid (VIII) in 70% yield: mp 221–222° dec; ir (KBr) $\nu_{C=O}$ 1630 cm^{-1}; uv max (acetonitrile) 224 mμ (log ε 4.42), 268 (4.00), 372 (4.31); nmr ($CDCl_3$) τ 0.35 (s, 1 H, formyl), 2.2–2.6 (m, 15 H, phenyl), 3.1 (m, 1 H, cyclopentadienyl), 3.6 (m, 2 H, cyclopentadienyl).

Anal. Calcd for $C_{24}H_{19}OP$: C, 81.35; H, 5.40; P, 8.74. Found: C, 81.01; H, 5.17; P, 9.18.

Triphenylphosphonium-2,5-diformylcyclopentadienylide (IX).—Phosphorus oxychloride, 40.4 ml (44.0 mmol), was added dropwise at 0–5° to a stirred solution of 6.52 g (20 mmol) of I in 40 ml of *N*,*N*-dimethylformamide under a nitrogen atmosphere. After the reaction proceeded for 2 hr at room temperature, the mixture was poured into ice–water and neutralized with aqueous sodium hydroxide. The light orange precipitate which deposited was collected by filtration, washed with water, and purified by reprecipitation from methylene chloride–methanol to give IX as a light pink solid in 80% yield: mp 225–227° dec; ir (KBr) $\nu_{C=O}$ 1640 cm^{-1}; uv max (acetonitrile) 220 mμ (log ε 4.29), 268 (4.21), 310 (4.01); nmr ($CDCl_3$) τ 0.2 (d, J = 1.5 Hz, 2 H, formyl), 2.0–2.5 (m, 15 H, phenyl), 2.95 (d, J = 5.0 Hz, 2 H, cyclopentadienyl).

Anal. Calcd for $C_{25}H_{19}O_2P$: C, 78.53; H, 5.01. Found: C, 78.31; H, 5.28.

Triphenylphosphonium-2,3,4,5-tetrabromocyclopentadienylide (X). **A.**—Bromine, 3.52 g (0.022 mol), was added dropwise to a stirred suspension of potassium *tert*-butoxide in acetonitrile at room temperature. After stirring additional 2 hr, the reaction mixture was poured into water, and the brown precipitate which separated was collected by filtration, washed with methanol, and recrystallized from methylene chloride–benzene to afford X (40% yield) as white crystals: mp 224–225° dec; uv max (acetonitrile) 225 mμ (log ε 4.51), 268 (4.15), 310 (sh); nmr ($CDCl_3$) τ 2.1–2.7 (m, 15 H, phenyl).

Anal. Calcd for $C_{23}H_{15}Br_4P$: C, 43.03; H, 2.33. Found: C, 43.04; H, 2.28.

B.—A solution of 7.74 g (0.044 mol) of *N*-bromosuccinimide in acetonitrile (10 ml) was added to a suspension of 3.26 g (0.01 mol) of I at room temperature. After stirring for 30 min and work-up afforded X in 90% yield.

Triphenylphosphonium-2,3,4,5-tetrachlorocyclopentadienylide (XI).—The reaction of I with *N*-chlorosuccinimide was carried out by the same procedure as above and worked up to afford XI as a white solid in 82% yield: mp 234–235°; uv max (acetonitrile) 268 mμ (log ε 3.89); nmr ($CDCl_3$) τ 2.1–2.7 (m, 15 H, phenyl).

Anal. Calcd for $C_{23}H_{15}Cl_4P$: P, 6.68; Cl, 30.55. Found: P, 6.35; Cl, 30.29.

Triphenylphosphonium-2,3,4,5-tetraiodocyclopentadienylide (XII).—The reaction of I with *N*-iodosuccinimide was carried out by the same procedure as above, and worked up to afford XII as white yellow solid in 87% yield: mp 204–205°; uv max (acetonitrile) 260 mμ (log ε 4.25), *ca.* 300 (sh).

Anal. Calcd for $C_{23}H_{15}I_4P$: P, 3.73. Found: P, 3.60.

Reaction of I with Benzaldehyde.—To a cooled solution of 3.26 g (0.01 mol) in tetrahydrofuran was added dropwise a solution of 1.06 g (0.01 mol) of benzaldehyde at room temperature. After reaction for 3 hr, the reddish violet solution was evaporated under reduced pressure, and the residue was chromatographed on polyamide using methylene chloride as an eluent. After removal of the solvent under reduced pressure from the eluate, the residue was recrystallized from methanol–ether to yield wine-red crystals (XIV), which decomposed at 185°: uv max (MeOH) 267 mμ (log ε 3.6), 315 (3.4), 520 (2.8); ir (KBr) ν_{OH} 3500 cm^{-1}; nmr (DMSO-d_6) τ 1.5 (s, 1 H, methyne), 1.8–3.0 (m, 20 H, phenyl), 3.1–3.6 (m, 3 H, cyclopentadienyl).

Anal. Calcd for $C_{30}H_{25}OP$: C, 83.31; H, 5.82; P, 7.16. Found: C, 84.13; H, 6.09; P, 6.45.

Reaction of I with Dichlorocarbene.—When 5.0 g (0.04 mol) of dry powdered potassium *tert*-butoxide was slowly added to a solution of 4.0 g (0.012 mol) of I dissolved in 200 ml of chloroform at 0–5° under a nitrogen atmosphere, the original yellow color of solution changed to dark red. After 2 hr at room temperature, the reaction mixture was poured into ice–water, and the organic layer was collected, dried over magnesium sulfate, and evaporated under reduced pressure. The oily residue was chromatographed on alumina to yield a light pink solid in 3.2% yield, mp 221–222°. This product was identical with triphenylphosphonium-2-formylcyclopentadienylide (VIII). A trace of triphenylphosphine oxide (mp 156–157°) and the starting material (I) were also obtained.

Acknowledgment.—The authors are very grateful for the experimental assistance of Messrs. H. Hashimoto, H. Takimoto, and T. Yato.

Registry No.—I uncharged form, 2224-32-0; I charged form, 29473-30-1; III uncharged form, 34411-82-0; III charged form, 33356-41-1; IV uncharged form, 15924-42-2; IV charged form, 33356-42-2; V uncharged form, 34411-84-2; V charged form, 33356-43-3; VI uncharged form, 41172-19-4; VI charged form, 41172-20-7; VII uncharged form, 41265-38-7; VII charged form, 41172-21-8; VIII uncharged form, 34299-42-8; VIII charged form, 41172-23-0; IX uncharged form, 33082-53-0; IX charged form, 41172-25-2; X uncharged form, 33082-54-1; X charged form, 41172-27-4; XI uncharged form, 41172-28-5; XI charged form, 41172-29-6; XII uncharged form, 41172-30-9; XII charged form, 41172-31-0; XIV uncharged form, 41172-32-1; XIV charged form, 41172-33-2.

A New Fungal Lactone, LL-P880β, and a New Pyrone, LL-P880γ, from a *Penicillium* sp.

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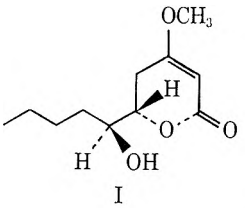
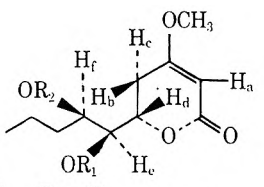
The novel metabolites LL-P880β or (6*S*,1′*S*,2′*R*)-4-methoxy-5,6-dihydro-6-(1′,2′-dihydroxypentyl)-2*H*-pyran-2-one and LL-P880γ or 4-methoxy-6-(1′,2′-dihydroxypentyl)-2*H*-pyran-2-one (as the acetate) have been isolated from an unidentified *Penicillium* sp. Use was made of the exciton chirality method to assign the stereochemistry of LL-P880β.

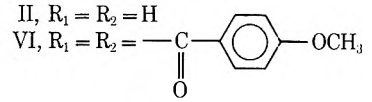
In connection with work on the antiprotozoal principles of fermentations of an unidentified *Penicillium* sp. (Lederle culture P880), we isolated the dihydropyrone I.[1] We now report the structures of two minor metabolites, II and III, from the same culture and the use of the exciton chirality method[2] to determine the stereochemistry of the vicinal glycol in II.

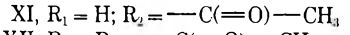


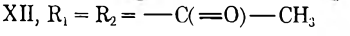
I

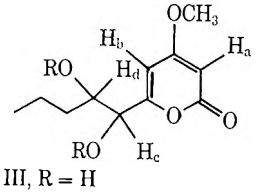


II, $R_1 = R_2 = H$

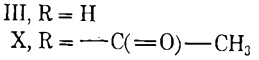
VI, $R_1 = R_2 =$ 

XI, $R_1 = H$; $R_2 =$ 

XII, $R_1 = R_2 =$ 



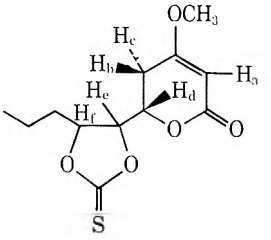
III, R = H

X, R = 

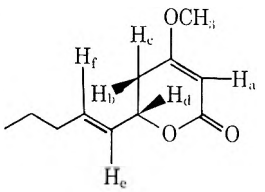
Strong ir bands at 1705 and 1640 cm^{-1}, a uv maximum at 234 nm (ε 13,800), and an nmr methoxyl signal at δ 3.80 in the various spectra of LL-P880β indicate that the unsaturated δ-lactone of I exists intact in this metabolite. A major fragmentation in the mass spectrum of the material results from the loss of a propyl group to give the peak *m/e* 187. Another large peak at *m/e* 127 is consistent with the loss of $C_5H_{11}O_2$ thus establishing II as the gross structure of this compound.

Refluxing of II with thiocarbonyldiimidazole in toluene[3] gives the 1,2-thionocarbonate IV. Compound IV undergoes cis elimination in refluxing trimethyl phosphite to give the olefin V. The coupling constant J_{ef} = 16 Hz in the nmr spectrum of V establishes the trans nature of this olefin.

A CD curve of II shows $\Delta\epsilon_{246} = -12.5$ indicating



IV



V

that the asymmetric center of the lactone ring has the same *S* configuration as in I which exhibited $\Delta\epsilon_{243}$ −7.9. The stereochemistry of the asymmetric centers at $C_{1'}$ and $C_{2'}$ is represented by one of the four possibilities: *SSS*, *SRR*, *SRS*, and *SSR*. The erythro isomers *SSS* and *SRR* may be discounted on the basis of the trans olefin V obtained as mentioned by the Corey procedure.

A dianisoate, VI, of II was prepared and the CD curve on this material shows two strong Cotton effects of opposite sign at 267.5 nm ($\Delta\epsilon$ −19.0) and 250 nm ($\Delta\epsilon \simeq +18.6$ when corrected for the nullifying effect of the enelactone Cotton effect at 243 nm). The location and magnitude of these effects clearly indicate that we are dealing with the Davydov-split Cotton effects of the *p*-methoxybenzoate chromophore.[4] Thus, on the basis of the exciton chirality method, a left-handed helix is indicated for the $C_{1'}$–$C_{2'}$ glycol arrangement.

An average value for the coupling constants of cis glycol protons in the gauche conformation is approximately 4.0 Hz while the average value for these protons in the trans conformation is about 8.0 Hz.[5,6]

It is quite conceivable that these values could be decreased due to the protons in question being squeezed closer together by bulky substituents. It is unreasonable to suggest that either approximate value would be markedly increased due to presence of bulky groups. Consequently, the observed value J_{ef} = 6.0 Hz for the glycol protons of VI means that they are trans to one another. The Newman projections shown below depict the trans conformations of the possible isomers *SRS* and *SSR* of II together with the kind of Cotton effect expected from each.

(1) G. A. Ellestad, W. J. McGahren, and M. P. Kunstmann, *J. Org. Chem.*, **37**, 2045 (1972).

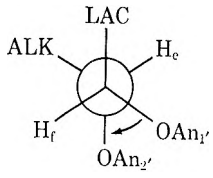
(2) N. Harada and K. Nakanishi, *Accounts Chem. Res.*, **5**, 257 (1972).

(3) E. J. Corey, F. A. F. A. Carey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965).

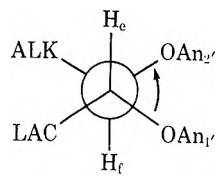
(4) N. Harada and K. Nakanishi, *Accounts Chem. Res.*, **5**, 258 (1972).

(5) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 292.

(6) H. El Hkadem, D. Horton, and J. D. Wander, *J. Org. Chem.*, **37**, 1630 (1972).



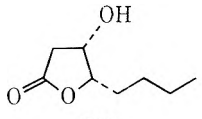
SRS positive
Davydov-split
Cotton effect



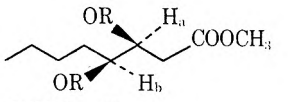
SSR negative
Davydov-split
Cotton effect

Conceivably, two of the groups, *i.e.*, the lactone and alkyl groups, have greater steric requirements so that the trans protons are skewed to a dihedral angle smaller than 180° which in turn reduces the value of the trans coupling constant to the observed value of 6 Hz. It follows then that *SSR* is the configuration of II.

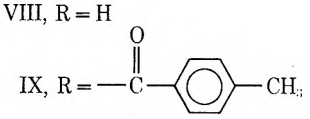
The exciton chirality method fails, of course, when the predominant rotameric population is such that the two anisoate groups are separated by about 180°. We observed this situation in regard to a degradation product of I. Ozonolysis of I yields mostly the lactone VII and also a small quantity of the cis glycol ester VIII. Because of its origin from I, the stereochemistry of VIII must be *SS*.



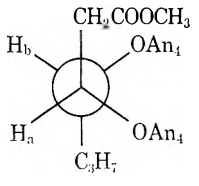
VII



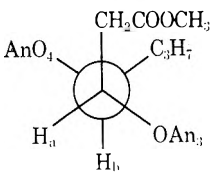
VIII, R = H



The dianisoate IX was prepared and in the nmr spectrum of this derivative the C_2 methylene protons appear as a doublet at δ 2.76 while H_a and H_b are represented by virtually identical multiplets at δ 5.70 and 5.40. Irradiation of the δ 2.76 doublet collapses the δ 5.70 multiplet to a doublet revealing the vicinal coupling constant J_{ab} = 3.5 Hz, indicating a gauche conformation to be predominant. Two gauche conformers may be drawn.



negative Davydov-split
Cotton effect



small normal anisoate
Cotton effect

In both these conformers, the massing of all the bulky groups together would tend to squeeze the H_a and H_b protons closer together thus accounting for the smaller than average gauche coupling constant of 3.5 Hz. The CD curve of IX shows a very small positive Cotton effect at 280 nm (Δε +0.90) and a larger effect at 252 nm (Δε −6.2); consequently, the preferred conformer is that shown on the right-hand side above since, when the dihedral angle between the anisoate groups is 180°, Davydov-splitting effects are absent.[7]

It is unexpected to find the gauche conformer predominate, but recently Birdsall, *et al.*,[8] showed that the gauche conformers of the glycol fragment of dipalmitoyllecithin represented about 37% of the total rotamer population.

Partition chromatography of the filtrate concentrate from which II was recovered yielded a crystalline solid, mp 114–115°, which by tlc was a single uv-absorbing spot. However, neither carbon–hydrogen analysis nor mass spectroscopy data gave a satisfactory molecular formula for the material. Under mild conditions, the material was acetylated to reveal two compounds on examination of the reaction mixture by tlc. The less polar material had a uv maximum at 280 nm (ε 6240) consistent with that of an α-pyrone[9] and the nmr confirmed this compound to be X. The more polar material proved to be the monoacetate XI. In the nmr spectrum of XI, irradiation at δ 5.09–5.11 (H_f and H_a) affects protons H_e, H_b, and the farthest downfield methylene protons of the propyl moiety.

Allylic coupling of H_a to H_c is superimposed on the vicinal coupling of H_f to H_e and the aforementioned methylene group. Irradiation of δ 3.60 (H_e) causes changes in the signals of H_d and H_f indicating a vicinal coupling to both. Irradiation at δ 4.43 (H_d) shows changes in H_e, H_b, and H_c again revealing the vicinal couplings. From these studies the confirmed coupling constants are as follows: J_{bc} = 17 (geminate), J_{cd} = 12 (trans), J_{bc} = 4 (cis), J_{ac} ~2 (allylic), J_{ed} = 4 (vicinal), J_{ef} = 4 (vicinal), and $J_{f,CH_2} \simeq 6.5$. In the spectrum of II, the H_f signal is hidden under the methoxy signal at δ 3.80 whereas, in that of the monoacetate, it is shifted to δ 5.20 which is, of course, diagnostic of the acetylation of a secondary alcohol. Acetylation of the cocrystallized mixture of II and III under normal conditions (pyridine and acetic anhydride) yields the diacetate X and XII.

Experimental Section

Tlc was carried out using Brinkmann silica gel thin layers. Solvents were dried overnight over 3A or 4A molecular sieves. Solutions were dried for 15–30 min over anhydrous $MgSO_4$. Uv curves were made on a Cary 11 instrument, ir spectra were recorded on a Perkin-Elmer Infracord, and nmr spectra were made using a Varian HA-100 spectrophotometer. CD spectra were made on a Cary 60 spectropolarimeter with CD attachment. All melting points are uncorrected and were obtained in capillary tubes. Mass spectra were run on an AE I MS9 high-resolution, direct-inlet mass spectrometer.

Isolation of II.—A 300-l. fermentation tank of Lederle culture P880 was processed by extraction of the whole mash with 0.5 vol. of ethyl acetate. Concentration of the extract to about 3 l. of dark red solution followed, which, on being allowed to remain in the cold room for 2 days, yielded 24 g of pure I. By replacing the ethyl acetate of the filtrate with ether, a further 27 g of I were recovered. The filtrate from this recovery was concentrated and allowed to sit for 24 hr to yield 3 g of II which was recrystallized from ethyl acetate–hexane to obtain 2.3 g of pure white crystals of II: mp 135.5–136°; $[\alpha]^{25}D$ −59.8 ± 1.0° (c 0.96, MeOH); λ_{max}^{MeOH} 234 nm (ε 13,800); ir (KBr) 1710 and 1624 cm^{-1}; nmr ($CDCl_3$) δ 0.93 ($-CH_2CH_3$, t), 1.50 ($(CH_2)_2CH_3$, m), 2.36 (H_c, dd, J_{cb} = 17.5, J_{cd} = 12.5 Hz), 2.87 (H_b, qq, J_{bd} = 4 Hz), 3.47 (H_e, dd, J_{ef} = 3.8, J_{ed} = 4.2 Hz), 3.78 (H_d, m, hidden by OCH_3 signal), 3.80 (OCH_3, s), 4.51 (H_d, tt), 5.16 (H_a, d, J_{ac} ~ 2 Hz); CD (MeOH) $\Delta\epsilon_{246}$ −12.5, $\Delta\epsilon_{220}$ +6.6, shoulder at $\Delta\epsilon_{210}$ +4.2 (concn 0.236 mg/ml, 1 mm cell, and 0.1° full scale deflection); mass spectrum *m/e* 230.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.02; H, 7.76.

(7) N. Harada, H. Sato, and K. Nakanishi, *Chem. Commun.*, 1691 (1970).
(8) N. J. Birdsall, J. Feeney, A. G. Lee, Y. K. Levine, and J. C. Metcaffe, *J. Chem. Soc.*, 1441 (1972).
(9) A. I. Scott, "Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 141.

Attempted Isolation of III.—The filtrate from which II was recovered was concentrated to a gum and subjected to silica gel chromatography using a gradient of ethyl acetate in hexane to obtain a further 12 g of I and 4.5 g of a mixture. Partition chromatography of this mixture over acid-washed diatomaceous earth using hexane–ethyl acetate–MeOH–H_2O as 70:30:15:6 yielded 2.0 g of pure II and 420 mg (appeared as a single spot on tlc) which upon recrystallization from ethyl acetate–hexane yielded 320 mg of beautiful white crystals; mp 114–115°; $[\alpha]^{25}D$ −27.8 ± 1.2° (c 0.82, MeOH); λ_{max}^{MeOH} 232, 280, and 320 nm (ratio of OD's 15:3:1).

Anal. Found: C, 57.45; H, 7.51.

About 70 mg of this material was dissolved in 4 ml of Ac_2O and 100 mg of anhydrous NaOAc added. The suspension was allowed to sit overnight. Work-up of the reaction by silica gel chromatography yielded 23 mg of white crystals which spectral data showed to be X: mp 125–126°; $[\alpha]^{25}D$ 0 ± 2.6° (c 0.37, MeOH); λ_{max}^{MeOH} 220 nm (ε 2000) and 280 (6240); nmr ($CDCl_3$) δ 0.90 (–$(CH_2)_2CH_3$, t), 1.45 (–$(CH_2)_2CH_3$, m), 2.05 (–C(=O)–CH_3, s), 2.17 (–C(=O)–CH_3, s), 3.80 (–OCH_3, s), 5.40 (H_b, H_c, and H_d, m), 5.95 (H_a, d, $J_{ab} \simeq 1.5$ Hz); mass spectrum *m/e* 312.

Approximately 10 mg of another crystalline material were also obtained, mp 116–117°. The nmr of this material, XI, which is the $C_{2'}$ monoacetate of II, is discussed in the body of the text, mass spectrum *m/e* 272.

Acetylation of the cocrystallized material, mp 114–115°, using pyridine and Ac_2O yielded the diacetate X and also the diacetate of II or XII which melts at 87–88°: nmr ($CDCl_3$) δ 0.90 (–$(CH_2)_2CH_3$, t), 1.50 (–$(CH_2)_2CH_3$, m), 2.09 (–C(=O)–CH_3, s), 2.16 (–C(=O)–CH_3, s), 5.40 (H_c, dd, J_{cb} = 17, J_{cd} = 10.4, Hz), 2.56 (H_b, qq, J_{bd} = 5.2 Hz), 3.75 (–OCH_3, s), 4.53 (H_d, qq), 5.14 (H_a, d, $J_{ac} \sim 1.2$ Hz), 5.20 (H_e and H_f, m, J_{ef} = 4.3 Hz).

Preparation of IV.—About 220 mg (1 mmol) of II was refluxed for 1 hr with 370 mg of thiocarbonyldiimidazole in 25 ml of dry toluene. Work-up of reaction using silica gel chromatography yielded 180 mg of an oil which crystallized from ether: mp 86–87°; nmr ($CDCl_3$) δ 0.98 (–$(CH_2)_2CH_3$, t), 1.60 (–$(CH_2)_2CH_3$, m), 2.36 (H_c, dd, J_{cb} = 17, J_{cd} = 13 Hz), 2.92 (H_b, qq, J_{bc} = 5.2 Hz), 3.77 (–OCH_3, s), 4.50 (H_d and H_e, m), 5.06 (H_f, q, $J_{ef} \sim 7.5$ Hz), 5.16 (H_a, d, $J_{ac} \sim 2$ Hz); mass spectrum *m/e* 272.

Note the value J_{ef} = 7.5 Hz makes it difficult to say whether these protons are cis or trans, a difficulty also encountered with cyclic carbonates. Recently Nakanishi, *et al.*, have differentiated between threo and erythro isomers of these types of compounds using the NOE effect.[10]

Preparation of V.—About 150 mg of VI were refluxed for 90 hr in 25 ml of trimethyl phosphite in a N_2 atmosphere. The trimethyl phosphite was evaporated off under reduced pressure, and the oily residue was purified over silica gel to yield 140 mg of a smelly oil. This was purified further by partition chromatography over diatomaceous earth using the system heptane–MeOH to obtain 60 mg of V: nmr ($CDCl_3$) δ 0.90 (–$(CH_2)_2CH_3$, t), 1.50 (–$CH_2CH_2CH_3$, m), 2.10 (–$CH_2CH_2CH_3$, m), 2.40 (H_b and H_c, m), 3.75 (–OCH_3, s), 5.07 (H_a virtual s), 5.50 (H_e, dd, J_{ef} = 16, $J_{ed} \sim 5$ Hz), 5.75 (H_f, m); mass spectrum *m/e* 196.

Preparation of VI.—Approximately 1 g of II in 5 ml of dry pyridine with 1 ml of freshly distilled *p*-methoxybenzoyl chloride added was allowed to sit for 3 days. Ice–water was added and the product extracted with ether; the pyridine and anisic acid impurities were removed by extraction with 4 *N* HCl and 7% K_2CO_3, respectively. Purification by both adsorption and partition chromatography followed to get 1.2 g of a gummy solid which failed to crystallize. By evaporation of solvent from a methanolic solution of the material, a white solid, mp 66–72°, could be obtained: λ_{max}^{MeOH} 225 nm (ε 38,300); nmr (CCl_4) δ 0.92 (–CH_2CH_3, t), 1.40 (–$CH_2CH_2CH_3$, m), 1.72 (–$CH_2CH_2CH_3$, m), 2.40 (H_c, dd, J_{cb} = 17, J_{cd} = 10 Hz), 2.5 8(H_b, dd, J_{bd} = 5.0 Hz), 3.63 (–OCH_3, s), 3.78 (2 aromatic –OCH_3, s), 4.63 (H_d, m), 4.98 (H_a, s), 5.50 (H_e and H_f, m, J_{de} = 4, J_{ef} = 6 Hz), 6.77 (4 aromatic protons ortho to –OCH_3, dd, $J \sim 9$ and 1.5 Hz), 7.88 (4 aromatic protons ortho to carbonyl, m); CD (MeOH) $\Delta\epsilon_{267.5}$ −19.0, $\Delta\epsilon_{250}$ +6.7, $\Delta\epsilon_{219}$ −4.9 (between maxima at 235 and 219 nm there was no crossover, just a minimum at 225 nm), $\Delta\epsilon_{211}$ +9.8 (concn 0.240 mg/ml, 1-mm cell, and full scale deflection setting 0.1°); mass spectrum *m/e* 498.

Anal. Calcd for $C_{27}H_{30}O_9$: C, 65.05; H, 6.08. Found: C, 64.61; H, 6.00.

Ozonolysis of I.—About 6 g of I were dissolved in 175 ml of MeOH, cooled to −78°, and subjected to a stream of O_2–O_3 from a Welsbach generator for 1.5 hr. The reaction solution was worked up using 5 ml of dimethyl sulfide and the products were resolved by silica gel chromatography. These included 320 mg of VIII: mp 54°; $[\alpha]^{25}D$ −32.1 ± 1.0° (c 0.98, MeOH); nmr ($CDCl_3$) δ 0.93 (–$(CH_2)_3CH_3$, m), 1.44 (–$(CH_2)_3CH_3$, m), 2.59 (–CH_2COOCH_3, d), 2.74 (2 exchangeable OH's), 3.46 (–CH(OH)–CH_2COOCH_3).

Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.52. Found: C, 57.01; H, 9.34.

Surprisingly, after VIII had been eluted off the column, a band was eluted off to yield about 4.0 g of crude lactone VII. A sample of the lactone was purified first by partition chromatography and then thick layer chromatography to get the analytical sample, $[\alpha]^{25}D$ −98.2 ± 1.3 (c 0.77, MeOH).

The ir and nmr of this material were identical with the corresponding curves on the same compound obtained as described in ref 1. However, the $[\alpha]^{25}D$ values are different as that of the latter material was −71.1° (c 0.73, MeOH).

Preparation of IX.—About 85 mg of VIII were dissolved in 0.4 ml of dry pyridine and 0.3 ml of anisoyl chloride and left for 3 days. Work-up yielded 55 mg of an oil which by nmr data was clearly IX: $[\alpha]^{25}D$ −98.2 ± 1.3° (c 0.77, MeOH); nmr ($CDCl_3$) δ 0.87 (–$(CH_2)_3CH_3$, t), 1.35 (–$CH_2(CH_2)_2CH_3$, m), 1.72 (–$CH_2(CH_2)_2CH_3$, m), 2.76 (–CH_2COOCH_3, d), 3.63 (–$COOCH_3$, s), 3.87 (2 aromatic –OCH_3, s), 5.40 (H_a, m), 5.70 (H_b, m), 6.93 (4 aromatic H's, dd), 8.02 (4 aromatic H's, m), J_{ab} = 3.5 Hz (determined by spin decoupling); CD (MeOH) $\Delta\epsilon_{290}$ 0, $\Delta\epsilon_{280}$ +0.9, $\Delta\epsilon_{272}$ 0, $\Delta\epsilon_{252}$ −6.18, $\Delta\epsilon_{231}$ 0 (concn 0.15 mg/ml, cell width 1 mm, 0.040 full scale deflection setting); mass spectrum (molecular ion) *m/e* 458.

Acknowledgments.—Our thanks are due to Mr. L. Brancone and associates for microanalytical data, to Mr. W. Fulmor and associates for spectral data and optical rotations, to Mr. A. J. Shay for the 300-l. fermentation tank, and to Mr. M. Dann for the extraction and concentration of this tank.

Registry No.—II, 41164-59-4; III, 41206-21-7; IV, 41164-60-7; V, 41164-61-8; VI, 41164-62-9; VII, 34565-37-2; VIII, 41164-64-1; IX, 41164-65-2; X, 41164-66-3; XI, 41164-67-4; XII, 41164-68-5.

(10) K. Nakanishi, D. A. Schooley, M. Koreeda, and I. Miura, *J. Amer. Chem. Soc.*, **94**, 2867 (1972).

Mass Spectrometry in Structural and Stereochemical Problems. CCXXX.[1] Preparation of 5α,20α- and 5α,17α,20α-Cholestane-3β,6α-diol. Electron Impact Induced Fragmentation of Steroidal $\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{20(22)}$ Olefins

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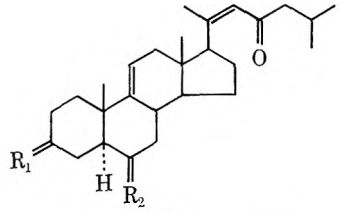
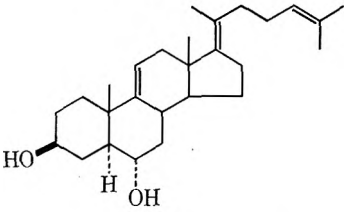
To find convenient ways to identify $\Delta^{17(20)}$ and $\Delta^{20(22)}$ steroidal olefins related to marine natural products 1, 2, and 3, our paper describes relevant synthesis of parent and deuterated compounds as well as nmr and mass spectral criteria for their differentiation. Also described is the preparation of 5α,20α-cholestane-3β,6α-diol (7) and 5α,17α,20α-cholestane-3β,6α-diol (10).

In recent reports[2] on the isolation and structure determination of the star fish genins 5α-cholesta-9(11),20(22)-diene-3β,6α-diol-23-one (**1a**), 5α-cholesta-9(11),17(20),24-triene-3β,6α-diol (**2**), and 24ξ-methyl-5α-cholesta-9(11),20(22),diene-3β,6α-diol (**3**) we indicated that hydrogenation (10% palladium on charcoal) of **1** furnished 5α-cholestane-3β,6α-diol-23-one (**4**, 20%) and an unknown isomeric keto diol **5** (80%). The keto diol **5** was assigned the epimeric configuration at C-20 because its Cotton effect was opposite to that of compound **4**. Wolff–Kishner reduction of **4** and **5** furnished 5α-cholestane-3β,6α-diol (**6**) and the unknown isomeric diol **7**, respectively. Oxidation of **6** and **7** provided two isomeric diones (**8** and **9**) which depicted similar spectral characteristics (ir, nmr, mass spectra, CD, and ORD) but differed substantially in their melting points and gas chromatographic mobilities.



1a, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H

1b, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H



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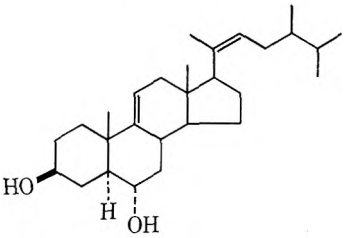

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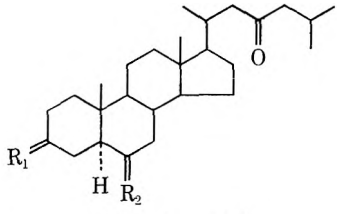
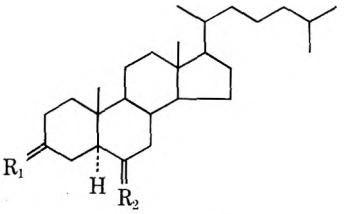


4, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H

4a, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H

5, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H (20α)

5a, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H (20α)



6, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H (20β)

6a, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H (20β)

7, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H (20α)

7a, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H (20α)

7b, $R_1 = R_2 = H_2$ (20α)

8, $R_1 = R_2 = O$ (20β)

9, $R_1 = R_2 = O$ (20α)

10, R_1 = 3α-OH, 3β-H; R_2 = 6α-OH, 6β-H (17,20α)

10a, R_1 = 3α-OAc, 3β-H; R_2 = 6α-OAc, 6β-H (17,20α)

11, $R_1 = R_2 = O$ (17,20α)

Examination of the literature indicated the existence of a considerable void concerning the spectral behavior[3]

(1) For preceding article, see S. Hammerum and C. Djerassi, *Org. Mass Spectrom.*, in press.

(2) Y. M. Sheikh, B. M. Tursch, and C. Djerassi, *J. Amer. Chem. Soc.*, **94**, 3278 (1972); Y. M. Sheikh, B. M. Tursch, and C. Djerassi, *Tetrahedron Lett.*, 3721 (1972).

(3) N. K. Chaudhuri, R. Nicholson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767 (1969), have recently described a new synthesis of cholesterol and related C_{27} steroids which includes the preparation and properties of *cis*-$\Delta^{17(20)}$- and -$\Delta^{20(22)}$-cholesterol.

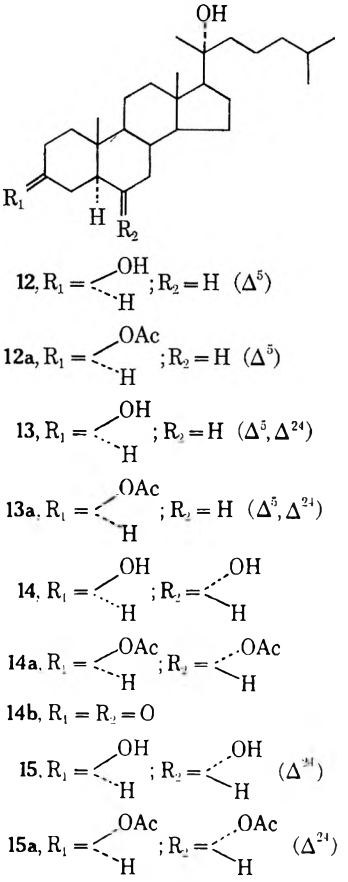
associated with the unusual $\Delta^{17(20)}$ and $\Delta^{20(22)}$ olefinic linkages in genins **1**, **2**, and **3**. The present work therefore was aimed toward (a) preparation of $\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{20(22)}$ steroidal olefins; (b) accumulation of nmr and gas chromatographic data thereby arriving at some parameters which could perhaps be used for structure elucidation of similar natural products, notably from marine sources; and (c) a detailed study of the mass spectrometric fragmentation of these olefins, thus supplementing the already available data on sterols with unsaturated side chains; and (d) finally to prepare 5α,20α-cholestane-3β,6α-diol (**7**) and 5α,17α,20α-cholestane-3β,6α-diol (**10**) so as to confirm the sterochemical assignment of **5**.

The $\Delta^{17(20)}$ olefinic linkage is a necessary feature[4] for bioactivity of the fungal metabolites of the fusidic acid and cephalosporin series. Presently no convenient way is available to introduce this unusual functionality. $\Delta^{20(22)}$-Unsaturated steroids can be obtained by dehydration of 22-hydroxy steroids[5] which can be prepared conveniently by a method developed by Cole and Julian[6] involving a Grignard reaction with bisnorcholenic acid derivatives. This method has been extensively used for the synthesis of naturally occurring steroids including cholesterol,[7] dihydrobrassicasterol,[8] campesterol,[9] ecdysone,[10] and 20-hydroxyecdysones.[11] More recently $\Delta^{20(22)}$ steroids, obtained by dehydration of 20-hydroxy precursors, have served as intermediates in synthesis of β-sitosterol[12] and bufadienolides.[13] Whereas the preparation of $\Delta^{20(22)}$ olefins by Wittig reaction generally results in poor yield,[14] the $\Delta^{20(21)}$ olefinic linkage has been introduced[15] by Wittig reaction of 21-nor-20-keto steroids (easily accessible from the corresponding etioallocholanic acid derivatives and organocadmium derivatives) and it, in turn, provides a facile entry[16] into 21-functionalized steroids of the 20*S* (α) configuration.

For our purpose we employed the method of Woodward, *et al.*,[17] which involves the reaction of appropriate 20-keto steroids with alkylmagnesium halide to furnish 20α-hydroxy steroids[17b] which after appropriate protection of nuclear functionalities can be dehydrated under a variety of conditions. The resulting olefins can then be separated by chromatography over silver nitrate impregnated silica gel.

The required starting ketone 5α-pregnane-3β,6α-diol-20-one diacetate[18] was prepared by hydroboration of Δ^5-pregnenolone acetate 20-ethylene ketal,[19] followed by reacetylation of the hydroxyl functions and acid-catalyzed cleavage of the ketal. Treatment of this ketone or of Δ^5-pregnenolone acetate with the Grignard complex of 1-bromo-4-methylpentane or 1-bromo-4-methyl-3-pentene (prepared by reaction of hydrobromic acid with cyclopropyldimethylcarbinol[20]) according to the general procedure of Petrow and Stuart-Webb[21] furnished the desired 20-hydroxy steroids (**12**–**15**). The expected 20α stereochemistry of the resulting carbinols was confirmed by nmr spectroscopy.[22]

Dehydration of the 20-hydroxylated steroids (**12**–**15**) gave varying proportions of the isomeric olefins



($\Delta^{17(20)}$, $\Delta^{20(21)}$, $\Delta^{20(22)}$) depending on the reaction conditions (see Table I). It is important to note that our results differ from those reported for 20-hydroxycholanic acid derivatives[13] (**16**) [$SOCl_2$/Py → 80%

(4) For structure activity study, see W. O. Gotfredsen, W. von Daehne, L. Tybring, and S. Vangedol, *J. Med. Chem.*, **9**, 15 (1966). Recently the $\Delta^{17(20)}$ double bond has been introduced into tumulosic acid: I. L. Batey, J. T. Pinhey, B. J. Ralph, J. J. H. Simes, and M. Wootton, *J. Chem. Soc., Perkin Trans.* **1**, 2260 (1972).

(5) K. Tsuda and R. Hyatsu, *J. Amer. Chem. Soc.*, **81**, 5987 (1959); L. F. Fieser and W. Y. Huang, *ibid.*, **75**, 5356 (1953).

(6) W. Cole and P. L. Julian, *J. Amer. Chem. Soc.*, **67**, 1369 (1945).

(7) A. Romeo and R. Villotti, *Ann. Chim. (Rome)*, **47**, 618 (1957).

(8) A. Martinez, A. Romeo, and V. Tortorella, *Gazz. Chim. Ital.*, **97**, 96 (1967).

(9) G. Tarzia, V. Tortorella, and A. Romeo, *Gazz. Chim. Ital.*, **97**, 102 (1967).

(10) J. B. Siddall, J. P. Marshal, A. Bowers, A. D. Cross, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **88**, 379 (1966); J. B. Siddall, A. D. Cross, and J. H. Freid, *ibid.*, **88**, 862 (1966); R. Wiechert, A. Furlenmeier, A. Furst, A. Langemann, and G. Waldvogel, *Helv. Chim. Acta*, **49**, 1601 (1966).

(11) G. Huppi and J. B. Sidall, *J. Amer. Chem. Soc.*, **89**, 6790 (1967).

(12) R. Ikan, A. Markus, and E. D. Bergman, *J. Org. Chem.*, **36**, 3944 (1971).

(13) S. Sarel, Y. Shalon, and Y. Yanuka, *Chem. Commun.*, 80 (1970).

(14) Unpublished results from this laboratory. Recently ylides prepared from methoxymethylphosphorane have been treated with 20-oxopregnanes [see G. R. Pettit, B. Green, G. L. Dunn, and P. Sander-Plassman, *J. Org. Chem.*, **35**, 1385 (1970)].

(15) F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, **80**, 3087 (1959).

(16) J. Bottin and M. Fetizon, *Chem. Commun.*, 1087 (1971).

(17) (a) R. B. Woodward, F. Sondheimer, D. Taube, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952). (b) N. K. Chaudhri, J. Williams, R. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759 (1969), have recently established the stereochemistry of the intermediates 20-carbinol.

(18) J. Gurst, Y. M. Sheikh and C. Djerassi, *J. Amer. Chem. Soc.*, **95**, 638 (1973).

(19) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956).

(20) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960).

(21) V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4675 (1956).

(22) E. J. Middleton, D. H. S. Horn, and M. N. Galbraith, *Austral. J. Chem.*, **25**, 1245 (1972).

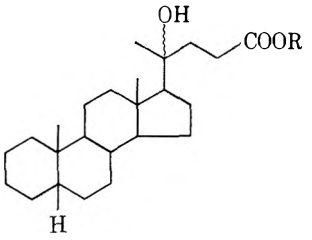
TABLE I

PRODUCT YIELDS[a] OF VARIOUS OLEFINS ON DEHYDRATION OF 20-HYDROXY STEROIDS (12a, 13a, 14a, AND 15a)

Compd	% dehydration	Method	Products (%) $\Delta^{17(20)}$	$\Delta^{20(22)}$	$\Delta^{20(21)}$
12a	100	$SOCl_2$/Py	20a (11)	22a (44)	21a (44)
	70	$POCl_3$/Py	20a (29)	22a (48)	21a (23)
13a	100	$SOCl_2$/Py	23a (16)	25a (28)	24a (52)
	80	$POCl_3$/Py	23a (31)	25a (31)	24a (31)
14a	100	$SOCl_2$/Py	26a (14)	28a (40)	27a (45)
	85	$POCl_3$/Py	26a (28)	28a (44)	27a (28)
		$CH_3CH_2CO_2H$, 12 hr	26a (10–15)	28a (80)	27a (<5)
15a	100	$SOCl_2$/Py	29a (15)	31a (23)	30a (54)
	85	$POCl_3$/Py	29a (30)	31a (34)	30a (36)

[a] Isolated yields.

$\Delta^{17(20)}$-17 (cis + trans); $POCl_3$/Py → principally $\Delta^{20(22)}$-19]. These results have recently been explained[23] by invoking thermodynamic control in the former ($SOCl_2$) and kinetic control in the latter ($POCl_3$) reaction.



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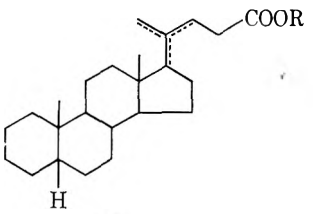
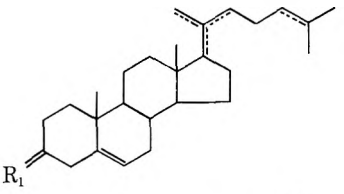


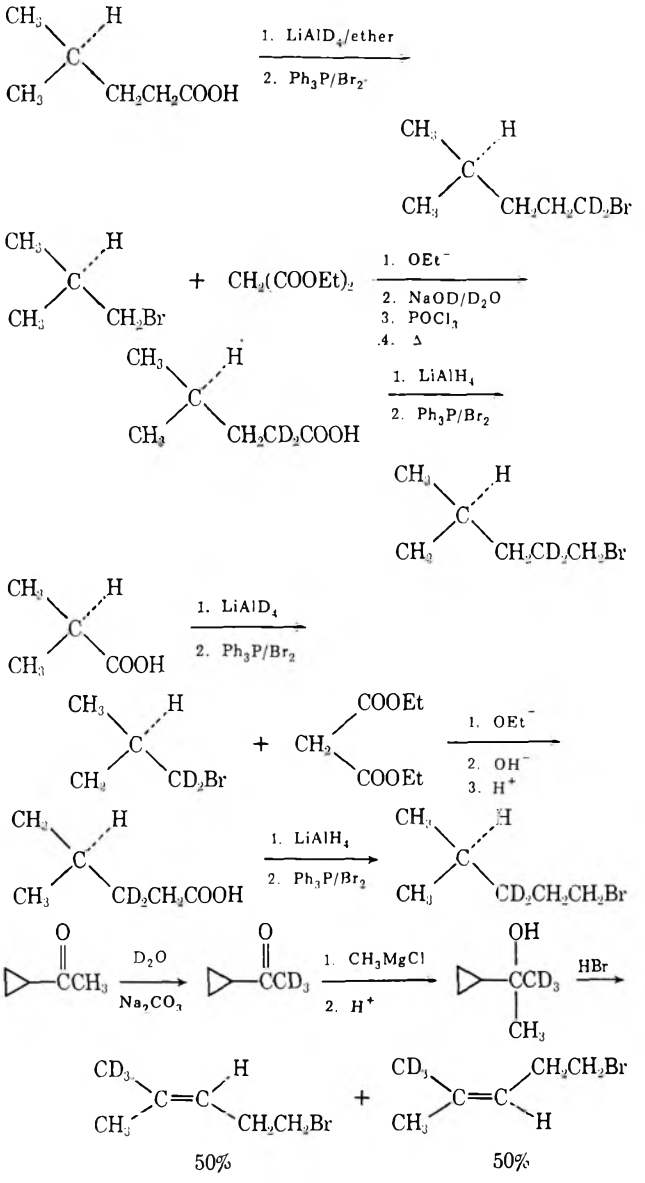
17, $\Delta^{17(20)}$ cis + trans
18, $\Delta^{20(21)}$
19, $\Delta^{20(22)}$



20, R_1 = 5α-OH ($\Delta^{17(20)}$)
20a, R_1 = 5α-OAc ($\Delta^{17(20)}$)
21, R_1 = 5α-OH ($\Delta^{20(21)}$)
21a, R_1 = 5α-OAc ($\Delta^{20(21)}$)
22, R_1 = 5α-OH ($\Delta^{20(22)}$)
22a, R_1 = 5α-OAc ($\Delta^{20(22)}$)
23, R_1 = 5α-OH ($\Delta^{17(20)}$,Δ^{24})
23a, R_1 = 5α-OAc ($\Delta^{17(20)}$,Δ^{24})
24, R_1 = 5α-OH ($\Delta^{20(21)}$,Δ^{24})
24a, R_1 = 5α-OAc ($\Delta^{20(21)}$,Δ^{24})
25, R_1 = 5α-OH ($\Delta^{20(22)}$,Δ^{24})
25a, R_1 = 5α-OAc ($\Delta^{20(22)}$,Δ^{24})

The structures of the resulting olefins were established by a combination of ir, nmr, and high resolution mass spectral measurements. The $\Delta^{20(21)}$ olefins depict a characteristic doublet around δ 4.70–4.90 due to the vinylic methylene protons, whereas the 22 vinylic proton in $\Delta^{20(22)}$ olefins appears as a triplet at 5.10 (J = 6 Hz). From the chemical shifts of the various $\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{20(22)}$ model olefins (see Table II) it was possible to deduce shift parameters for the C-18 and C-19 methyls. Introduction of a $\Delta^{17(20)}$ linkage results in a downfield shift of the C-18 methyl signal by δ 0.17 ± 0.01, whereas both $\Delta^{20(21)}$ and $\Delta^{21(22)}$ double bonds shift the C-18 protons upfield by a value of 0.11 and 0.13, respectively. The C-19 methyl signal remains essentially unaffected in either case. The validity of these parameters, which

SCHEME I



(23) D. N. Kirk in Specialists Periodical Report, "Terpenoids and Steroids," Vol. 1, The Chemical Society, London, 1970, pp 289, 290.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA

Compd		C-18		C-19		C-21		C-26,27		Olefinic protons	
Parent	Acetate	Parent	Acetate	Parent	Acetate	Parent	Acetate	Parent	Acetate	Parent	Acetate
6 (20β)		0.65		0.81		0.90		0.86			
7 (20α)		0.65		0.81		0.90		0.86			
10 (17α,20α)		0.65		0.81		0.90		0.86			
12	12a		0.86		1.03		1.26		0.86		5.36
13	13a	0.86	0.85	1.00	1.00	1.28	1.26	1.60	1.63	5.10	5.10
								1.66	1.66	5.33	5.35
14	14a	0.81	0.82	0.83	0.86	1.24	1.23	0.86	0.85		
15	15a	0.81	0.83	0.83	0.88	1.25	1.25	1.62	1.60	5.13	5.08
									1.65		
20[a]	20a	0.86		1.01		1.68		0.88		5.36	
21	21a	0.58	0.58	1.00	1.01			0.83	0.89	4.76, 4.86	4.76, 4.86
										5.33	5.33
22	22a	0.55		1.01		1.63		0.88		5.33–5.41	
23	23a	0.85	0.86	1.01	1.00	1.60 or 1.68	1.60 or 1.68	1.60 or 1.68	1.60 or 1.68	5.15	5.13
										5.38	5.36
24	24a	0.56	0.58	1.00	1.00			1.60	1.60	4.78, 4.86	4.76, 4.83
								1.66	1.66	5.10, 5.33	5.10, 5.36
25	25a		0.55		1.03		1.63 or 1.68		1.63		5.15
									1.68		5.35
26	26a	0.84	0.83	0.84	0.90	1.68	1.66	0.87	0.87		
27	27a		0.55		0.87				0.86		4.76
											4.85
28	28a	0.51	0.50	0.83	0.87	1.60	1.62	0.86	0.88	5.13	5.13
29	29a	0.81	0.82	0.81	0.87	1.60 or 1.66	1.60 or 1.66	1.60 or 1.66	1.60 or 1.66	5.13	5.13
30	30a	0.55	0.56	0.80	0.89			1.60 or 1.66	1.62 or 1.70	4.78, 4.85	4.78, 4.88
										5.10	5.10
31	31a		0.53		0.90		1.63		1.63 or 1.66		5.10

[a] See ref 3.

should be useful in the identification of marine sterols, is supported by the good agreement of calculated and observed chemical shifts for the angular methyl groups in genin 2 (calculated for C-18 0.75 and C-19 0.94, observed 0.72 and 0.94) and genin 3 (calculated for C-18 0.48 and C-19 1.01, observed 0.49 and 1.01).

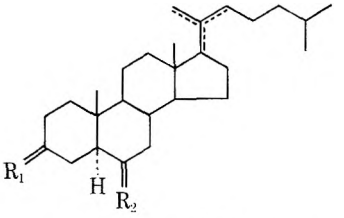
Deuterated analogs of the $\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{20(22)}$ olefins required for the mass spectrometric analysis were obtained by dehydration of the labeled 20-hydroxy steroids which in turn were prepared as described above but substituting the appropriately deuterated Grignard reagents. The labeled reagents were prepared by the methods outlined in Scheme I.

Hydrogenation (10% Pd/C, EtOAc) of $\Delta^{20(21)}$-cholestene-3β,6α-diol (**27a**) and $\Delta^{20(21),24}$-cholestadiene-3β,6α-diol diacetates (**30a**) furnished the 20β- and 5α,20α-cholestane-3β,6α-diol diacetates (**6a** and **7a**) which on subsequent saponification provided the parent diols (**6** and **7**). Similar hydrogenation of **26a** and **29a** followed by saponification furnished the normal and 17α,20α-diols (**6** and **10**). Jones oxidation of **7** and **10** gave the corresponding diketones (**9** and **11**). Identity of the 20α-diol **7** and the diketone **9** with those derived from the natural starfish genin **1** could be established by spectral comparison (ir, nmr, mass spectra, and gc) and mixture melting point determination.

The C-20 isomeric nature of **6** could be established independently by comparison (gc, mass spectra) of hydrocarbons derived from the diketone **9** and 20α-cholestanol.[24]

Discussion of Mass Spectra

The mass spectra of steroidal $\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{20(22)}$ olefins are shown in Figures 1–5. Although they bear a superficial resemblance to the analogous



26, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{17(20)}$)

26a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{17(20)}$)

27, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{20(21)}$)

27a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{20(21)}$)

28, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{20(22)}$)

28a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{20(22)}$)

28b, $R_1 = R_2 = O$ ($\Delta^{20(22)}$)

29, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{17(20)},\Delta^{24}$)

29a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{17(20)},\Delta^{24}$)

30, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{20(21)},\Delta^{24}$)

30a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{20(21)},\Delta^{24}$)

31, R_1 = 20β-OH; R_2 = 17α-OH ($\Delta^{20(22)},\Delta^{24}$)

31a, R_1 = 20β-OAc; R_2 = 17α-OAc ($\Delta^{20(22)},\Delta^{24}$)

(24) G. V. Nair and E. Mosettig, *J. Org. Chem.*, **27**, 4659 (1962).

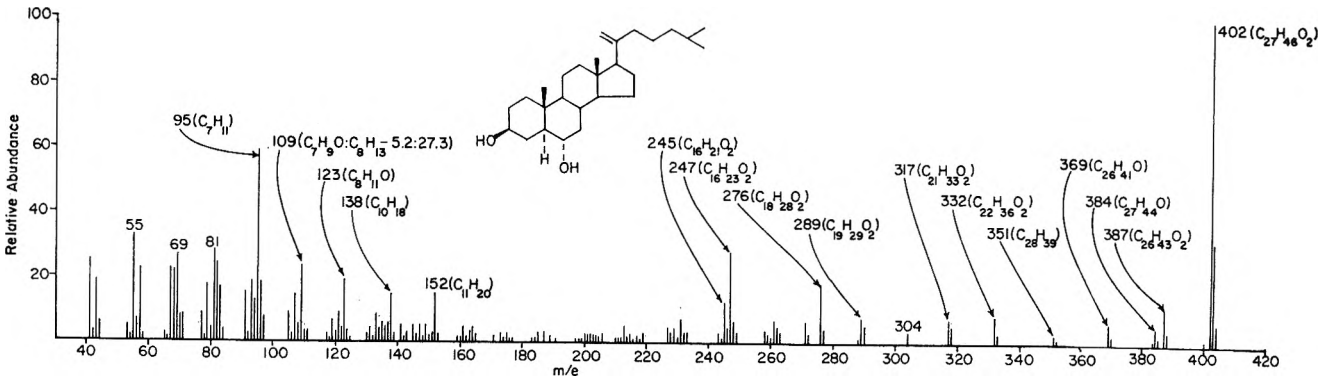


Figure 1.—Mass spectrum (70 eV) of 5α-cholest-20(21)-ene-3β,6α-diol (27).

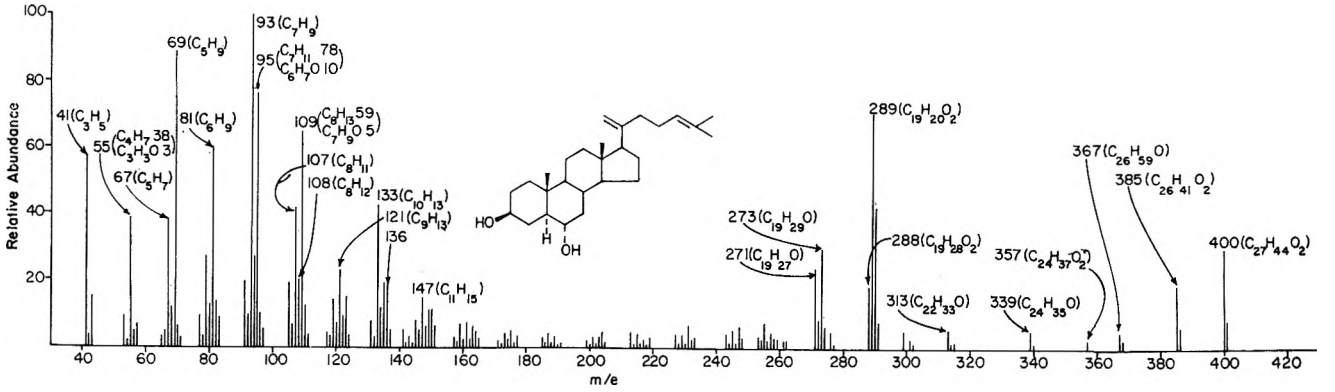


Figure 2.—Mass spectrum (70 eV) of 5α-cholesta-20(21),24-diene-3β,6α-diol (30).

TABLE III

SHIFTS OF THE PRINCIPAL PEAKS, *m/e* (RELATIVE INTENSITIES), IN THE MASS SPECTRA (70 EV) OF DEUTERATED 5α-CHOLEST-20(21)-ENE-3β,6α-DIOL (27)

Compd	Isotopic purity	M⁺ (%)	*m/e* (%)					
27 (d_0)		402 (100)	332 (9)	276 (17)	247 (30)	152 (15)	138 (15)	95 (57) 96 (17) 97 (5)
27b (17,21,21-d_3)	94% d_3 4% d_2 2% d_1	405 (100)	335 (13)	276 (17)	247 (46)	155 (20)	141 (9)	95 (45) 96 (19) 97 (25) 98 (23)
27c (22-d_2)	93% d_2 6% d_1 1% d_0	404 (100)	334 (12)	276 (15)	247 (40)	154 (22)	140 (5)	95 (67) 96 (21) 97 (27)
27d (23-d_2)	91% d_2 7% d_1 2% d_0	404 (100)	332 (10)	276 (15)	247 (31)	154 (15)	140 (6)	95 (45) 96 (15) 97 (31)
27e (24-d_2)	85% d_2 8% d_1 7% d_0	404 (100)	333 (6.0) 332 (6.0)	276 (17)	247 (41)	154 (21)	140 (7)	95 (73) 96 (20) 97 (7)
27f (26-d_3)	50% d_3 20% d_2 15% d_1		332 (9.0)	276 (—)	247 (31)			

Δ^{22}, Δ^{23}, and Δ^{24} sterols,[25] they display marked differences from those observed for sterols possessing a saturated side chain.[26]

$\Delta^{20(21)}$ Olefins (27) (Figure 1).—The peak shifts found in the various labeled $\Delta^{20(21)}$ steroids are summarized in Table III.

The spectrum (Figure 1) of the $\Delta^{20(21)}$ olefin **27** is characterized by an intense molecular ion (base peak), a complete absence of allylic fission, and a weak "McLafferty ion" of mass 332 arising (Scheme II) both *via* six- and seven-membered transition states.

Minor peaks at *m/e* 290 and 289 are generated by loss of the side chain with transfer of one and two hydrogens. Since deuterium labeling indicated the complete loss of the C_{17} H, it is likely that this fragmentation corresponds to that elucidated[25] earlier in Δ^{23} and Δ^{24} steroids. However the peak at *m/e* 276 (Figure 1), involving loss of the side chain in addition to C_{17}, has no precedent among Δ^{23} and Δ^{24} steroids.[25]

(25) S. G. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968).

(26) J. Karliner, H. Budzikiewicz, and C. Djerassi, *J. Org. Chem.*, **31**, 710 (1966).

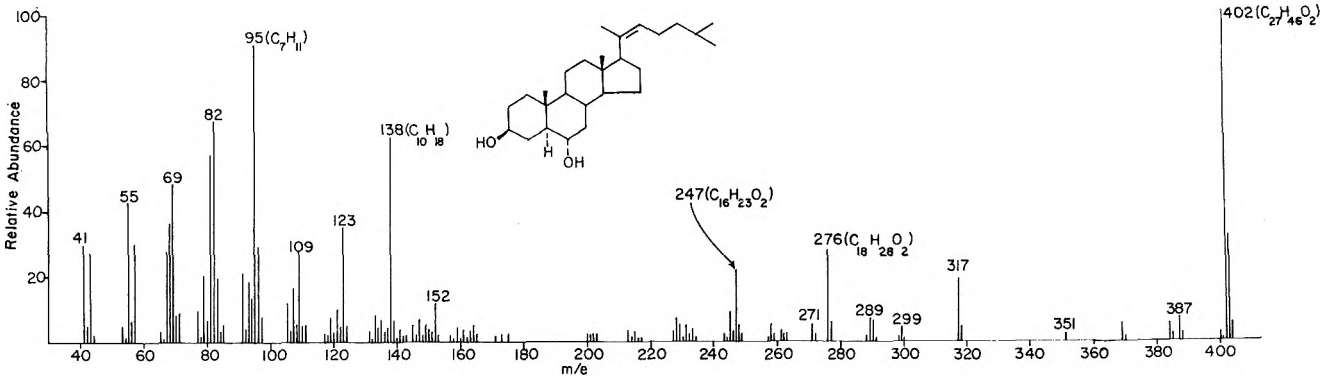


Figure 3.—Mass spectrum (70 eV) of 5α-cholest-20(22)-ene-3β,6α-diol (28).

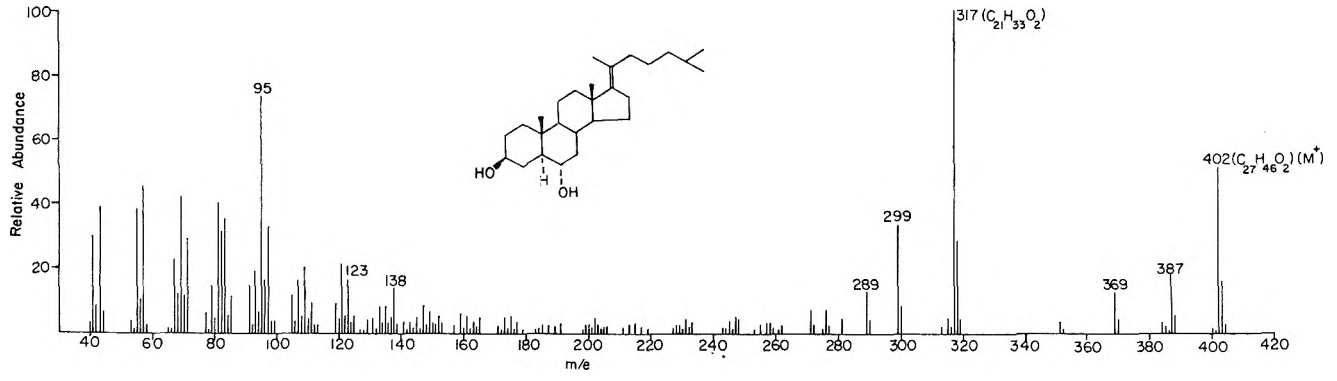
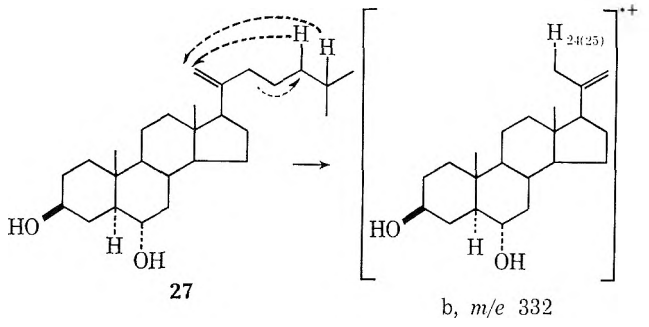
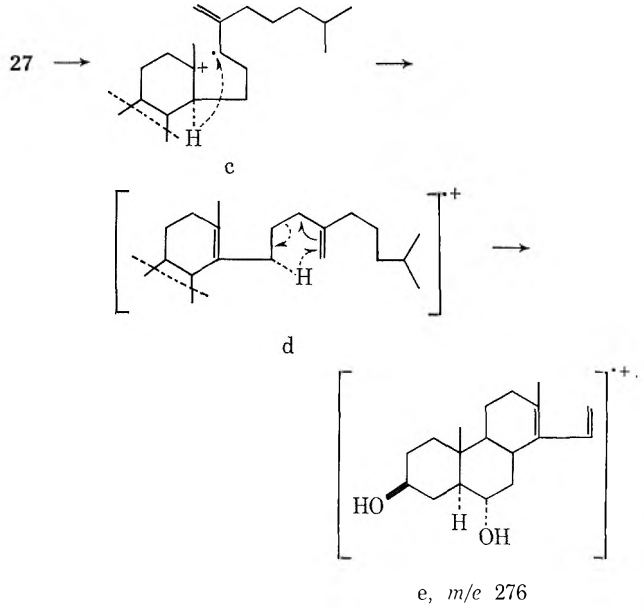


Figure 4.—Mass spectrum (70 eV) of 5α-cholest-17(20)ene-3β,6α-diol (26).

SCHEME II



SCHEME III



Its formation can be explained by invoking ionization of the 13–17 bond to furnish c (tertiary carbonium ion and allylic radical) which after abstraction of the 14α hydrogen[27] could undergo a normal McLafferty rearrangement to furnish ion e (Scheme III). The ion of mass 247 formally corresponds to ring D cleavage[27] but includes the added feature of an unprecedented (among steroids) unidirectional transfer of three hydrogens from rings A, B, or C. The lower mass region is populated by peaks at *m/e* 152, 138, and 95, all of which remain also at low voltage. Possible representations are summarized in Scheme IV and are consistent with the appropriate shifts in the deuterated analogs.

Introduction of an additional double bond in the Δ^{24} position (**30**) radically alters the spectrum (see Figure 2). The molecular ion intensity is reduced while the ion (*m/e* 289) corresponding to loss of the side chain and transfer of two hydrogens[25] (*m/e* 289) becomes an important ion. Labeling work (Table IV) indicated a quantitative transfer of the hydrogen attached to C-17 thus suggesting that its formation is completely analogous to that of other Δ^{24} steroids.[25] In other words the Δ^{24} double bond overshadows the effect of the $\Delta^{20(21)}$ linkage.

The expected cleavage (*m/e* 331) of the doubly, allylically activated 22–23 bond is absent from the spectrum (Figure 2). The ion of mass 273 arises from the molecular ion by loss of the side chain (no transfer of hydrogen) and a mole of water.

By a combination of exact mass measurements (see Figure 2) and deuterium labeling, it could be deter-

(27) L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

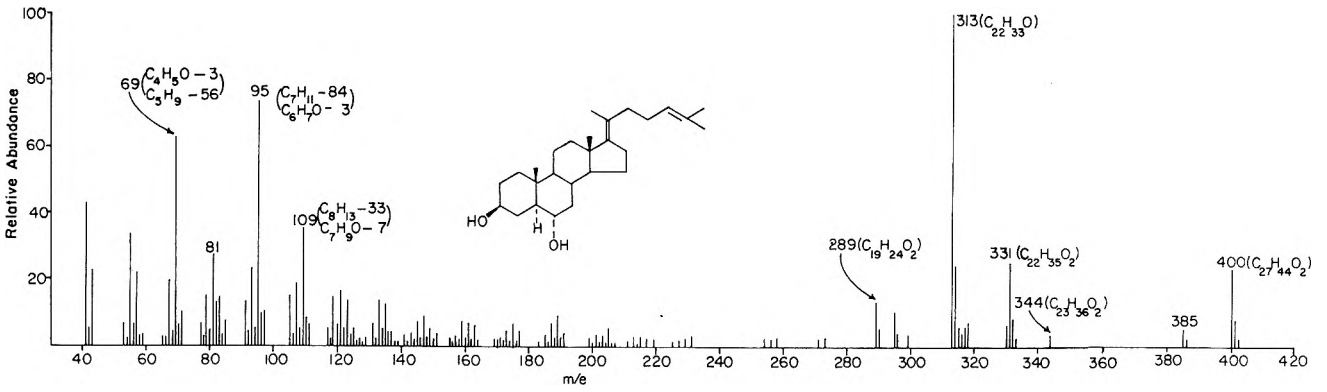


Figure 5.—Mass spectrum (70 eV) of 5α-cholesta-17(20),24-diene-3β,6α-diol (29).

SCHEME IV

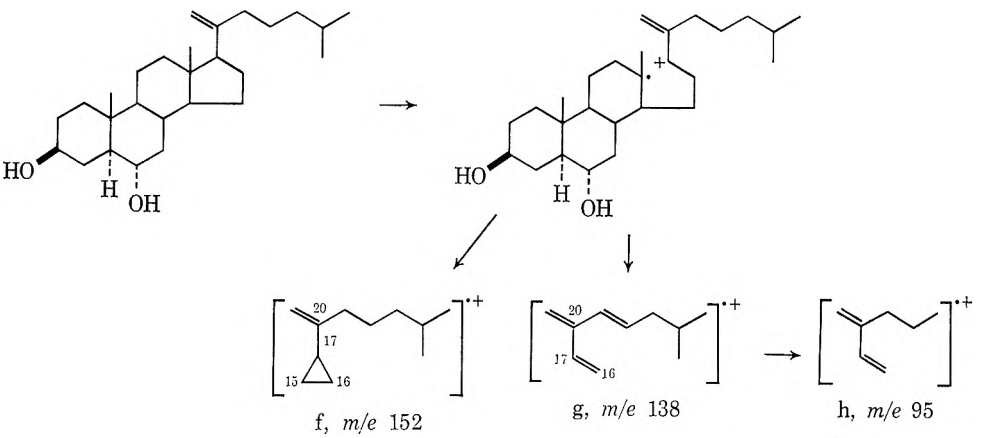


TABLE IV

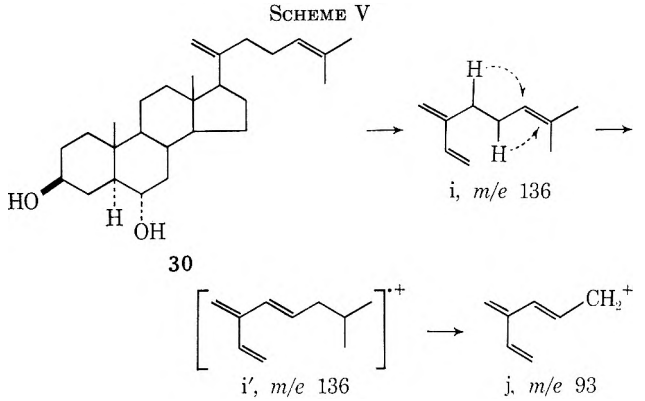
SHIFT IN THE PRINCIPAL PEAKS (*m/e*) IN THE MASS SPECTRA OF DEUTERATED 5α-CHOLESTA-20(21),24(25)-DIENE-3β,6α-DIOL (30)

Compd	M⁺ (%)	*m/e* (%)								
30 (d_0)	400 (30)	290 (41)	289 (71)	273 (30)	271 (23)	109 (65)	107 (42)	93 (100)	81 (60)	69 (89)
30b[a] (17,21,21-d_3)	403 (23)	290 (36)	289 (73)	273 (14)	272 (37)	111 (65)	107 (34)	96 (75)	81 (80)	69 (64)
				274 (17)			108 (19)			
							109 (27)			
30c[a] (26-d_3)	403 (30)	290 (53)	289 (92)	273 (38)	271 (44)	112 (61)	107 (65)	93 (100)	81 (50)	72 (69)
							108 (11)			71 (26)
							109 (27)			

[a] Isotopic purity of **30b** (94% d_3, 5% d_2) and **30c** (88% d_2, 6% d_2, 6% d_1).

mined that the ion of mass 109 consists of the entire side chain, whereas the ion of mass 93 contains carbons 16, 17, 20, 21, 22, and 23 and at least in part is generated by loss of isopropyl (25, 26, 27) from *m/e* 136 (Scheme V).

SCHEME V



Δ[20(22)] Olefins (Figure 3).—The mass spectrum of the Δ[20(22)] olefin **28** differs from that of the corresponding Δ[20(21)] isomer **27** in the more intense fragment of mass 138 which on subsequent loss of isopropyl furnishes *m/e* 95. This parent–daughter relationship (*m/e* 138 → 95) is confirmed by an appropriate metastable peak and the reversal of intensity upon lowering the electron voltage. Deuterium labeling (Table V) indicated that 75% of the ion of mass 95 arises in part (50%) from the reciprocal exchange of the C-17 or C-21 allylic hydrogens with the C-25 hydrogen as depicted in Scheme VI.

Δ[17(20)] Olefins (Figure 4).—The mass spectrum of 5α-cholest-17(20)-ene-3β,6α-diol (**26**) is characterized by a strong molecular ion peak and a base peak at *m/e* 317 corresponding to the loss of C_6H_{13}. Formally this represents an *a priori* unfavorable vinylic cleavage as depicted in structure p and labeling with deuterium at positions 21, 22, 23, and 26 confirms this conclusion.

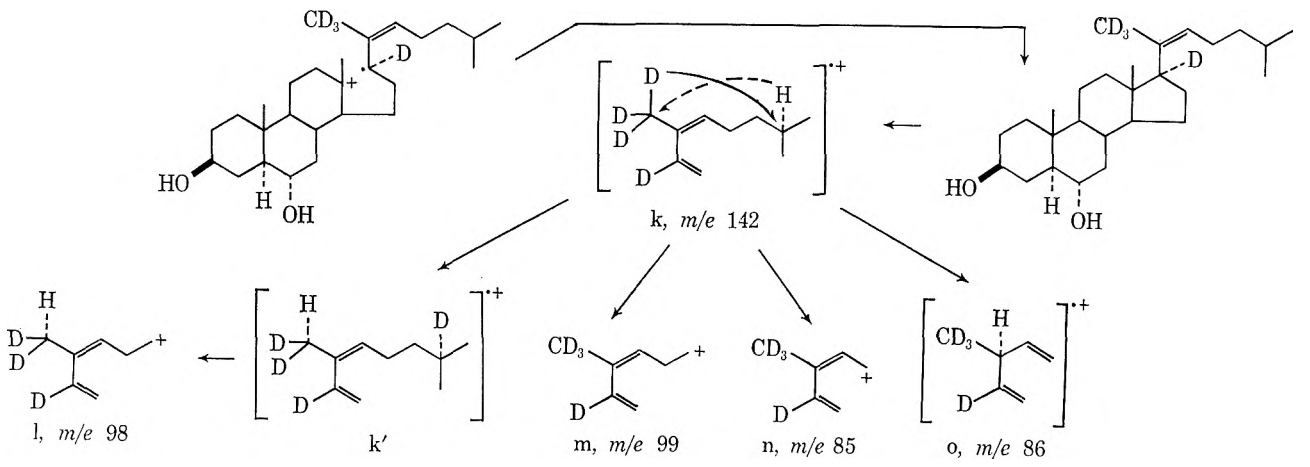
TABLE V

SHIFTS IN THE PRINCIPAL PEAKS (*m/e*) IN THE MASS SPECTRA OF DEUTERATED 5α-CHOLEST-20(22)-ENE-3β,6α-DIOL (28)

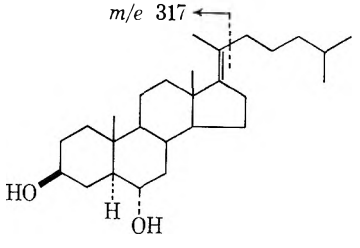
Compd	M⁺ (%)	*m/e* (%)								
28 (d_0)	402 (100)	371 (3)	317 (18)	290 (6) 289 (7)	276 (27)	247 (20)	152 (12)	138 (63)	95 (100)	82 (67) 81 (57)
28b[a] (17,21,21,21-d_4)	406 (100)	373 (4)	320 (10)	290 (8) 289 (9)	276 (37)	247 (31)	156 (10) 155 (7)	142 (67)	99 (99) 98 (71) 95 (57)	86 (72) 85 (46) 82 (45) 87 (30)
28c[a] (22-d_1)	403 (100)		317 (5)	290 (7) 289 (8)	276 (27)	247 (24)	153 (11)	139 (65)	96 (76) 95 (57)	83 (85) 82 (58) 87 (45)
28d[a] (23,23-d_2)	404 (100)	371 (3)	317 (4)	290 (6) 289 (8)	276 (34)	247 (23)	154 (12	140 (49)	97 (89) 95 (55)	84 (46) 83 (51) 82 (26) 87 (34)
28e[a] (24,24-d_2)	404 (100)	371 (7)		290 (10) 289 (12)	276 (38)	247 (30)	154 (15)	140 (82)	97 (64) 96 (72) 95 (100)	83 (73) 82 (70) 87 (66)

[a] Isotopic purity of 28b (86% d_4, 7% d_3, 7% d_2), 28c (88% d_2, 12% d_1), 28d (91% d_2, 4% d_1), and 28e (94% d_2, 5% d_1).

SCHEME VI



It is conceivable that this fragmentation is triggered by ionization of the 13–14 bond followed by bond formation between C-20 and C-14. Otherwise the spectrum (Figure 4) is characterized by complete absence of ring D cleavage,[27] a minor peak (*m/e* 289) due to loss of side chain and two hydrogens, and the complete absence of any diagnostic ions in the lower mass region.



p, *m/e* 317

Introduction of an additional Δ^{24} double bond (**29**) again alters dramatically the spectrum (see Figure 5). The doubly allylic cleavage (*m/e* 331) which is absent in the spectrum (Figure 2) of the $\Delta^{20(21),24}$-diene **30** becomes an important fragment; subsequent loss of water furnishes the base peak (*m/e* 313). The spectrum is devoid of any ring D cleavage or any other diagnostic ions.

Experimental Section

Melting points (Kofler) are uncorrected. All rotations were determined using chloroform as solvent unless otherwise mentioned. Nmr spectra were recorded ($CDCl_3$ with tetramethylsilane as internal standard) on a Varian T-60 or HA-100 spectrometer. All chemical shifts are reported in δ (parts per million) values. Mass spectra (direct inlet system) were obtained by Mr. R. Ross and Mr. R. T. Conover with an AEI MS-9 or Atlas CH-4 mass spectrometer. All gc was carried out at oven temperatures of 280–285° (unless otherwise specified) using a Hewlett-Packard hp 402 high efficiency gas chromatograph equipped with all-glass U-tube columns packed with 3% OV 25, OV 17 and OV 3 stationary phases coated over Gas-Chrom Q (100–120 mesh). All tlc was performed using E. Merck silica gel Hf_{254}.

5α-Cholestane-3β,6α-diol-23-one (4) and 5α,20α-Cholestane-3β,6α-diol-23-one (5).—Starfish sapogenin[2] diacetate **1b** (50 mg) was dissolved in ethyl acetate (15 ml) and hydrogenated over 10% palladium on charcoal (300 mg) at atmospheric pressure for 50 hr. The mixture was freed of the catalyst and evaporated to furnish a colorless gum which could be fractionated into two components by preparative gc.

4a (retention time 16 min): oil (20%); ir λ_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); CD (MeOH) θ_{290} −2367; nmr δ 0.66, 0.84 (C-18,-C-19 CH_3), 0.86 (d, J = 6.0 Hz, C-26,C-27 CH_3) 2.00 (s, 6 H, 2 $OOCCH_3$), 4.60 (c, 2 H, CHOAc); M^+ 502.

5a (retention time 18 min): oil (80%); ir λ_{max} ($CHCl_3$) 1720 cm^{-1}; CD (MeOH) θ_{290} +1732; nmr δ 0.66, 0.84 (C-18,C-19, CH_3), 0.86 (d, J = 6.0 Hz, C-26,C-27 CH_3), 2.00 (s, 6 H, 2 $OOCCH_3$), 4.60 (c, 2 H, CHOAc); M^+ 502.

Saponification (10% KOH in MeOH) of **4a** furnished **4**: mp 185–187° (plates from MeOH, three crystallizations); λ_{max}

($CHCl_3$) 1700 cm^{-1}; CD (MeOH) θ_{289} −2042; nmr δ 0.66, 0.84 (s, C-18, C-19 CH_3), 0.87 (d, J = 6 Hz, C-26, C-27 CH_3), 3.58 (c, 2 H, CHOH); M^+ 418.34228 (calcd for $C_{27}H_{46}O_3$, 418.34467); mass spectrum m/e (rel intensity) 400 (7, $M^+ - H_2O$), 361 (6%, $M^+ - C_4H_9$), 318 [100, $M^+ - CH_2{=}C(OH)C_4H_9$], 303 (32, 318 − CH_3), 300 (318 − H_2O), 289 (16, M^+ − side chain + 2 H), 285 (21, 303 − H_2O), 231 (7, ring D cleavage + H_2O + 1 H), 213 (11, 231 − H_2O), 161 (14), 141 (21), 127 (37), 122 (58), 95 (57), 85 (57), 81 (43), 57 (53), 43 (36), 41 (35).

Similar saponification of **5a** provided **5**: mp 165–167° (needles from MeOH, three crystallizations); λ_{max} ($CHCl_3$) 1700 cm^{-1}; CD (MeOH) $\theta_{287.5}$ +1693; nmr δ 0.66, 0.83 (s, 6 H, C-18,-C-19 CH_3), 0.87 (d, J = 6 Hz C-26, C-27 CH_3), 3.58 (b, 2 H, 3,6 CHOH); mass spectrum m/e (rel intensity) 418 (M^+, 3), 400 (4, $M^+ - H_2O$), 361 (5), 318 (100), 303 (30), 300 (27), 289, 285, 213, 175 (7), 161 (14), 127 (33), 122 (32), 95 (21), 81 (17), 69 (17), 57 (29), 55 (23), 43 (27), 41 (20).

5α-Cholestane-3β,6α-diol (6) and 5α,20α-Cholestane-3β,6α-diol (7).—Keto diol **4** (10 mg) was heated to 120° with diethylene glycol (0.2 ml) and hydrazine hydrate (0.8 ml) for 5 hr. Potassium hydroxide (0.7 g) was added and the temperature raised to 200° and maintained for 12 hr while a stream of nitrogen was blown over the reaction mixture. Dilution with water, extraction with chloroform, and tlc (chloroform–methanol 9:1, R_f 0.4) followed by crystallization from aqueous methanol furnished **6**, mp 216–218°, M^+ 404, identical in all respects (ir, nmr, mass spectrum) with a synthetic[28] sample of 5α-cholestane-3β,6α-diol.

Similar Wolff–Kishner reduction of **5** furnished **7**: mp 181–182° (methanol); ir λ_{max} (KBr) 3420 cm^{-1}; nmr δ 0.65, 0.82 (s, C-18,C-19 CH_3), 0.88 (d, J = 6.5 Hz, C-26,C-27 CH_3), 3.50 (b, 2 H, 3.6 >CHOH); mass spectrum m/e (rel intensity) 404 (72, M^+), 386 (61, $M^+ - H_2O$), 371 (386 − CH_3), 249 (21, ring D cleavage + 1 H), 231 (59, 249 − H_2O), 213 (21, 231 − H_2O), 141 (26), 123 (32), 109 (36), 95 (100), 87 (47), 69 (46), 57 (52), 55 (69), 43 (100).

Chromium trioxide–pyridine oxidation of **7** furnished the corresponding diketone **9**: mp 125–127° (methanol); ir λ_{max} ($CHCl_3$) 1715 cm^{-1}; nmr δ 0.76, 0.96 (s, C-18,C-19 CH_3), 0.87 (d, J = 6 Hz) (C-26,C-27 CH_3), 1.0–3.0 (c); mass spectrum m/e (rel intensity) 400 (100, M^+) 385 (7, $M^+ - CH_3$), 382 (3, $M^+ - H_2O$), 287 (21, M^+ − side chain), 245 (27, ring D cleavage), 169 (23), 149 (63).

5α-Pregnane-3β,6α-diol-20-one Diacetate.—To a solution of pregnenolone acetate 20-ethylene ketal[19] (6 g) at 0° was added dropwise BH_3–THF (1 *M*, 40.0 ml) (Alfa Inorganics Ventron). After the mixture stirred at 0° for 30 min, 5% NaOH (125 ml) was carefully added and stirring was continued for an additional 30 min. Hydrogen peroxide (30%, 63 ml) was then added. After 30 min the mixture was poured into ice–water. Chloroform extraction, washing with saturated ferrous sulfate, drying, and acetylation of the residue with acetic anhydride–pyridine for 24 hr afforded, after crystallization from methanol, 4.5 g (60%) of 5α-pregnane-3β,6α-diol-20-one 20-ethylene ketal diacetate: mp 165–167°; $[\alpha]^{21}D$ +31.01° (*c* 1.138); ir λ_{max} (KBr) 1717–1735 cm^{-1}. A solution of the ketal diacetate (1.2 g) in acetone (50 ml)–water (20 ml) was refluxed with *p*-toluenesulfonic acid (50 mg) for 5 hr. Dilution with water and ether extraction provided 5α-pregnane-3β,6α-diol-20-one diacetate as colorless gum: ir λ_{max} ($CHCl_3$) 1717–1735 cm^{-1}; nmr δ 0.56, 0.90 (s, C-18,C-19 CH_3), 2.0 (s, 6 H, 2 $OOCCH_3$), 2.03 (s, $COCH_3$), 4.50–5.10 (c, 2 H, 2 CHOAc); M^+ 418.

20-Hydroxy Steroids (12–15).—To a Grignard reagent prepared from isohexyl bromide or 1-bromo-4-methyl-3-pentene (5.0 g) and magnesium (600 mg) was added 800 mg of 5α-pregnane-3β,6α-diol-20-one diacetate or pregnenolone acetate in benzene (25 ml). After removal of ether by distillation, the mixture was refluxed for 15 hr. The complex was hydrolyzed by saturated ammonium chloride and the mixture extracted with chloroform to yield a gummy solid. Preparative tlc over silica gel Hf_{254} (benzene–acetone), crystallization from acetone–hexane, and subsequent multiple crystallizations from aqueous acetone furnished the pure 20α-hydroxy steroids **12–15** (50–60% yield).

Cholest-5-ene-3β,20α-diol[21] (12): mp 120–122°; diacetate **12a** mp 150–151° (lit.[21] mp 123–125 and 155–156°).

Cholesta-5,24-diene-3β,20α-diol (13): mp 96–98° (needles from MeOH, dried over boiling benzene under vacuum); $[\alpha]^{21}D$ −61.1° (*c* 0.77); mass spectrum m/e (rel intensity) 382 (23, $M^+ - H_2O$), 317 (19, $M^+ - C_6H_{11}$), 297 (28, 317 − H_2O), 271 (90, M^+ − side chain + 2 H + H_2O), 256 (17), 255 (15), 241 (8), 229 (5), 213 (7), 199 (5), 189 (5), 185 (6), 159 (20), 127 [22, $CH_3C(=^+OH)(CH_2)_2CHC(CH_3)_2$], 109 (100, 127 − H_2O), 95 (30), 82 (44), 69 (62), 55 (34), 43 (66).

Acetylation of **13** furnished the monoacetate **13a**, mp 143–145° (needles from hexane).

5α-Cholestane-3β,6α,20α-triol (14): mp 191–193° (aqueous acetone); $[\alpha]^{21}D$ +21.6° (*c* 0.485); mass spectrum m/e (rel intensity) 402 (32, $M^+ - H_2O$), 384 (402 − H_2O), 369 (6, 384 − CH_3), 335 (91, $M^+ - C_6H_{13}$), 299 (42, 335 − $2H_2O$), 273 (31), 271 (65), 256 (25), 241 (13), 159 (20), 147 (19), 129 [55, $CH_3(=^+OH)(CH_2)_3CH(CH_3)_2$], 95 (90), 81 (50), 69 (100), 55 (77), 43 (51), 41 (36).

Oxidation of **14** with CrO_3/Py furnished **14b**: $[\alpha]^{21}D$ −12.0° (*c* 0.25); mp 142–144° (needles from aqueous methanol); mass spectrum m/e (rel intensity) 416 (3, M^+), 331 (100, $M^+ - C_6H_{13}$), 313 (60, 331 − H_2O), 288 (46), 287 (35), 138 (57), 129 [69, $CH_3C(=^+OH)(CH_2)_3CH(CH_3)_2$], 111 (48, 129 − H_2O), 69 (50), 55 (33), 43 (32).

5α-Cholest-24-ene-3β,6α,20α-triol (15): mp 162–165° (needles from aqueous acetone); $[\alpha]^{21}D$ +22.6° (*c* 0.415); mass spectrum m/e (rel intensity) 403 (1), 400 (3), 335 (13), 318 (11), 317 (16), 299 (12), 290 (13), 289 (44), 273 (20), 241 (6), 229 (5), 161 (8), 159 (12), 135 (18), 127 (24), 109 (100), 95 (48), 82 (86), 69 (88), 55 (31), 43 (67).

$\Delta^{17(20)}$, $\Delta^{20(21)}$, and $\Delta^{21(22)}$ Steroidal Olefins (20–31). A. Dehydration of 20-Hydroxy Steroids (12a–15a) by Phosphorus Oxychloride.—Freshly distilled phosphorus oxychloride (0.4 ml) was added dropwise with vigorous stirring to a solution of 100 mg of the 20-hydroxy steroid (**12a–15a**) in pyridine (4.0 ml). After 12 hr the mixture was poured into ice–water and extracted with ether. Preparative tlc over silica gel HF_{254} (PhH–EtOAc, 9:1) furnished a mixture of olefins which was further fractionated over 15% siliver nitrate impregnated silica gel. The order of elution (benzene) was $\Delta^{17(20)} > \Delta^{20(22)} > \Delta^{20(21)}$ (without Δ^{24}) and $\Delta^{20(22)} > \Delta^{17(20)} > \Delta^{20(21)}$ (with Δ^{24}); percentage yields and gc mobilities of these olefins are presented in Tables I and VI. Both

TABLE VI

RETENTION TIMES[a] RELATIVE TO CHOLESTEROL OVER OV 25 AND OV 3 COLUMNS

		OV 25, 3% over Gas-Chrom Q		OV 3, 3% over Gas-Chrom Q	
Compd	Acetate	Parent	Acetate	Parent	Acetate
6	6a			1.84	
7	7a			1.66	
10	10a			1.66	
12	12a		2.13		1.96
13	13a	2.25	2.63	1.75	2.16
14	14a	4.10	4.90	2.90	3.96
15	15a	5.05	6.20	3.27	4.36
20	20a		0.95, 1.10		1.15, 1.23
21	21a	1.00	1.20	0.95	1.26
22	22a	1.10	1.255	0.975	1.35
23	23a	1.20	1.45	1.02	1.30
24	24a	1.20	1.45	1.02	1.38
25	25a		1.60		1.50
26	26a	2.05, 2.20	2.32, 2.55	1.56, 1.75	2.20, 2.38
27	27a	2.30	2.65	1.72	2.39
28	28a	2.55	2.76	1.85	2.56
29	29a	2.70	3.30	1.90	2.31, 2.47
30	30a	2.78	3.35	1.92	2.52
31	31a		3.90		2.75

[a] For gas chromatographic mobilities of 11-functionalized 20α steroid, see J. J. Schneider and L. J. Haffner, *J. Chromatogr.*, **70**, 194 (1972); J. J. Schneider, *Tetrahedron*, **28**, 2717 (1972).

cis and trans $\Delta^{17(20)}$ olefins were produced and separated by preparative gc, whereas only one of the two possible $\Delta^{20(22)}$ olefins could be detected by analytical gc over OV 25, OV 17, and OV 3.

B. Dehydration of 20-Hydroxy Steroids (12a–15a) by Thionyl Chloride.—Thionyl chloride (0.5 ml) was added dropwise to a vigorously stirred ice-cold solution of the 20-hydroxy steroid (100 mg) in pyridine (4.0 ml). After 10 min the mixture was poured into ice–water and worked up as described in A.

(28) S. Wolf, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

C. Dehydration of 14 by Propionic Acid.—The hydroxy steroid 14 (200 mg) was refluxed in propionic acid (5.0 ml) for 12 hr. The mixture was poured into saturated ice-cold sodium carbonate solution and extracted with ether. The ether extract, after saponification with 10% potassium hydroxide in methanol (10 ml) at room temperature for 6 hr, was acetylated to furnish the crude acetate (for details see Table I).

Cholesta-5,20(21)dien-3β-ol (21): mp 111–112°; acetate **21a** mp 101–102° (lit.[15] mp 100–101°); mass spectrum *m/e* (rel intensity) 384 (100, M^+), 369 (9, $M^+ - CH_3$), 366 (9, $M^+ - H_2O$), 351 (23, 369 − H_2O), 314 (6, $M^+ - C_5H_{10}$), 299 (5, 314 − CH_3), 281 (3, 299 − H_2O), 272, 271 (5, 4, M^+ − side chain + 1 H and 2 H), 229 (15, ring D cleavage + 3 H), 213 (13, ring D cleavage + H + H_2O), 159 (7), 152 (4), 145 (12), 138 (3), 133 (8), 95 (31), 81 (25), 69 (27), 55 (36), 43 (68).

Cholesta-5,20(22)-dien-3β-ol (22): mp 135–138° (lit.[3] mp 135–138°); mass spectrum *m/e* (rel intensity) 384 (100%, M^+), 369 (7, $M^+ - CH_3$), 366 (6, $M^+ - H_2O$), 351 (14, 369 − H_2O), 299 (7, $M^+ - C_6H_{13}$), 272, 271 (5, 8, M^+ − side chain + 1 H and 2 H), 258 (10, $M^+ - C_9H_{18}$), 229 (9, ring D cleavage + 3 H), 138 (17, $C_{10}H_{18}$), 95 (35), 81 (23), 69 (19), 57 (17), 55 (20), 43 (15).

Cholesta-5,17(20),24-trien-3β-ol (23): mp 44° (plates from aqueous methanol); $[\alpha]^{21}D$ −64.7° (*c* 0.235); mass spectrum *m/e* (rel intensity) 382 (57, M^+), 367 (9, $M^+ - CH_3$), 313 (95, $M^+ - C_5H_9$), 295 (100, 313 − H_2O), 272, 271 (12, 20, M^+ − side chain + 1 H and 2 H), 187 (21), 159 (31), 149 (45), 145 (28), 135 (32), 133 (37), 121 (31), 119 (40), 109 (55), 107 (42), 105 (37), 95 (88), 93 (37), 91 (39), 81 (52), 69 (70), 55 (46), 41 (70).

Cholesta-5,20(21),24-trien-3β-ol (24): mp 88–91° (needles from aqueous MeOH); $[\alpha]^{21}D$ −55.7° (*c* 0.35); mass spectrum *m/e* (rel intensity) 382 (65, M^+), 367 (23, $M^+ - CH_3$), 364 (11, $M^+ - H_2O$), 349 (23, 367 − H_2O), 272, 271 (49, 100, M^+ − side chain + 1 H and 2 H), 255 (21), 253 (22, 271 − H_2O), 229 (13), 213 (28, ring D cleavage + 1 H + H_2O), 159 (30), 145 (52), 133 (36), 121 (30), 109 (73), 107 (57), 105 (50), 95 (55), 93 (77), 91 (47), 81 (67), 79 (63), 69 (75), 67 (47), 55 (53), 41 (67).

Acetylation of 24 furnished the monoacetate **24a**, mp 75–77° (MeOH).

Cholesta-5,20(22),24-trien-3β-ol acetate (25a): mass spectrum *m/e* (rel intensity) 424 (4, M^+), 364 [100, $M^+ - CH_3C(=O)OH$], 313 (7, M^+ − side chain + 2 H), 282 (67), 254, 253 (32, 43, 364 − side chain + 1 H and 2 H), 228 (19), 213 (21), 211 (17), 199 (8), 185 (6), 173 (7), 159 (15), 158 (18), 157 (15), 147 (21), 145 (29), 143 (18), 136 (27), 135 (29), 133 (24), 121 (38), 119 (23), 117 (11), 109 (45), 107 (37), 105 (36), 95 (33), 93 (55), 91 (27), 82 (21), 81 (36), 80 (25), 79 (26), 69 (30), 67 (26), 58 (17), 55 (30), 43 (52).

5α-Cholest-17(20)ene-3β,6α-diol (26): mp 156–158° (small needles from aqueous MeOH); 98% trans by gc; M^+ 402 (Figure 4).

5α-Cholest-20(21)-ene-3β,6α-diol (27): mp 176–178° (needles from aqueous MeOH); $[\alpha]^{21}D$ +30.4° (*c* 0.31); M^+ 402 (Figure 1).

5α-Cholest-20(22)-ene-3β,6α-diol (28): mp 156–158° (small needles from MeOH–H_2O); $[\alpha]^{21}D$ +23.5° (c 0.21); M^+ 402 (Figure 3).

The corresponding diacetate **28a** had M^+ 486. Oxidation of **28** with CrO_3/Py furnished two polymorphic forms of the diketone **28b**: mp 102–103 and mp 124–127° (needles from MeOH); mass spectrum *m/e* (rel intensity) 398 (83, M^+), 383 (12, $M^+ - CH_3$), 328 (8, $M^+ - C_5H_{10}$), 313 (25, $M^+ - C_6H_{13}$), 285 (31, M^+ − side chain + 2 H), 272 (53), 259 (51), 245 (17, ring D cleavage + 1 H), 138 (65, $C_{10}H_{18}$), 123 (35), 109 (45), 95 (100), 81 (65), 69 (61), 55 (60), 41 (46).

5α-Cholesta-17(20),24-diene-3β,6α-diol (29): mp 153–155°; $[\alpha]^{21}D$ +22.17° (*c* 0.212); M^+ 400 (Figure 5). Acetylation furnished the diacetate **29a**, M^+ 484.

5α-Cholesta-20(21),24-diene-3β,6α-diol (30): mp 167–168° (plates from aqueous EtOH); $[\alpha]^{21}D$ +25.0° (*c* 0.30); M^+ 400 (Figure 2). The corresponding diacetate **30a** had mp 108–109° (needles from MeOH); M^+ 484.

5α-Cholesta-20(22),24-diene-3β,6α-diol diacetate (31a): mass spectrum *m/e* (rel intensity) 484 (42 M^+), 424 (14, $M^+ - CH_3CO_2H$), 373 (90, M^+ − side chain + 2 H), 364 (424 − CH_3CO_2H), 342 (15), 315 (7), 314 (25), 313 (16), 283 (22), 255 (32), 253 (14), 227 (17), 213 (17), 161 (35), 136 (74), 135 (75), 133 (62), 121 (60), 110 (70), 109 (90), 107 (58), 95 (58), 93 (88), 82 (89), 81 (64), 80 (53), 69 (60), 67 (43), 55 (53), 43 (100), 41 (49).

5α,20α-Cholestane-3β,6α-diol (7).—5α-Cholest-20(21)-ene-3β,6α-diol (**27**, 25 mg) was dissolved in methanol (7 ml) and hydrogenated over platinum dioxide (80 mg) at atmospheric pressure for 12 hr. The product mixture (gc analysis) was composed of 47% 5α,20α-cholestane-3β,6α-diol (**7**) and 53% 5α-cholestane-3β,6α-diol (**6**). Preparative glc followed by crystallization from aqueous methanol furnished **7**: mp 178–181° (star shaped needles); $[\alpha]^{21}D$ 31.0° (*c* 0.08); undepressed mixture melting point with α diol derived from natural star fish genin **1**. Both diols depicted identical spectral characteristics (ir, nmr, mass spectra). Oxidation of **7** with CrO_3/Py furnished 5α,20α-cholestane-3,6-dione, mp 118–121°, M^+ 400. A similar hydrogenation [10% Pd/C (100 mg), EtOAc (7 ml)] of **27a** and **30a** (25 mg) for 24 hr furnished **6a** and **7a** which on subsequent saponification gave **6** and **7**.

5α,17α,20α-Cholestane-3β,6α-diol (10).—The $\Delta^{17(20)}$ olefinic diacetates **26a** and **29a** (35 mg) were hydrogenated at atmospheric pressure over 10% palladium on charcoal (100 mg) in ethyl acetate (12 ml) for 18 hr. Preparative gc followed by saponification and crystallization furnished **10** (60%), mp 178–180°, which was depressed (mp 175–178°) upon admixture with diol (mp 181–182°) derived from natural starfish genin **1**. Oxidation of **10** with CrO_3/Py furnished 5α,17α,20α-cholestane-3,6-dione (**11**), mp 140–142° (needles from MeOH), M^+ 400.

5α,20α-Cholestane (7b).—Hydrocarbons derived by Wolff–Kishner reduction of the diketone **9** (from natural starfish genin **1**) and from 20α-cholestanol[24] depicted identical mass spectra and gc retention times (OV 25).

1-Bromo-4-methyl-3-pentene-*4*-d_3.—Cyclopropyl methyl ketone (10.0 g, Aldrich Chemical Co.) was mixed with D_2O (50.0 ml). Anhydrous potassium carbonate (200 mg) was added and the mixture stirred at room temperature for 1 week. The mixture, after saturation with sodium chloride, was extracted with ether. Fractionation of the ether residue furnished cyclopropyl-d_3 methyl ketone (4.5 g) which on reaction with a 10-fold excess of methylmagnesium chloride gave cyclopropyl-*methyl*-d_3-methylcarbinol (3.7 g, 70%).

Reaction of the deuterated carbinol with ice-cold hydrobromic acid (35%, 10 ml) for 1 hr furnished 1-bromo-4-methyl-3-pentene-*4*-d_3 (cis:trans 1:1) which was used directly in the Grignard reaction.

Deuterated 2-Bromo-4-methylpentanes.—1-Bromo-4-methylpentane-*1,1*-d_2 was prepared by $LiAlD_4$ reduction of isohexanoic acid followed by reaction of the intermediate 1,1-d_2 alcohol with triphenylphosphine and bromine in DMF. 1-Bromo-4-methylpentane-*2,2*-d_2 was synthesized by condensation of isobutyl bromide with diethyl malonate, reaction of the intermediate diethyl isobutylmalonate with NaOD in D_2O and then $POCl_3$, followed by reduction of the intermediate isocaproic acid-*2,2*-d_2 with $LiAlH_4$ with subsequent conversion of the 2-2-d_2 alcohol to the corresponding bromide. Isohexyl bromide-*2,2*-d_2 was prepared by a similar sequence except that the deuterated bromide was employed.

Acknowledgment.—We are indebted to the National Institutes of Health (Grant No. GM-06840) for financial assistance and to Mr. R. Ross, Mr. R. E. Conover, and Dr. L. J. Durham for mass spectral and nmr measurements.

Registry No.—**1b**, 37717-06-9; **4**, 41083-69-6; **4a**, 37717-07-0; **5**, 41083-71-0; **5a**, 37717-08-1; **6**, 41083-73-2; **7**, 41083-74-3; **7b**, 41083-75-4; **9**, 41083-76-5; **10**, 41083-77-6; **10b**, 41083-78-7; **12**, 516-72-3; **12a**, 7484-20-0; **13**, 41083-81-2; **13a**, 41083-82-3; **14**, 24339-14-8; **14a**, 41083-84-5; **14b**, 24339-15-9; **15**, 41083-86-7; **15a**, 41083-87-8; *cis*-**20**, 41083-88-9; *trans*-**20**, 21903-19-5; **21**, 41083-90-3; **21a**, 33168-77-3; **22**, 21903-21-9; *cis*-**23**, 41083-93-6; *trans*-**23**, 41083-94-7; *cis*-**23a**, 41083-95-8; *trans*-**23a**, 41083-96-9; **24**, 41083-97-0; **24a**, 41083-98-1; **25a**, 41083-99-2; *trans*-**26**, 41084-00-8; *trans*-**26a**, 41084-01-9; **27**, 41084-02-0; **27a**, 41084-03-1; **27b**, 41084-04-2; **27c**, 41084-05-3; **27d**, 41084-06-4; **27e**, 41084-07-5; **27f**, 41113-70-6; **28**, 41084-08-6; **28a**, 41084-09-7; **28b**, 41084-10-0; **28b**-*17,21,21,21-d_4*, 41084-11-1; **28c**, 41084-12-2; **28d**, 41084-13-3; **28e**, 41084-14-4; *cis*-**29**, 41084-15-5; *trans*-**29**, 41084-16-6; *cis*-**29a**, 41084-17-7; *trans*-**29a**, 41084-18-8; **30**, 41084-19-9; **30a**, 41084-20-2; **30b**, 41084-21-3; **30c**, 41084-22-4; **31**, 41084-23-5; **31a**, 41084-24-6; 5α-pregnane-3β,6α-diol-20-one diacetate, 37772-22-8; pregnenolone acetate 20-ethylene ketal, 40148-10-5; 5α-pregnane-3β,6α-diol-20-one 20-ethylene ketal diacetate, 40148-12-7.

Silyl Derivatives of Steroids. Evidence for Intramolecular Silylation Processes and Electron Impact Induced Reciprocal Exchange of Trimethylsilyl Groups

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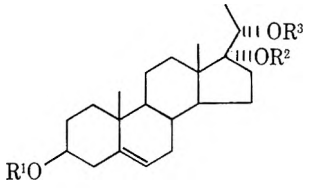
The preparation of mixed trimethylsilyl-d_0 and trimethylsilyl-d_9 derivatives of 17α,20-dihydroxy steroids is described, in which the labeled silyl groups occupy specific positions. The reaction products are analyzed by mass spectrometry and evidence is presented for migration of the 20-trimethylsilyl group to the 17α position during silylation. Electron impact ionization is shown to cause reciprocal exchange of the 17α- and 20α-trimethylsilyl groups in the formation of certain ions in the mass spectrum of the trimethylsilyl derivative of 5-pregnene-3β,17α,20α-triol.

Trimethylsilylation is a well-established technique for the study of numerous types of compounds by gas chromatography–mass spectrometry. Replacement of hydroxylic or other labile hydrogen atoms with trimethylsilyl groups enhances the volatility of most compounds. Consequently the technique has been particularly useful in the identification of hydroxylated steroids as their derived trimethylsilyl ethers.[1] The mass spectra of the trimethylsilyl derivatives of many compounds often exhibit abundant rearrangement ions due to the interaction of the silyl group with other functional groups in the molecule.[2] These ions are often structurally diagnostic and thus recognition of their trimethylsilyl content is of major importance. This has been greatly facilitated by the introduction of perdeuteriotrimethylsilylating reagents.[3]

We have recently reported the preparation of mixed trimethylsilyl (silyl-d_0) and perdeuteriotrimethylsilyl (silyl-d_9), derivatives of hydroxy steroids in which the silyl-d_9 group was selectively introduced in a certain position with a specificity of 90% or more.[4] This selective silylation was accomplished by utilizing the different rates of reaction of sterically hindered and unhindered hydroxyl groups towards various trimethylsilylating reagents.[5] A typical example[4] of the method employed is shown in reaction 1, and it involved (a) the silylation of unhindered hydroxyl groups by treating the sample with a relatively weaker silylating reagent such as bis(trimethylsilyl)trifluoroacetamide (BSTFA) under mild conditions (step I), (b) removal of solvent and reagents, and (c) reaction of the hindered hydroxyl groups under more severe conditions with *N*-trimethylsilyl-d_9-imidazole (TSIM-d_9) (step II). Selectively labeled silyl-d_0 and silyl-d_9 derivatives were helpful in the interpretation of the mass spectra of trimethylsilyl steroidal ethers, since one could identify the parts of the steroid structure involved in the formation of the various trimethylsilyl-containing ions.

In the examples discussed previously the hydroxyl groups selectively silylated with silyl-d_0 and silyl-d_9 groups were widely separated, and this positional identity was retained in the fragment ions produced upon electron impact. We report here on our efforts to introduce selectively silyl-d_0 and silyl-d_9 groups in hydroxyl functions which are attached to adjacent carbon atoms. As examples we have chosen steroids of the pregnane and pregnene series containing both a sterically hindered (17α-) and an unhindered (20α- or 20β-) hydroxyl group. The compounds studied were 5-pregnene-3β,17α,20α-triol (**1**), 5α-pregnane-3β,17α,-20α-triol, and their 20β isomers. Only compound **1** will be discussed in detail here since virtually identical results were obtained with the other compounds as well. The mass spectra of the partial trimethylsilyl ethers (**2** and **3**) of **1** and of its pertrimethylsilyl ether (**4**) are discussed below, and the observed fragmentation patterns are used as a guide to ascertain the mechanism of silylation of the hydroxyl groups.



1, $R^1 = R^2 = R^3 = H$

2, $R^1 = R^3 = Si(CH_3)_3$; $R^2 = H$
2a, $R^1 = R^3 = Si(CD_3)_3$; $R^2 = H$
2b, $R^1 = R^2 = Si(CH_3)_3$; $R^2 = D$
2c, $R^1 = R^2 = Si(CH_3)_3$; $R^2 = H$; 20-^{18}O

3, $R^1 = R^2 = Si(CH_3)_3$; $R^3 = H$
3a, $R^1 = R^2 = Si(CD_3)_3$; $R^3 = H$
3b, $R^1 = R^2 = Si(CH_3)_3$; $R^3 = D$
3c, $R^1 = R^2 = Si(CH_3)_3$; $R^3 = H$; 20-^{18}O

4, $R^1 = R^2 = R^3 = Si(CH_3)_3$
4a, $R^1 = R^2 = R^3 = Si(CD_3)_3$
4b, $R^1 = R^2 = Si(CH_3)_3$; $R^3 = Si(CD_3)_3$
4c, $R^1 = R^2 = Si(CD_3)_3$; $R^3 = Si(CH_3)_3$

Results and Discussion

Structures of Partially Silylated Steroids.—The high efficiency of the selective silylation observed in reaction 1[4] would *a priori* suggest a silylation sequence according to pathway a outlined in reaction 2. Gas chromatography (9-ft, 1% OV-17 column) of the partially silylated steroid from reaction of **1** with BSTFA (step I) revealed in each case a well-resolved doublet

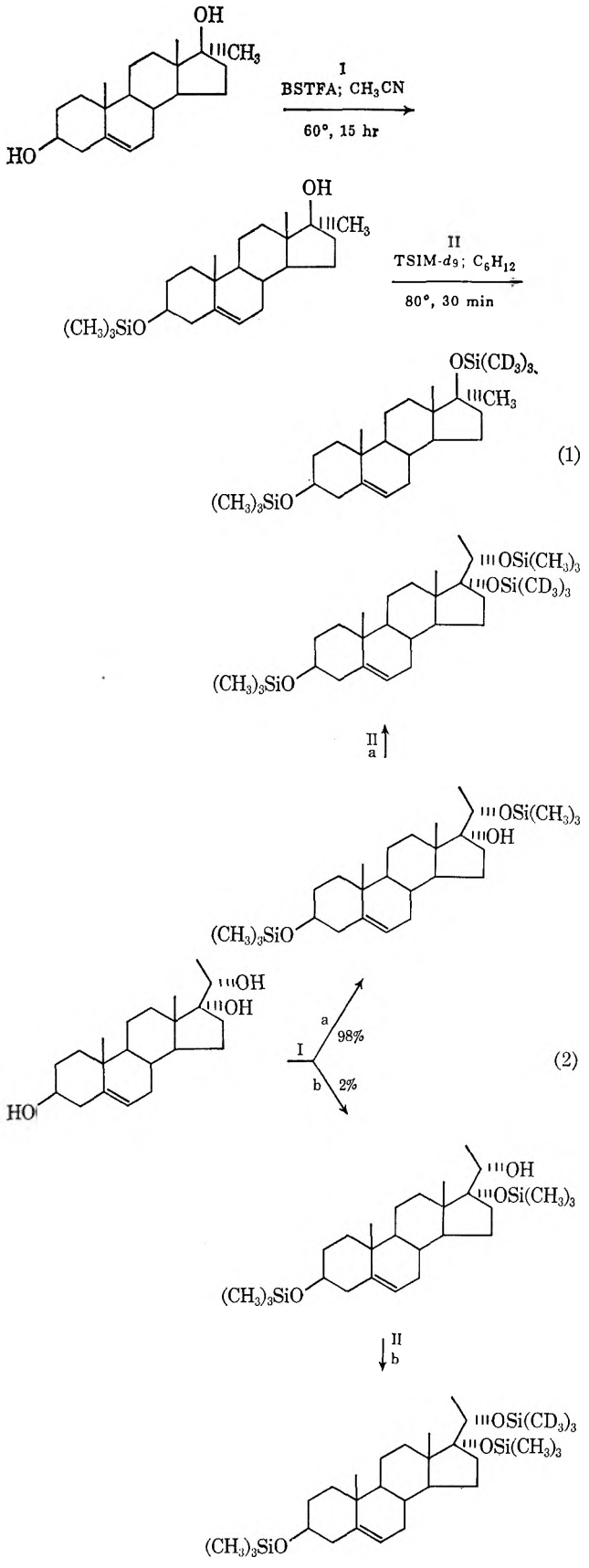
(1) (a) E. C. Horning, C. J. W. Brooks, and W. J. A. VandenHeuvel, *Advan. Lipid Res.*, **6**, 273 (1968); (b) C. J. W. Brooks and B. S. Middleditch, "Modern Methods of Steroid Analysis," E. Heftmann, Ed., Academic Press, New York, N. Y., in press.

(2) (a) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967); (b) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968); (c) E. White, V, and J. A. McCloskey, *J. Org. Chem.*, **35**, 4241 (1970), and references cited therein.

(3) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968).

(4) P. Vouros and D. J. Harvey, *Anal. Chem.*, **45**, 7 (1973).

(5) (a) E. M. Chambaz and E. C. Horning, *Anal. Lett.*, **1**, 201 (1967); (b) E. M. Chambaz and E. C. Horning, *Anal. Biochem.*, **30**, 7 (1969); (c) E. Sakauchi and E. C. Horning, *Anal. Lett.*, **4**, 41 (1971).



consisting of a major (>98%) and a minor component. The fraction of the latter was observed to increase to ~5% on occasions when step I was carried out at temperatures as high as 68°. This temperature effect suggests that the minor component is formed mainly during silylation rather than as a result of thermal isomerization during gas chromatography. The mass spectra of the principal and minor components following partial silylation of the Δ^5 steroid (**1**) are shown in Figures 1 and 2, respectively.

A major fragmentation process in the mass spectra of 20-trimethylsilyloxy pregnanes or pregnenes involves cleavage of the C-17/20 bond,[6] resulting in the formation of ions of the type $(CH_3)_3\overset{+}{S}iO{=}CHCH_2R$ and/or $[M - (CH_3)_3SiO\dot{C}HCH_2R]^+$ depending on the disposition of the positive charge. The mass spectrum of the principal product (Figure 1) of partial silylation of 5-pregnene-3β,17α,20α-triol (**1**) exhibits strong and significant peaks at $[M - 117]^+$ (*m/e* 361) and *m/e* 117 corresponding to the presence of a 20α-trimethylsilyloxy function. A metastable peak at *m/e* 359.2 indicates the further decomposition of $[M - 117]^+$ to *m/e* 360 by loss of a hydrogen radical. The intense peak at *m/e* 129[6a,7] confirms the formation of a 3β,20α-bis(trimethylsilyloxy)-5-pregnen-17α-ol (**2**) according to path a of reaction 2. By contrast, the spectrum of the isomeric minor component (Figure 2) exhibits no peak at $[M - 117]^+$, but shows a loss of 45 amu from the molecular ion, providing an ion formed by cleavage of the 17β side chain and elimination of $CH_3\dot{C}HOH$ (*m/e* 433). The intensity of the *m/e* 129 peak is consistent with the presence of a Δ^5-3β-trimethylsilyloxy function as in structure **3**.

The cleavage of the 17β side chain in the mass spectra of the partially silylated products following step I, clearly indicates that silylation step I (reaction 2) proceeds mainly (>98%) *via* reaction path a, and **2** represents the structure of the main component formed. It might be noted here that the aforementioned fragmentations of the 17β side chain were confirmed by deuterium labeling of the C-20 hydrogen and of the free hydroxylic hydrogen, ^{18}O labeling of the C-20 oxygen, and preparation of perdeuteriotrimethylsilyl derivatives (compounds **2a–c**, **3a–c**).

A significant common feature in the mass spectra of both isomers **2** and **3** is the favorable elimination of methane—or the elements thereof—from the respective molecular ions to give the peak at *m/e* 462. The isotope labeling data support the fragmentation mechanism proposed in Scheme I, involving interaction of the 20α and the 17α substituents. This interaction is presumably responsible for the elimination of $C_2H_5O\cdot$ and C_2H_5OH from the molecular ion of the 20-trimethylsilyloxy derivative (**2**) to give the small (<2% R.I.) peaks at *m/e* 432 and 433. Formation of these ions requires reciprocal exchange of the 20α-silyl group and 17α hydrogen and the significance of this observation will become evident in the discussion of the spectra of the fully silylated derivative **4**.

Structures of Selectively Silylated (Silyl-d_0, Silyl-d_9) Steroids. (a) Reaction of 5-Pregnene-3β,17α,20α-triol (1).—As indicated above the initial silylation reaction of **1** (step I) produced mainly a 3β,20α-bis(trimethylsilyloxy) derivative (**2**). Elucidation of the structure of the selectively silylated steroid, following step II, and of the disposition of the silyl-d_0 and silyl-d_9 groups requires

(6) (a) C. J. W. Brooks, E. M. Chambaz, W. L. Gardiner, and E. C. Horning, *Excerpta Med. Found. Int. Congr. Ser.*, **132**, 366 (1966); (b) J. Sjövall and R. Vihko, *Steroids*, **7**, 447 (1966); (c) J.-Å. Gustafsson, C. H. L. Shackleton, and J. Sjövall, *Eur. J. Biochem.*, **10**, 302 (1969).

(7) (a) P. Eneroth, K. Hellström, and R. Ryhage, *J. Lipid Res.*, 245 (1964); (b) J. Diekman and C. Djerassi, *J. Org. Chem.*, **32**, 1005 (1967).

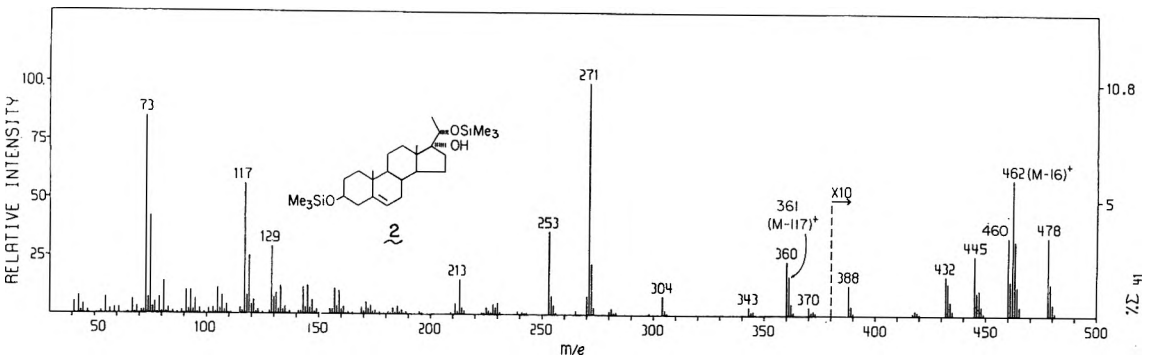


Figure 1.—Mass spectrum of major component following partial silylation of 1 with BSTFA and identified as 3β,20α-bis-(trimethylsilyloxy)-5-pregnen-17α-ol (2).

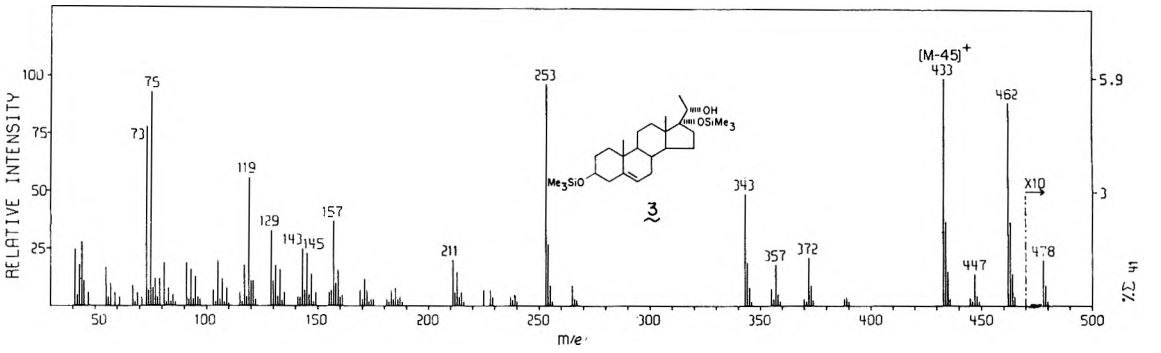
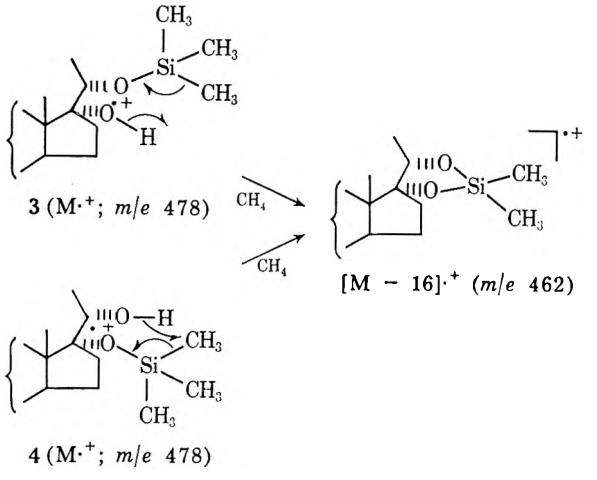


Figure 2.—Mass spectrum of minor component following partial silylation of 1 with BSTFA and identified as 3β,17α-bis-(trimethylsilyloxy)-5-pregnen-20α-ol (3).

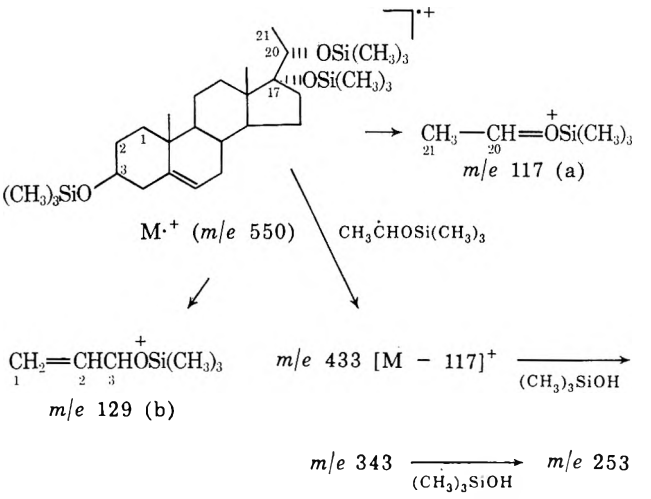
SCHEME I

ELIMINATION OF METHANE (OR CH_3 + H) IN THE MASS SPECTRA OF 2 AND 3



SCHEME II

PRINCIPAL FRAGMENTATIONS IN THE MASS SPECTRUM OF 5-PREGNENE-3β,17α,20α-TRIS(TRIMETHYLSILYL) ETHER (4)



comprehension of the major fragmentation pathways of the fully silylated derivative (4). The mass spectrum of 4, prepared by overnight reaction of 1 with *N*-trimethylsilylimidazole (TSIM) at 90°, is shown in Figure 3a and the major fragmentation pathways outlined in Scheme II. The silyl content of the major fragment ions can easily be recognized upon examination of the spectrum of the perdeuteriotrimethylsilyl derivative of 1 (4a, Figure 3b). The mechanism of formation of the ion at *m/e* 129 has been described before.[6b,7] The ion at *m/e* 147 [$(CH_3)_3SiOSi(CH_3)_2^+$, c] is a rearrangement ion typical of many compounds containing two or more trimethylsilyloxy groups.[8] Ion c is formed here apparently by interaction of the 17α- and 20α-trimethylsilyloxy groups.[9]

Figure 3c shows the mass spectrum of the mixed silyl-d_0 and silyl-d_9 derivative of 1 prepared as described above by treating initially with BSTFA and

(8) (a) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968); (b) J. Dieckman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **33**, 2271 (1968); (c) D. C. DeJongh, T. Radford, J. D. Hribar, S. Hanessian, M. Bieber, G. Dawson, and C. C. Sweeley, *J. Amer. Chem. Soc.*, **91**, 1728 (1969).

(9) S. Sloan, D. J. Harvey, and P. Vouros, *Org. Mass Spectrom.*, **6**, 789 (1971).

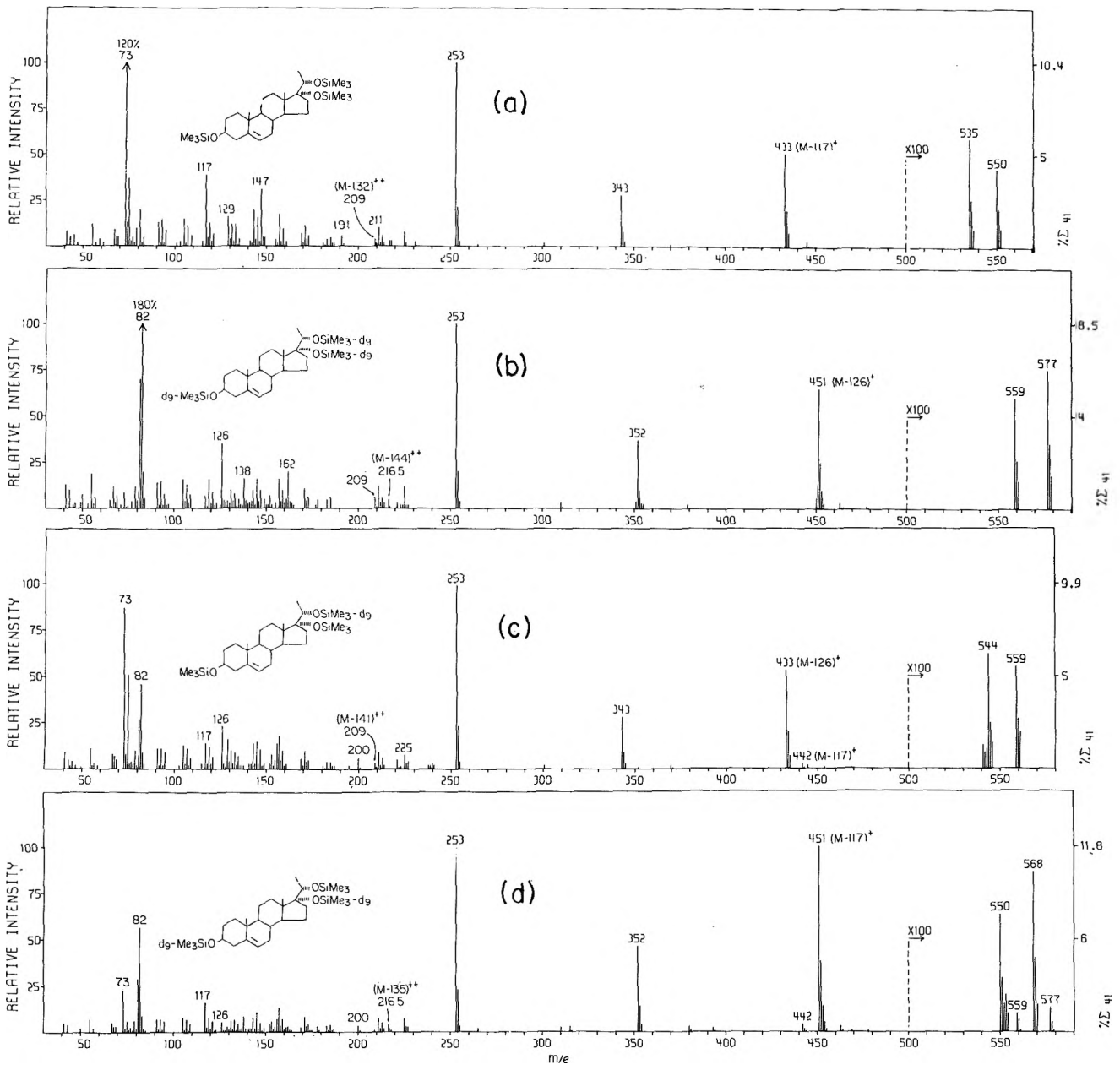
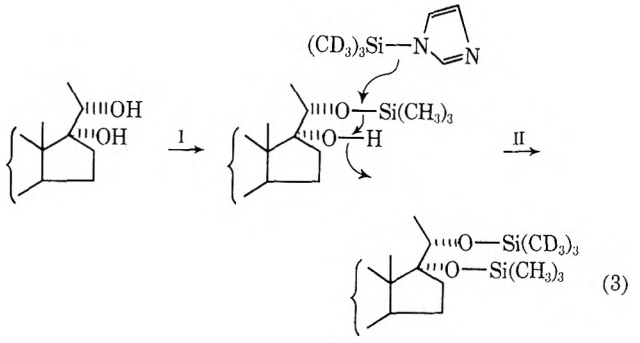


Figure 3.—(a) Mass spectrum of 5-pregnene-3β,17α,20α-tris(trimethylsilyl-d_0) ether (**4**); (b) mass spectrum of 5-pregnene-3β,17α,-20α-tris(trimethylsilyl-d_9) ether (**4a**); (c) mass spectrum of 3β,17α-bis(trimethylsilyloxy-d_0)-5-pregnene-20α-trimethylsilyloxy-d_9 (**4b**); (d) mass spectrum of 3β,17α-bis(trimethylsilyloxy-d_9)-5-pregnene-20α-trimethylsilyloxy-d_0 (**4c**).

then with TSIM-d_9. The shift of the molecular ion from m/e 550 to 559 indicates incorporation of one silyl-d_9 group. If the silylation had proceeded according to the sequence shown in IIa (reaction 2), one would expect loss of 117 amu [$CH_3\dot{C}HOSi(CH_3)_3$] from the molecular ion (m/e 559) to give a peak at m/e 442. Instead of that, however, a predominant loss of 126 amu (95% *vs.* 5%) is observed, corresponding to the elimination of $CH_3\dot{C}HOSi(CD_3)_3$ from $M\cdot^+$. Similarly, an ion of m/e 126 corresponding to $CH_3CH{=}\overset{+}{O}Si(CD_3)_3$ is formed in preference to one of m/e 117 (m/e 126:m/e 117 = 100:38). It thus appears that the final reaction product has a structure corresponding to a 3β,17α-bis(trimethylsilyloxy)-5-pregnene-20α-trimethylsilyloxy-d_9 derivative (**4b**) rather than the anticipated 3β,20α-bis(trimethylsilyloxy)-5-pregenene-17α-trimethylsilyloxy-d_9.

To assess further the validity of the reactions and conclusions drawn above, the selective silylation reaction was performed by reversing the sequence of silyl-d_0 and silyl-d_9 group introduction. A sample of the 5-pregnenetriol (**1**) was first treated under mild conditions with bis(trimethylsilyl)acetamide-d_{18} (BSA-d_{18}), and, after complete incorporation of two silyl-d_9 groups, the solvents and reagent were vaporized. The monohydroxy compound was then treated with TSIM. The spectrum of the resultant bis(silyl-d_9)silyl-d_0-5-pregnene is shown in Figure 3d. The molecular ion has been shifted by 18 amu to m/e 568 indicative of the presence of two silyl-d_9 groups, and the preferential loss of 117 amu rather than 126 amu supports reaction mechanism 3 rather than IIa (reaction 2), and thus the formation of a 3β,17α-bis(trimethylsilyloxy-d_9)-5-pregnene-20α-trimethylsilyloxy-d_0 derivative (**4c**). The peak at m/e 577 in Figure 3d represents the molecular



(3)

ion of the perdeuteriotrimethylsilyl derivative (**4a**) produced during the reaction with BSA-d_{18} and not separated from **4c** during gas chromatography–mass spectrometry. The ion of m/e 559 is formed by the loss of $\cdot CD_3$ from that of m/e 577.

(b) **Mechanism of Selective Silylation.**—Since step Ib in reaction 2 does not appear to occur in any appreciable amount, an intramolecular trimethylsilylation process (reaction 3) would have to be invoked to explain the data in Figures 3a–d. This may be rationalized by the supposition that, following initial silylation of the unhindered 20α-hydroxyl group, the increased steric hindrance inhibits direct attack of the 17α-hydroxyl function by the relatively bulky TSIM-d_9 molecule. The favorable stereochemical disposition of the 20α,β and 17α functions combined with the high mobility of the silyl group provide a suitable pathway for intramolecular completion of the persilylation process. Operation of such an intramolecular silylation mechanism is not surprising in view of previous reports of thermally or otherwise induced intramolecular silyl rearrangements in *N*,*O*-bis(trimethylsilyl)amides,[10] silylacetic acids,[11] tris(organosilyl)hydroxylamines[12] and other systems.[13] The favorable disposition of the 17α and 20α or 20β groups for interaction and intramolecular group transfer is further demonstrated by the fact that pregnane-20α,21-diacetates can be prepared from 17α,21-diacetoxy-20β-tosylpregnanes. Participation of the 17α- or 21-acetoxy groups has been proposed as instrumental in the solvolysis of the 20β-tosyl function and inversion of configuration about C-20.[14] On the other hand, a reverse transfer—from C-20 to C-17—occurs in the Serini reaction,[15] where it was shown that in a 20-acetoxy-17α-hydroxypregnane a hydrogen atom migrates from C-20 to C-17 with inversion at the latter site, resulting in formation of a 20-keto pregnane.[16]

(c) **Electron Impact Induced Exchange of Trimethylsilyl Groups.**—The 100:44 ratio of m/e 117:m/e 126 in the spectrum of **4c** also reflects the presence of a C-20 silyl-d_0 group, but the different ratios of $[M - 117]^+$:$[M - 126]^+$ and m/e 117:m/e 126 in both **4b** and **4c** are mutually inconsistent and indicative of some loss of positional specificity of the trimethylsilyl functions in the process of formation of m/e 117. No change in these ratios was observed when the mass spectra of **4b** and **4c** were determined from sample aliquots taken at different times during step II of the selective silylation reaction. This indicates that the discrepancy in the ratios of m/e 117:m/e 126 and $[M - 117]^+$:$[M - 126]^+$ is not necessarily a reaction related phenomenon, and so we proceeded to investigate the dependence of the relative intensities of those ions on ionizing energy. The results are summarized in Table I. A definite variation of the ratio of m/e 117:m/e 126 with electron beam energy is apparent while the ratio of $[M - 117]^+$:$[M - 126]^+$ remains constant. The variation of m/e 117:m/e 126 with ionizing energy is indicative of scramble of the C-17- and C-20-trimethylsilyl groups upon electron impact. The proximity of the functional groups, coupled with the capability of silicon atom to form additional bonds with its 3d orbitals, and the high energy of formation of the Si–O bond[17] are presumably instrumental in accomplishing this intramolecular scramble (Scheme III).

TABLE I

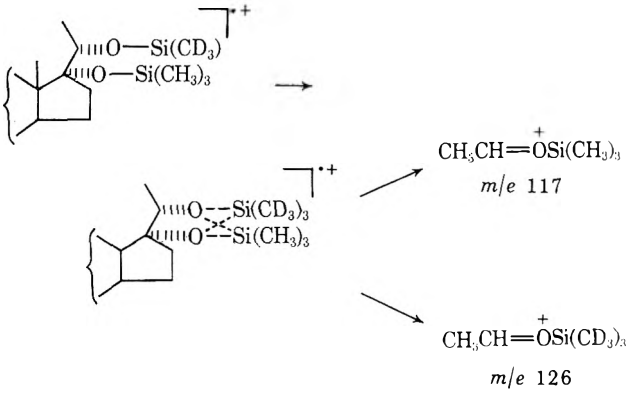
VARIATION OF RELATIVE ABUNDANCE OF THE m/e 117, m/e 126 AND $[M - 117]^+$, $[M - 126]^+$ IONS AS A FUNCTION OF ELECTRON ENERGY IN THE SPECTRA OF **4b** AND **4c**

	4b				4c			
Electron energy, eV	m/e 117	m/e 126	$[M - 117]^+$	$[M - 126]^+$	m/e 117	m/e 126	$[M - 117]^+$	$[M - 126]^+$
100	40[a]	100	5	100				
70	38	100	5	100	100	44	100	5
20	52	100	5	100	100	65	100	5
18	54	100	4	100	100	80	100	4
15	73	100	5	100	95	100	100	5
13.5	75	100	5	100	100	87	100	5
12	100	93	4	100	100	95	100	5

[a] All values have been corrected for contributions from other ions.

SCHEME III

ELECTRON IMPACT INDUCED SCRAMBLE OF 17α- AND 20α-SILYL GROUPS IN THE SPECTRUM OF 3β,17α-BIS(TRIMETHYLSILYLOXY-*d*)-5-PREGNENE-20α-TRIMETHYLSILYLOXY-d_9 (**4b**)



Examples of scrambling of trimethylsilyl hydrogens with other hydrogens during fragmentation[2b,18] as well

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as of intermolecular transfer of trimethylsilyl groups[19] have been reported before. This is, however, the first evidence for electron impact induced intramolecular positional exchange of entire silyl functions. It is significant that, at the lowest energies, there is complete randomization (Table I) of the silyl-d_0 and silyl-d_9 groups resulting in essentially 1:1 ratios of m/e 117:126. This is consistent with the observations of Williams and coworkers[20] that an increase in molecular ion lifetime enhances opportunity for interchange. The observed variation of the ratio m/e 117:m/e 126 (Table I) is a reflection of competition between rearrangement and fragmentation. The decreased scramble at higher energies[20] is further evidence that **4b** and **4c** reflect the structures of the products of the selective silylation reaction. The lack of reciprocal exchange of trimethylsilyl groups in the $[M - 117]^+$ ion is surprising in view of the randomization observed in the actual formation of m/e 117. This may be partially due to different charge stabilization and redistribution effects during cleavage of the C-17/20 bond. It is conceivable that charge retention with the 17β side chain requiring charge localization on the oxygen atom at C-20 will enhance bond formation with the 17α-silicon atom, whereas loss of the side chain will result in charge delocalization throughout the remaining steroid structure. The latter hypothesis, together with the high energy of formation of the Si–O bond could in part explain the reason for the occurrence of ions of m/e 117 (~15% R.I.) in the spectrum of the partially silylated derivative **3** but of no ion at $[M - 117]^+$.

Electron impact induced intramolecular exchange of the 17α- and 20α-trimethylsilyl groups was also observed in the mixed silyl-d_0, silyl-d_9 derivatives of 5α-pregnane-3β,17α,20α-triol, the saturated analogs of **4b** and **4c**. It is interesting, however, that no variation was observed in the ratio of m/e 117:m/e 126 with ionizing energy. In all likelihood the Δ^5 double bond in **4b** and **4c** is instrumental in providing sufficient stability or ion lifetime to enhance the intramolecular scramble and complete randomization of the 17α- and 20α-trimethylsilyl groups.

Conclusions

The data presented in the preceding section can be summarized in terms of information pertaining to (a) mechanisms of silylation, and (b) mass spectrometric properties of trimethylsilyl groups. Through the use of selective labeling with silyl-d_0 and silyl-d_9 groups it has been shown that under certain reaction conditions trimethylsilyl groups undergo intramolecular shifts during silylation. Proper stereochemical disposition of the functional groups undergoing silylation appears to be a requirement for the proposed intramolecular migration of trimethylsilyl groups.

Preparation of mixed silyl-d_0 and silyl-d_9 derivatives has shown that in compounds containing vicinal trimethylsilyloxy groups electron impact ionization can cause reciprocal exchange of the entire trimethylsilyl functions. Consequently, although the use of selectively labeled silyl-d_0, silyl-d_9 derivatives can be extremely helpful in mass spectral interpretations, some caution should be exercised in cases involving compounds which contain vicinal trimethylsilyloxy functions. In addition to mutual exchange of trimethylsilyl groups the mass spectra of partially silylated compounds show the occurrence of a hydrogen–trimethylsilyl group interchange upon electron impact. The latter type of reciprocal exchange can occur to a significant extent in certain compounds[21] and thus introduce uncertainties in structural interpretations of mass spectra. Occurrence of such processes further justifies the trend toward the preparation of fully silylated derivatives.[5,22]

Experimental Section

Samples of steroids used in this work were obtained from commercial sources. The methods used for the preparation of their trimethylsilyl derivatives[5] and for selective introduction of silyl-d_0 and silyl-d_9 groups[4] have been described before. The 20-^{18}O labeled analog of **1** was prepared by lithium aluminum hydride reduction of 20-ketopregnene-3β,17α-diol following exchange of the 20-keto oxygen in a mixture of isopropyl alcohol, hydrochloric acid, and 50% ^{18}O-enriched water.[23] Compounds **2b** and **3b** were prepared by exchange of the labile hydroxyl hydrogens of **2** and **3** in the gas chromatographic column attached to the mass spectrometer.[24] The purity of all compounds was checked by combined gas chromatography–mass spectrometry.

Mass spectra were recorded with an LKB-9000 mass spectrometer. The ionizing voltage was 70 eV unless otherwise noted, the accelerating voltage was 3.5 kV, and the ion source temperature was 270°. The samples were introduced to the mass spectrometer *via* the gas chromatographic inlet (6-ft or 9-ft, 1% OV-17 column). The column temperature was programmed over the range of 225–260° at a rate of 3°/min.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health (GM-13901).

Registry No.—**1**, 903-67-3; **2**, 41259-41-0; **3**, 41164-18-5; **4**, 41164-19-6; **4a**, 41164-20-9; **4b**, 41164-21-0; **4c**, 41164-22-1.

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Human Pituitary Growth Hormone. 36. The Solid-Phase Synthesis of the Carboxyl Terminal Cyclic Dodecapeptide

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The COOH-terminal cyclic dodecapeptide of human growth hormone Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (I) has been synthesized by the solid-phase method. New amino acid derivatives, N^{α}-Boc-*S*-3,4-dimethylbenzylcysteine and N^{α}-Boc-γ-*p*-bromobenzylglutamic acid, were synthesized and used in a second synthesis of I. The corresponding linear carbamidomethyl derivative, Val-Gln-Cys-(CH_2CONH_2)-Arg-Ser-Val-Glu-Gly-Ser-Cys(CH_2CONH_2)-Gly-Phe (II) has also been synthesized. Peptide I was readily converted to peptide II by reduction of I with dithiothreitol and alkylation with iodoacetamide.

One of the two disulfide bridges in the human growth hormone (HGH) molecule is present in a small loop near COOH-terminal phenylalanine.[1,2] During the course of total synthesis[3] of HGH-like protein, we synthesized by the solid-phase procedure[4] the COOH-terminal cyclic dodecapeptide Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (I).[5] Subsequent examination of protecting groups[6] for cysteine and glutamic acid suitable for solid-phase synthesis of proteins has now led to the use of the 3,4-dimethylbenzyl group for cysteine and the *p*-bromobenzyl for glutamic acid in the synthesis of I as reported herein. Previous studies showed that the disulfide bridges are unnecessary for the biological activity of the hormone since the reduced tetra-S-carbamidomethylated HGH is as active as the natural hormone.[7] It is, therefore, of interest to synthesize the corresponding linear carbamidomethyl derivative Val-Gln-Cys(CH_2CONH_2)-Arg-Ser-Val-Glu-Gly-Ser-Cys(CH_2CONH_2)-Gly-Phe (II). The synthesis of II is also reported herein.

For the synthesis of I (Chart I) N^{α}-Boc protection was employed along with the following side-chain protecting groups: cysteine, *p*-methoxybenzyl; serine, benzyl; glutamic acid, *p*-bromobenzyl; and arginine, tosyl. Since γ-benzyl protection of glutamic acid was reported[8] to not be entirely stable under conditions for deblocking the Boc group, we explored the use of *p*-bromobenzyl protection which is about four times as stable as benzyl protection.[9] The choice of tosyl protection for arginine has recently been discussed[10] Since the present work was initiated before introduction of the modified Loffet procedure[11,12] for attachment, it should be noted that the starting Boc-Phe resin used in the syntheses reported herein was prepared by the triethylamine procedure.[4] Removal of the protecting groups from the dodecapeptide and cleavage of the peptide from the solid support were performed with hydrogen fluoride.[13] Oxidation of the disulfhydryl dodecapeptide[14] was accomplished by the use of ferricyanide as previously employed[15] for deaminooxytocin. Purification by gel filtration on Sephadex G-25 was followed by chromatography on carboxymethylcellulose[16] (Figure 1). Cyclic dodecapeptide I was isolated in highly purified form as indicated by thin layer and paper chromatography, paper electrophoresis, and amino acid analysis. Evidence that the synthetic product was a monomer was obtained by partial reaction of the single amino group with 2,4-dinitrofluorobenzene[17] and examination of the products by electrophoresis.

It has been reported that the *p*-methoxybenzyl group can more readily be removed from *p*-methoxybenzylcysteine by hydrogen fluoride than the benzyl group.[8,18] However, for synthesis of very large peptides by the solid-phase procedure, a high degree of stability to repeated deblocking conditions is demanded for side-chain protection in addition to its facile removal at the end of the synthesis. Thus, N^{α}-acetyl-*S*-(*p*-methoxybenzyl)cysteinamide[6] was prepared and its stability tested by treatment with 50% trifluoroacetic acid in dichloromethane for 23 hr at 24°. Determination of sulfhydryl groups liberated showed that 27% of the protection was lost. This degree of instability suggests that this protecting group, if used in conjunction with N^{α}-Boc protection, might not be suitable for very large

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CHART I

OUTLINE OF THE SYNTHESIS OF I.

Boc-Phe-OCH_2 resin

↓ 1. TFA–CH_2Cl_2 2. diisopropylethylamine–$CHCl_3$ 3. Boc-Gly, DCC

Boc-Gly-Phe-OCH_2 resin

↓ etc.

Boc-Val-Gln-Cys(*p*-MeOBzl)-Arg(Tos)-Ser(Bzl)-Val-Glu(*p*-BrBzl)-Gly-Ser(Bzl)-Cys(*p*-MeOBzl)-Gly-Phe-OCH_2 resin

↓ 1. HF, 0°, 1 hr

H-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-OH

↓ 2. $K_3Fe(CN)_6$, pH 8 3. gel filtration on Sephadex G-25 4. CMC

H-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-OH

I

CHART II

OUTLINE OF THE SYNTHESIS OF II

Boc-Phe-OCH_2 resin

↓ 1. TFA–CH_2Cl_2 2. diisopropylethylamine–$CHCl_3$ 3. Boc-Gly, DCC

Boc-Gly-Phe-OCH_2 resin

↓ etc.

Boc-Val-Gln-Cys(CH_2CONH_2)-Arg(Tos)-Ser(Bzl)-Val-Glu(*p*-BrBzl)-Gly-Ser(Bzl)-Cys(CH_2CONH_2)-Gly-Phe-OCH_2 resin

↓ 1. HF, 0°, 1 hr 2. gel filtration on Sephadex G-25 3. partition chromatography on Sephadex G-25 4. CMC

H-Val-Gln-Cys(CH_2CONH_2)-Arg-Ser-Val-Glu-Gly-Ser-Cys(CH_2CONH_2)-Gly-Phe-OH

II

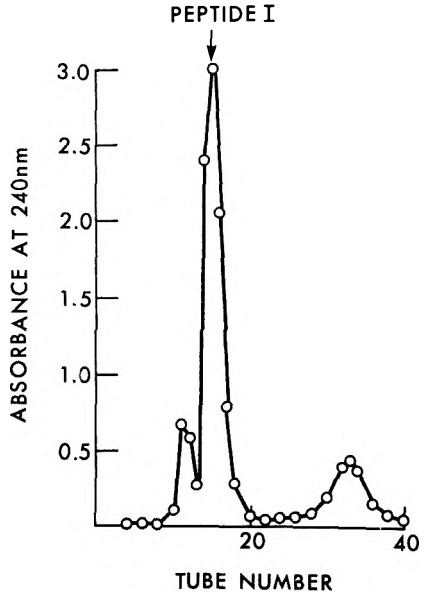

Figure 1.—Carboxymethylcellulose chromatography of partially purified peptide I.

peptides. We therefore prepared N^{α}-acetyl-*S*-(3,4-dimethylbenzyl)cysteinamide[6] and subjected it to the same treatment with trifluoroacetic acid and found that only 0.2% of the sulfhydryl protection was lost. When the compound was treated with hydrogen fluoride for 10 min at 0° the protecting group was completely removed. The suitability of 3,4-dimethylbenzyl protection for cysteine was then demonstrated by a second synthesis of I with use of N^{α}-Boc-*S*-(3,4-dimethylbenzyl)cysteine. Cyclic dodecapeptide I was obtained in highly purified form and was in complete identity with the preparation described above.

For synthesis of the linear carbamidomethyl dodecapeptide II, the carbamidomethylcysteine residues were introduced by use of the *p*-nitrophenyl ester of N^{α}-Boc-*S*-carbamidomethylcysteine. Active ester coupling was selected rather than coupling with dicyclohexylcarbodiimide to avoid any possibility of nitrile formation.[19] With this exception, synthesis of II (Chart II) was carried out in the same manner as the synthesis of I. Deprotection of the linear dicarbamidomethyl dodecapeptide and cleavage from the resin was again achieved with hydrogen fluoride.[13] Purification by gel filtration on Sephadex G-25, partition chromatography[20] on Sephadex G-25 (Figure 2), and chromatography on CMC gave II (~29% yield based on starting Boc-Phe resin) in highly purified form as judged by thin layer and paper chromatography, paper electrophoresis, and amino acid analyses.

Earlier work in this laboratory has shown that the disulfide bridges of HGH can be reduced with dithrothreitol and alkylated with iodoacetamide.[7] We decided to carry out these same reactions with peptide I which should then lead to II and serve as an additional check on our synthetic procedures. When I was so treated the resulting product, after purification by gel filtration on Sephadex G-10 and chromatography on CMC, was found to be identical with II synthesized with *S*-carbamidomethylcysteine.

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Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Thin layer chromatography (tlc) was run on silica gel in the following solvents: chloroform–methanol, 1:1 (CM); chloroform–methanol–acetic acid, 15:2:1 (CMA); 1-butanol–acetic acid–water, 4:1:1 (BAW); 1-butanol–pyridine–acetic acid–water 30:20:6:24 (BPAW). Thin layer data cited refer to single-spot chromatograms. Paper chromatography was carried out on Whatman No. 1. Carboxymethylcellulose chromatography was performed in a 1.0 × 55 cm column with a buffer of 0.01 *M* ammonium acetate of pH 4.5. Peaks were detected spectrophotometrically at 240 nm. Styrene–divinylbenzene resin (Bio-Beads S-X1, 200–400 mesh, Bio-Rad Laboratories) served as starting material for solid-phase synthesis, and attachment of Boc-phenylalanine was performed by the standard triethylamine procedure in absolute ethanol.

N^{α}-Boc-*S*-Carbamidomethylcysteine.—*S*-Carbamidomethylcysteine[21] (25.0 g, 140.5 mmol) was converted to the N^{α}-*tert*-butyloxycarbonyl derivative by the procedure of Schnabel[22] with Boc-azide (~214 mmol) at 45° for 10 hr with addition of 4 *N* NaOH to maintain the pH between 9.4 and 9.8. Dioxane was removed *in vacuo;* the solution was diluted with water (300 ml) and washed with three 75-ml portions of ether. The aqueous phase was cooled in ice and acidified to pH 3 with 3 *N* HCl. The product was extracted into ethyl acetate (350 ml), washed with two 50-ml portions of saturated NaCl, and dried over anhydrous $MgSO_4$. Removal of the drying agent and solvent gave an oil which crystallized on standing: yield, 17.4 g. For analysis, a sample (1.40 g) was recrystallized from ethyl acetate (30 ml): 1.24 g, mp 128–131°, tlc (CMA) R_f 0.3, $[\alpha]^{24}D$ −15.2° (*c* 2.00, absolute ethanol).

Anal. Calcd for $C_{10}H_{18}N_2O_5S$ (278.34): C, 43.15; H, 6.52; N, 10.07. Found: C, 43.33; H, 6.42; N, 9.94.

***p*-Nitrophenyl N^{α}-Boc-*S*-Carbamidomethylcysteinate.**—N^{α}-Boc-*S*-carbamidomethylcysteine (5.0 g, 18 mmol) and *p*-nitrophenol (10.0 g, 72 mmol) were dissolved in 15 ml of DMF and cooled to −10°. At 4°, over a period of 30 min, DCC (4.11 g, 19.5 mmol) dissolved in 5 ml of DMF was added. After 18 hr at 4° and 7 hr at 24°, the mixture was filtered at 4° and the solid washed with 50 ml of DMF. Removal of solvent in the combined filtrate and washings gave an oil which crystallized from ether: yield, 6.2 g; mp 145°. Recrystallization from DMF–water gave 5.36 g, mp 161–162°. Further recrystallization of 1.0 g from ethyl acetate gave 0.83 g, mp 162–164°, tlc (BAW) R_f 0.65, $[\alpha]^{24}D$ −41.5° (c 2.01, DMF).

Anal. Calcd for $C_{16}H_{21}N_3O_7S$ (399.42): C, 48.11; H, 5.30; N, 10.52. Found: C, 48.04; H, 5.57; N, 10.49.

γ-*p*-Bromobenzyl Glutamate.—To a stirred solution of 51.5 g of sodium copper glutamate[23] in 426 ml of water was added a solution of 64.0 g of *p*-bromobenzyl bromide in 853 ml of DMF. After the mixture stirred for 24 hr at 35–40°, the product was precipitated by addition of 1.3 l. of acetone and then filtered and washed with 200-ml portions of water and acetone. The material (~75 g) was suspended in 5.5 l. of water, 75 g of (ethylenedinitrilo)tetraacetic acid disodium salt was added, and the mixture was boiled until a solution was obtained. The product which came out of solution upon cooling was filtered and washed with 200-ml portions of water and acetone: yield, 25 g (32%); mp 180–181°; tlc (BAW) R_f 0.62; $[\alpha]^{24}D$ +1.4° (*c* 1, 80% acetic acid).

Anal. Calcd for $C_{12}H_{14}NO_4Br$ (316.15): C, 45.59; H, 4.46; N, 4.43. Found: C, 45.64; H, 4.01; N, 4.39.

N^{α}-Boc-γ-(*p*-Bromobenzyl)glutamic Acid.—To a stirred suspension of 18.5 g γ-*p*-bromobenzyl glutamate in 250 ml of DMSO, 16.0 ml of triethylamine (117 mmol) and 13.5 ml of Boc-azide (87.75 mmol) were added.[24] The mixture was stirred for 23 hr at 24°. The solution was diluted with water (840 ml) and washed with two 150-ml portions of ether. The aqueous phase was then cooled and acidified with 50 ml of 3 *N* HCl to pH 2. The product was extracted with two 200-ml portions and one 100-ml portion of ethyl acetate. The ethyl acetate solution was washed with three 50-ml portions of water and then dried over anhydrous $MgSO_4$. Removal of the drying agent and solvent gave an oil which crystallized from ether–petroleum ether (bp 30–60°) in a cold room (4°) overnight. The product was filtered and washed with ether–petroleum ether (1:4): yield, 19.3 g (46.4 mmol, 79%); mp 91–92°; tlc (CM) R_f 0.69; $[\alpha]^{24}D$ −10.7° (*c* 2.01, DMF).

Anal. Calcd for $C_{17}H_{22}NO_6Br$ (416.27): C, 49.05; H, 5.33; N, 3.37. Found: C, 49.26; H, 5.16; N, 3.17.

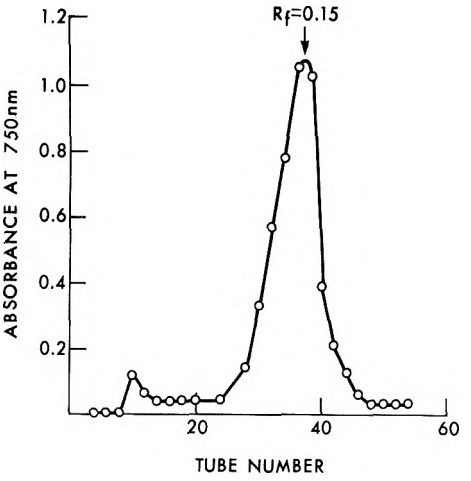

Figure 2.—Partition chromatography on Sephadex G-25 of partially purified peptide II.

3,4-Dimethylbenzylcysteine.—A mixture of cysteine free base (29 g, 240 mmol), ammonium chloride (13 g, 243 mmol), and water (1 ml) was stirred in 900 ml of liquid ammonia at the boiling point while 3,4-dimethylbenzyl chloride (55.5 g, 0.36 mol) was added over a period of 1 hr. The mixture was allowed to stir and evaporate to air overnight. The solid residue was dissolved in 850 ml of 1 *N* NaOH and washed with two 500-ml portions of ether. The aqueous solution was cooled in ice and the pH was adjusted to 7 with concentrated HCl. After 4 hr at 4° the solid was collected and washed with 1 l. of cold water. This material was boiled in 3.5 l. of water and filtered while hot. The filtrate was stored at 4° overnight. The product was collected and washed with cold water and acetone: yield, 26.1 g (46% yield); mp 193–196°. For analysis a sample was recrystallized twice from hot water: mp 195–197°, tlc (BAW) R_f 0.57, $[\alpha]^{24}D$ −15.7° (*c* 2, 80% acetic acid).

Anal. Calcd for $C_{12}H_{17}NO_2S$ (239.34): C, 60.22; H, 7.16; N, 5.85. Found: C, 60.45; H, 7.43; N, 5.95.

N^{α}-Boc-*S*-(3,4-Dimethylbenzyl)cysteine Dicyclohexylamine Salt.—3,4-Dimethylbenzylcysteine (6.0 g, 25 mmol) in 60 ml of 67% aqueous dioxane was treated over a 3-hr period with Boc-azide (7.0 ml, 50 mmol) at pH 9–9.5 at 45° with addition of 4 *N* NaOH. The solution was evaporated *in vacuo* to remove dioxane, diluted with water (60 ml), washed with two 40-ml portions of ether, and acidified with cooling to below pH 3 with 3 *N* HCl. The product was extracted with ethyl acetate (75 ml). The ethyl acetate solution was washed with three 25-ml portions of water and dried over anhydrous $MgSO_4$. Removal of the drying agent and solvent gave 8.9 g of oil, tlc (CM) R_f 0.65. The dicyclohexylamine salt was formed in ether by addition of 5.0 ml of dicyclohexylamine with cooling. Crystalline product was obtained from ether–petroleum ether: yield, 11.6 g. Two recrystallizations from chloroform–petroleum ether gave 8.8 g of the salt: mp 122–124°, $[\alpha]^{24}D$ −20.0° (*c* 2.25, 80% acetic acid).

Anal. Calcd for $C_{29}H_{48}N_2O_4S$ (520.78): C, 66.75; H, 9.47; N, 5.37. Found: C, 66.88; H, 9.34; N, 5.39.

For use in synthesis, 5.2 g (10 mmol) of salt was stirred at 4° with ethyl acetate (50 ml) and 1 *N* H_2SO_4 (11 ml). The ethyl acetate layer was washed with four 10-ml portions of cold water and then dried at room temperature over anhydrous $MgSO_4$. Removal of drying agent and solvent gave 3.7 g of oil, tlc (CM) R_f 0.63.

Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (I). A. With N^{α}-Boc-*S*-(*p*-Methoxybenzyl)cysteine.—Boc-Phenylalanyl resin (1.00 g, 0.43 mmol of phenylalanine) was treated by the following schedule of synthesis at 24° for the introduction of each

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residue: (1) 2 × 35 ml of CH_2Cl_2, retention volume of resin 7 ml; (2) 35 ml of 50% (v/v) TFA–CH_2Cl_2, 1 min; (3) 35 ml of 50% (v/v) TFA–CH_2Cl_2, 10 min; (4) 3 × 35 ml of CH_2Cl_2; (5) 3 × 35 ml of 50% EtOH–$CHCl_3$; (6) 3 × 35 ml of $CHCl_3$; (7) 35 ml of 3% (v/v) diisopropylethylamine in $CHCl_3$, 5 min; (8) 3 × 35 ml of $CHCl_3$; (9) 3 × 35 ml of CH_2Cl_2; (10) 1.72 mmol (4 equiv) of the appropriate Boc-amino acid in 15 ml of CH_2Cl_2, 10 min; (11) 1.71 mmol of dicyclohexylcarbodiimide in 4.10 ml of CH_2Cl_2, 2 hr; (12) 2 × 35 ml of CH_2Cl_2; (13) 3 × 35 ml of EtOH; (14) 3 × 35 ml of CH_2Cl_2. Side-chain protecting groups employed were benzyl for serine, *p*-bromobenzyl for glutamic acid, tosyl for arginine, and *p*-methoxybenzyl for cysteine. For introduction of the glutamine residue, the three washings in step 9 were replaced by DMF, Boc-glutamine *p*-nitrophenyl ester (4.29 mmol) in 15 ml of DMF was added in step 10 followed by an 18-hr coupling time, and step 11 was replaced with washings of two 35-ml portions of DMF. The valine residues were incorporated by employing 2.58 mmol (6 equiv) of N^{α}-Boc-valine in 15 ml of dichloromethane in step 10 and by addition of 2.57 mmol of DCC in 6.15 ml of dichloromethane in step 11; for the arginine residue, N^{α}-Boc-N^{G}-tosylarginine was dissolved in 16.5 ml of 10% DMF in dichloromethane for step 10, and a 4-hr coupling time was used in step 11. Final weight of finished protected peptide resin was 1.63 g.

A portion (761 mg) of resin was treated with HF (15 ml) for 1 hr at 0° in the presence of anisole (1.0 ml). After removal of the HF, the resin was dried *in vacuo* and then stirred with TFA (15 ml) for 15 min and filtered. The filtrate was evaporated *in vacuo*, and the oily residue was stirred with 75 ml of 0.18 *N* acetic acid and washed with two 25-ml portions of ethyl acetate. The aqueous phase was made up to 500 ml with water. The Ellman test[25] for sulfhydryl content on an aliquot indicated 190 μmol of sulfhydryl groups to be present in the total crude product. The pH was adjusted to 8.1 with 1 *N* NH_4OH (~14 ml), and over a period of 30 min with stirring 0.01 *N* $K_3Fe(CN)_6$ (20.0 ml) was added. The Ellman test on an aliquot taken 15 min after the end of the titration indicated ~6.7 μmol of sulfhydryl groups remaining. To the solution, 20 ml (wet volume) of AG3-X4A resin (chloride form) (Bio-Rad Laboratories, Richmond, Calif.) was added and, after stirring for 15 min, the mixture was filtered and the filtrate lyophilized. The resulting material was subjected to gel filtration on a 2.5 × 133 cm Sephadex G-25 column in 0.5 *N* acetic acid. The peptide material in the major peak (elution volume 472 ml) as detected spectrophotometrically at 240 nm was isolated (93 mg) and submitted to chromatography on CMC (Figure 1). A major peak was detected (elution volume 60–80 ml) and isolation by lyophilization gave 66.5 mg of cyclic dodecapeptide I (~26% yield based on starting resin): tlc (BPAW) R_f 0.28; paper chromatography (BPAW) R_f 0.25; $[\alpha]^{24}D$ −34.9° (*c* 0.62, 0.1 *N* acetic acid).

Paper electrophoresis in pyridine–acetate buffer (pH 3.7, 400 V, 4 hr) showed one ninhydrin-positive, chlorine-positive spot at R_f 0.31 (with respect to lysine). Paper electrophoresis in collidine–acetate buffer (pH 6.9, 400 V, 4 hr) showed one ninhydrin-positive, chlorine-positive spot at R_f 0.10. Amino acid analysis of an acid hydrolysate gave $Gly_{2.00}Glu_{1.99}Val_{1.98}Ser_{1.77}Arg_{0.96}Phe_{0.90}$ and half-cystine$_{1.96}$.

The monomeric nature of I was established by the partial dinitrophenylation method[17] in which a monomer of I should give two products while a dimer of I would give three products. A sample of I (1 mg) was dissolved in 100 μl of 80% aqueous DMSO and treated with 5 μl of 0.1 *M* 2,4-dinitrofluorobenzene in 75% aqueous dioxane for 4 min at 24°. Paper electrophoresis (pH 2.1, 2 kV, 1 hr) gave two spots: one with R_f 0.37 (ninhydrin and Pauly positive) relative to lysine corresponding to I and the second at the origin (yellow, Pauly positive and ninhydrin negative). Further dinitrophenylation of I gave a decreased amount of unreacted I and an increase in the second spot with no appearance of a third spot.

B. With N^{α}-Boc-*S*-(3,4-dimethylbenzyl)cysteine.—Boc-phenylalanyl resin (0.97 g, 0.415 mmol of phenylalanine) was placed in a Beckman Model 990 peptide synthesizer and submitted to the same schedule as in the aforementioned synthesis except that chloroform was replaced by dichloromethane. The side-chain protecting groups employed were also the same as in the aforementioned synthesis with the exception that 3,4-dimethylbenzyl protection for cysteine was employed. Final weight of finished protected peptide resin was 1.50 g.

A portion (682 mg) of resin was treated with HF (15 ml) for 1 hr at 0° in the presence of anisole (1.0 ml). The crude product was worked up as above. The sulfhydryl group content before and after oxidation with 0.01 *N* $K_3Fe(CN)_6$ were 170 and 4.5 μmol, respectively. The major peptide material after the gel filtration on Sephadex G-25 as above (elution volume 465 ml) was isolated (71.0 mg). An aliquot (36.5 mg) of the product was then submitted to the chromatography on CMC as described above. A major peak was detected (elution volume 52–72 ml), and isolation by lyophilization gave 24.8 mg (~20% yield based on starting resin) of cyclic dodecapeptide I, $[\alpha]^{24}D$ −33.1° (*c* 0.60, 0.1 *N* acetic acid). This material was identical to the preparation described in part A on paper electrophoresis, tlc (BPAW), and paper chromatography. Amino acid analysis of an acid hydrolysate gave $Gly_{2.00}Glu_{1.97}Val_{1.94}Ser_{1.81}Arg_{0.93}Phe_{1.03}$ and half-cystine$_{1.87}$.

Val-Gln-Cys(CH_2CONH_2)-Arg-Ser-Val-Glu-Gly-Ser-Cys(CH_2CONH_2)-Gly-Phe (II).—Boc-Phenylalanyl resin (1.00 g, 0.43 mmol of phenylalanine) was carried through the same cycle of steps as described above for the synthesis employing *p*-methoxybenzylcysteine with the following exceptions for the introduction of the *S*-carbamidomethylcysteine residues: the three washings in step 9 were replaced by DMF; 3.86 mmol (9 equiv) N^{α}-Boc-*S*-carbamidomethylcysteine *p*-nitrophenyl ester in 15 ml of DMF was added in step 10 followed by an 18-hr coupling time; step 11 was replaced by washing with two 35-ml portions of DMF. The other side-chain protecting groups employed were the same as in the aforementioned syntheses. Final weight of finished protected peptide resin was 1.52 g.

A portion (760 mg) of resin was treated with HF (15 ml) for 1 hr at 0° in the presence of anisole (1.0 ml). After removal of the HF, the resin was dried *in vacuo* and then stirred with TFA (15 ml) for 15 min and filtered. The filtrate was evaporated *in vacuo*, and the oily residue dissolved in 10 ml of 0.5 *N* acetic acid and washed with two 10-ml portions of ether. The aqueous solution was lyophilized and the resulting material was subjected to gel filtration on Sephadex G-25 as described above and the peptide material in the major peak (elution volume 446 ml) was isolated (167 mg). An aliquot (52.2 mg) was then subjected to partition chromatography on Sephadex G-25 (1.92 × 69 cm) in the solvent system 1-butanol–pyridine–0.2 *N* aqueous NH_4OH containing 0.1% acetic acid (5:3:12). As determined by Folin–Lowry analysis[26] a single symmetrical peak with R_f 0.15 was obtained (Figure 2). The isolated material (40.9 mg) was then submitted to the chromatography on CMC. One peak was detected (elution volume 48–63 ml) and isolation by lyophilization gave 27.1 mg (~29% yield based on starting resin) of linear dodecapeptide II: tlc (BPAW) R_f 0.22, paper chromatography (BPAW) R_f 0.10, $[\alpha]^{24}D$ −49.3° (*c* 0.46, 0.1 *N* acetic acid).

On paper electrophoresis at pH 3.7 and at pH 6.9 peptide II migrated as a single spot at the same rate as peptide I. Amino acid analysis of an acid hydrolysate gave $Gly_{2.00}Glu_{2.05}Val_{2.12}Cys(CH_2COOH)_{2.06}Ser_{1.80}Arg_{1.00}Phe_{1.03}$. Amino acid analysis of a 24-hr leucine aminopeptidase digest gave $Gly_{2.00}Glu_{1.00}(Ser + Gln)_{2.80}Val_{2.10}Cys(CH_2CONH_2)_{0.82}Arg_{0.96}Phe_{0.99}$. When an authentic sample of carbamidomethylcysteine is treated under conditions for enzyme digest, ~60% of the compound disappears as judged by amino acid analysis and quantitatively accounts for the low value obtained on II.

Conversion of I to II.—A sample (30.8 mg) of I was dissolved in 0.01 *M* NH_4HCO_3 (6.0 ml) of pH 8.3 under conditions described previously.[27] Reduction with dithiothreitol[28] (37.6 mg) was followed by treatment with iodoacetamide (449.9 mg). The solution was subjected to gel filtration on Sephadex G-10 (2.2 × 25 cm) in 0.01 *M* NH_4HCO_3 of pH 8.3. The peptide material (elution volume of peak, 48 ml) was isolated (35.8 mg) and submitted to chromatography on CMC. One peak was detected in the position expected for II (elution volume 49–65 ml) and isolation by lyophilization gave 24.8 mg (~74%): tlc (BPAW) R_f 0.22 and paper chromatography (BPAW) R_f 0.10 identical with those of an authentic sample of II; $[\alpha]^{24}D$ −50.7° (*c* 0.402, 0.1 *N* acetic acid). Amino acid analyses of an acid hydrolysate and a leucine aminopeptidase digest gave $Gly_{2.00}Glu_{2.05}Val_{1.99}Cys(CH_2COOH)_{2.19}Ser_{1.98}Arg_{0.95}Phe_{1.02}$ and $Gly_{2.00}Glu_{0.97}(Ser + Gln)_{2.95}Val_{1.90}Cys(CH_2CONH_2)_{0.93}Arg_{1.02}Phe_{0.99}$, respectively.

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Registry No.—I, 41174-26-9; II, 41117-58-2; N^{α}-Boc-*S*-carbamidomethylcysteine, 41117-59-3; *S*-carbamidomethylcysteine, 17528-66-4; *p*-nitrophenyl N^{α}-Boc-*S*-carbamidomethylcysteinate, 41117-61-7; γ-*p*-bromobenzyl glutamate, 20806-21-7; *p*-bromobenzyl bromide, 589-15-1; N^{α}-Boc-γ-(*p*-bromobenzyl)-glutamic acid, 41117-62-8; triethylamine, 121-44-8; Boc-azide, 1070-19-5; 3,4-dimethylbenzylcysteine, 41594-21-2; cysteine, 52-90-4; ammonium chloride, 12125-02-9; 3,4-dimethylbenzyl chloride, 102-46-5; N^{α}-Boc-*S*-(3,4-dimethylbenzyl)cysteinedicyclohexylamine salt, 41117-64-0; N^{α}-Boc-*S*-(*p*-methoxybenzyl)-cysteine, 18942-46-6; N^{α}-Boc-*S*-(3,4-dimethylbenzyl)cysteine, 41117-66-2; human pituitary growth hormone, 9002-72-6.

o-Nitrophenyl Esters of *tert*-Butyloxycarbonylamino Acids and Their Application in the Stepwise Synthesis of Peptide Chains by a New Technique[1]

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Synthesis of the protected nonapeptide *tert*-butyloxycarbonyl-L-leucyl-L-glutaminyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide, corresponding to the C-terminal sequence of a secretin analog, is described. Acylation of L-valinamide with the *o*-nitrophenyl ester of *tert*-butyloxycarbonyl-L-leucine yielded a dipeptide derivative which, after deprotection with trifluoroacetic acid, was converted to a protected tripeptide amide by reaction with *tert*-butyloxycarbonylglycine *o*-nitrophenyl ester. The chain was lengthened in the same manner; *o*-nitrophenyl esters of Boc-amino acids were used as acylating agents. All the operations were carried out in the same vessel, from which the intermediates were not removed throughout the synthesis. The preparation and properties of *o*-nitrophenyl esters of Boc-amino acids are also reported.

Stepwise synthesis of peptide chains was proposed, and demonstrated on the example of oxytocin, by Bodanszky and du Vigneaud.[2] This approach proceeds through isolated intermediates. If unequivocal methods are used in the acylation and deprotection reactions, it permits rapid chain lengthening, since an extensive purification of the intermediates is often unnecessary. Removal of excess reagents and of by-products was accomplished, in the majority of steps, simply by washing with appropriately chosen solvents. Active esters, such as *p*-nitrophenyl esters, were found as the acylating agents of choice in this method. The repetitiveness of the operation led to the suggestion[3] that mechanization and automation of the procedure would eventually be possible. In the following years, the stepwise strategy indeed lent itself to the development of mechanized and automated syntheses of long chains, but only through the introduction of the solid-phase method by Merrifield.[4] Without a solid support, peptides of only moderate size[5-7] were built by the stepwise approach. In this paper we propose a new technique by which the stepwise synthesis of peptides, *not attached to an insoluble polymer*, can be considerably facilitated.

tert-Butyloxycarbonyl-L-valinamide was deprotected with trifluoroacetic acid, the reagent was removed *in vacuo*, and the residue was triturated with dry ether. These operations were carried out in a centrifuge tube provided with a standard tapered joint through which the tube could be attached to a rotary evaporator. After separation of the trifluoroacetate salt of L-valinamide from the ethereal solution by centrifugation, the supernatant was removed, and the precipitate was washed with ether and dried *in vacuo*. After dissolution of the trifluoroacetate salt in dimethylformamide and the addition of a tertiary amine,[8] the amino component was acylated with an active ester. *o*-Nitrophenyl esters of protected amino acids, reagents that remain efficient even under hindered conditions,[9,10] *e.g.*, in solid-phase synthesis,[11] performed quite satisfactorily in this procedure. High concentration of the reactants is desirable for practical rates and for the suppression of intramolecular side reactions.[12] Therefore, with the growing chain length, the *o*-nitrophenyl esters were applied in gradually increasing excess, their concentration at the start of each acylation being not less than 0.1 *M*. Completion of the acylation was ascertained by a spot test with ninhydrin. The amount of the released *o*-nitrophenol also is a good measure of the extent of acylation. Evaporation of the solvent was followed by the addition of a "nonsolvent." Ethyl acetate is particularly useful in this role[13] because it precipitates many of the common protected peptide intermediates while keeping in solution the excess active esters, the released *o*-nitrophenol and—importantly—also the trifluoroacetate salts of triethyl-

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TABLE I

o-NITROPHENYL ESTERS OF *tert*-BUTYLOXYCARBONYLAMINO ACIDS

Registry no.	*tert*-Butyloxycarbonylamino acid *o*-nitrophenyl ester	Mp, °C	$[\alpha]^{25}D$ (*c* 1–2), DMF containing 1% AcOH	Tlc R_fA	Tlc R_fB	Formula	Mol wt	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
41120-55-2	Ala	86–87	−79	0.70	0.60	$C_{14}H_{18}N_2O_6$	310.3	54.2	5.8	9.0	54.3	5.9	9.0
41120-56-3	Asp(Bzl)	94–95	−42	0.87	0.77	$C_{22}H_{24}N_2O_8$	444.4	59.5	5.4	6.3	59.7	5.6	6.3
38605-58-2	Asn	144.5–146.5	−55	0.77	0.41	$C_{15}H_{19}N_3O_7$	353.3	51.0	5.4	11.9	50.8	5.6	11.6
38605-57-1	Cys(Bzl)	103–105	−75	0.82	0.67	$C_{21}H_{24}N_2O_6S$	432.5	58.3	5.6	6.5	58.1	5.5	6.8
41120-59-6	Glu(Bzl)	123–125	−54	0.87	0.77	$C_{23}H_{26}N_2O_8$	458.5	60.3	5.7	6.1	60.5	5.8	6.2
38605-59-3	Gln	149.5–151	−55	0.79	0.40	$C_{16}H_{21}N_3O_7 \cdot {}^1/_2H_2O$	367.4	51.1	5.9	11.2	51.3	5.9	11.3
38605-09-6	Gly	96.5–98		0.85	0.63	$C_{13}H_{16}N_2O_6$	296.3	52.7	5.4	9.5	52.8	5.4	9.4
41120-62-1	Ile	Oil	−37	0.84	0.74	$C_{17}H_{24}N_2O_6$	352.4	57.9	6.9	8.0	58.0	6.7	7.9
24868-52-8	Leu	56–57	−68	0.87	0.65	$C_{17}H_{24}N_2O_6$	352.4	57.9	6.9	8.0	58.0	6.7	8.1
41120-64-3	Lys(DCZ)[a]	135–137	−37	0.87	0.74	$C_{25}H_{29}N_3O_8Cl_2$	570.4	52.6	5.1	7.4	52.6	5.1	7.3
41120-65-4	Lys(INOC)[a]	94–98	−41	0.64	0.47	$C_{24}H_{30}N_4O_8$	502.5	57.4	6.0	11.1	57.4	5.8	10.9
41120-66-5	Met	104–105	−73	0.80	0.73	$C_{16}H_{22}N_2O_6S$	370.4	51.9	6.0	7.6	51.8	6.0	7.5
41120-67-6	Phe	146–146.5	−65	0.80	0.66	$C_{20}H_{22}N_2O_6$	386.4	62.2	5.7	7.3	62.1	5.7	7.2
38605-56-0	Pro	63–70	−84	0.84	0.66	$C_{16}H_{20}N_2O_6$	337.4	57.1	6.0	8.3	57.0	6.2	8.1
41120-69-8	Ser(Bzl)	49–52	−30	0.88	0.77	$C_{21}H_{24}N_2O_7$	416.4	60.6	5.8	6.7	60.6	5.9	6.7
41120-70-1	Trp	155–156	−62	0.80	0.64	$C_{22}H_{23}N_3O_6$	425.4	62.1	5.5	9.9	62.3	5.7	9.8
41120-71-2	Tyr(Bzl)	139–140	−51	0.82	0.78	$C_{27}H_{28}N_2O_7$	492.5	65.8	5.7	5.7	66.1	5.7	5.7
41120-72-3	Val	53–56	−44	0.84	0.64	$C_{16}H_{22}N_2O_6$	338.4	56.8	6.6	8.3	57.0	6.3	8.3

[a] DCZ, 2,6-dichlorobenzyloxycarbonyl; INOC, isonicotinyloxycarbonyl.

amine or diisopropylethylamine, etc. The protected peptide, lengthened by one amino acid, was separated by centrifugation and washed with the "nonsolvent" in the same way. Drying *in vacuo* completed the cycle. The next residue was incorporated in the same manner. An essential feature of this technique is that the *intermediates of the synthesis remain in the centrifuge tube throughout the operations and throughout the series of chain-lengthening steps.*[14] The use of a reaction vessel that permits mixing, evaporation, centrifugation, and drying simplifies the necessary manipulations and may lend itself to further developments, including mechanization and automation of the procedure. In the Experimental Section, further details of the synthesis of the protected nonapeptide, *tert*-butyloxycarbonyl-L-leucyl-L-glutaminyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide, corresponding to the C-terminal sequence of a secretin analog, are described (*cf.* also Chart I). A nonapeptide with an analogous sequence had been prepared earlier,[7] but with different protecting groups. In the present study the N^{ϵ}-amino group of the lysine residue, which replaced arginine in position 21 of secretin, was protected with the 2,6-dichlorobenzyloxycarbonyl group. This protection is not affected during the removal of *tert*-butyloxycarbonyl groups with trifluoroacetic acid. The synthesis of the C-terminal hexapeptide portion was carried out both by conventional operations and by the new technique.

It seems to be possible to apply acylation methods other than the active ester procedure with the same technique; *e.g.*, dicyclohexylcarbodiimide[15] or carbonyldiimidazole[16] (but not mixed anhydrides[17]) could be used for activation in the coupling steps. However, in order to avoid overactivation[18] and the concomitant formation of by-products that in turn might necessitate extensive purification between the chain-lengthening steps, we feel that it is imperative to use moderately active and therefore sufficiently selective acylating agents.

After preliminary comparisons of different active esters,[9,10] *o*-nitrophenyl esters were found to be practical tools in the execution of the technique proposed here and therefore we include methods for their preparation and list in Table I the physical properties of *o*-nitrophenyl esters of the more commonly used *tert*-butyloxycarbonylamino acids.[19]

In the preparation of some *o*-nitrophenyl esters, difficulties were encountered when the reactions were carried out in ethyl acetate, the solvent commonly applied in the synthesis of *p*-nitrophenyl esters.[20] The progress of active ester formation was monitored with ir spectra and its completion was indicated by the disappearance of the band at 4.8 μ, which is characteristic for the condensing agent, dicyclohexylcarbodiimide. Slow rates, especially in the case of protected amino acids with bulky side chains, led to the formation of *N*-acyldicyclohexylureas in not insignificant amounts. This undesirable side reaction was avoided by applying *o*-nitrophenol in excess and particularly by the use of pyridine as solvent. The nucleophilic character of the hydroxyl of *o*-nitrophenol is enhanced

(14) On the other hand, if necessary, intermediates can be removed from the apparatus, purified, and returned into the centrifuge tube for subsequent cycles.

(15) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

(16) H. A. Staab, *Justus Liebigs Ann. Chem.*, **609**, 75 (1957). G. W. Anderson and R. Paul, *J. Amer. Chem. Soc.*, **80**, 4423 (1958); **82**, 4596 (1960).

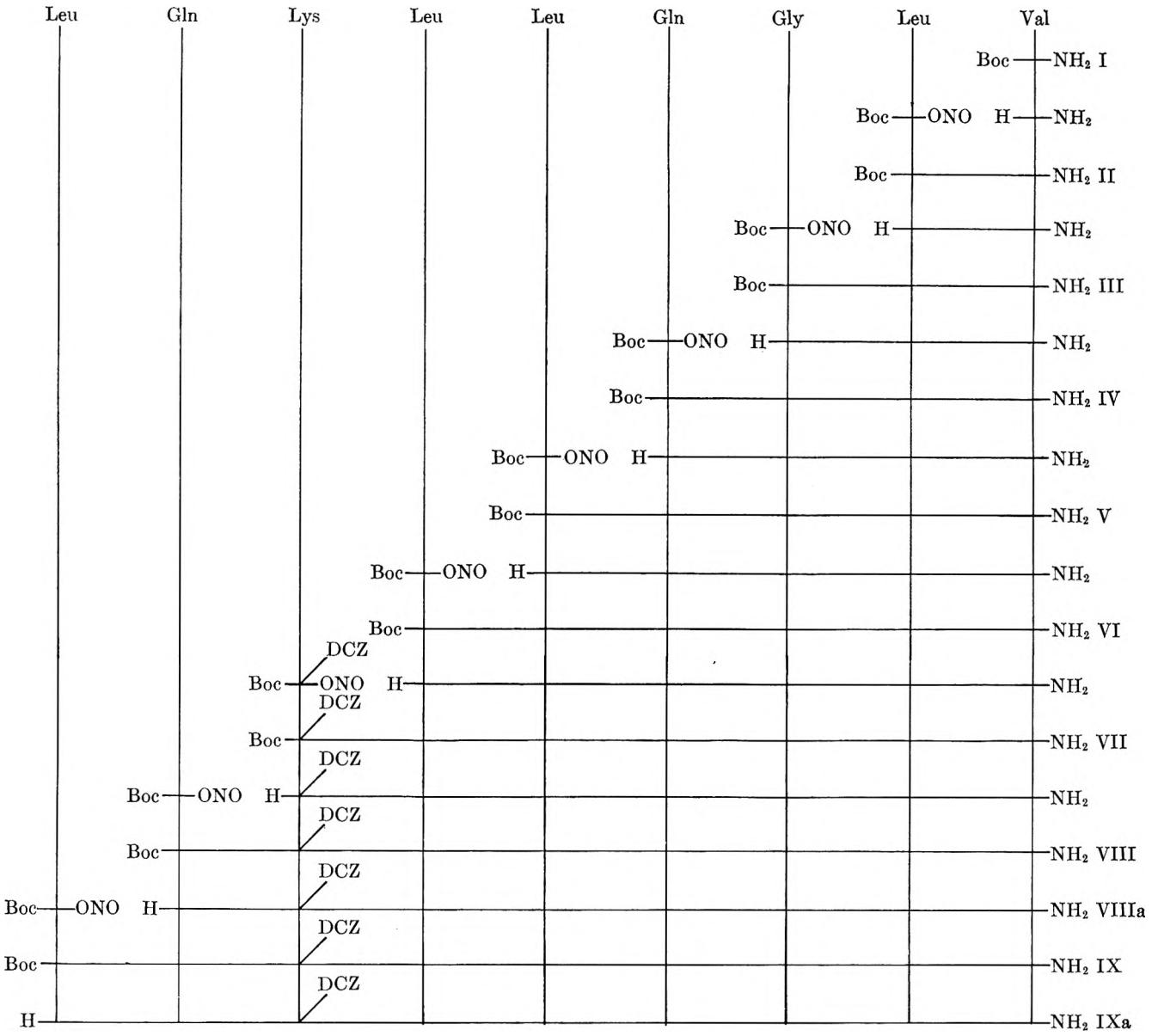
(17) Concerns about the use of mixed anhydrides in stepwise syntheses of larger chains were mentioned earlier (ref 2). Nevertheless, such syntheses were carried out with the exclusive application of mixed anhydrides by R. Sarges and B. Witkop [*J. Amer. Chem. Soc.*, **86**, 1862 (1964)] and also by M. A. Tilak [*Tetrahedron Lett.*, 849 (1970)]. The absence of the expected urethanes (*cf.* also H. C. Beyerman in "Chemistry and Biology of Peptides," J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 351) was not demonstrated in these studies. The coupling reagent EEDQ [B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, **90**, 1651 (1968)] that produces ethoxycarbonyl mixed anhydrides as reactive intermediates indeed gives rise to the formation of urethanes (A. Bodanszky and M. Bodanszky, unpublished; *cf.* also Y. S. Klausner, C. Yang Lin, V. Mutt, and M. Bodanszky, *Bioorg. Chem.*, in press).

(18) M. Brenner in "Proceedings of the Eighth European Peptide Symposium, 1966," H. C. Beyerman, A. Van de Linde, and W. Maassen-van den Brink, Ed., North-Holland Publishing Co., Amsterdam, 1967, p 1.

(19) An extension of the same technique to benzyloxycarbonylamino acid *o*-nitrophenyl esters is being carried out in this laboratory.

(20) M. Bodanszky and V. du Vigneaud, *Biochem. Prep.*, **9**, 110 (1962).

CHART I



in this solvent, perhaps because of interference with intramolecular hydrogen bonding between the hydroxyl and nitro groups.

The higher reactivity of *o*-nitrophenyl esters as compared with *p*-nitrophenyl esters[9,10] is reflected also in their ir spectra: the active ester carbonyl appears at 5.62–5.63 μ in *o*-nitrophenyl esters and at 5.65 μ in their para isomers. The rates of aminolysis of *o*-nitrophenyl esters are less solvent dependent than the rates observed with *p*-nitrophenyl esters.[9] This difference points to some intramolecular engagement of the nitro group. The rotations of *o*-nitrophenyl esters are consistently and significantly higher than those of the corresponding para isomers, and this suggests that the asymmetric carbon atom is part of a rigid system in the ortho esters.[21] A diminished conformational freedom in these molecules might explain why they are not overly sensitive to steric hindrance such as that encountered in solid-phase syntheses.[9-11]

Since stepwise synthesis with *o*-nitrophenyl esters by the here-outlined technique permits facile chain lengthening, and also the purification of any intermediate should this be necessary, we continue our studies of this new approach for which the expression "peptide synthesis *in situ*" is proposed.

(21) W. Kauzmann and H. Eyring, *J. Chem. Phys.*, **9**, 41 (1941).

Experimental Section

Uncorrected capillary melting points are reported. On thin layer chromatograms, the protected peptides were revealed by *tert*-butyl hypochlorite–KI–starch reagents.[22,23] Active esters were detected by their uv absorption and through exposure to ammonia. For development, the following systems were applied: A, *n*-BuOH–AcOH–H_2O (4:1:1); B, $CHCl_3$–MeOH (9:1); C, EtOAc–pyridine–AcOH–H_2O (60:20:6:11). Reagent-grade commercial solvents were used without purification, but DMF was dried over a molecular sieve (Linde 4A or 4AXH). For amino acid analyses, samples were hydrolyzed with constant-boiling 6 *N* HCl in evacuated, sealed ampoules at 110° for 16 hr and analyzed by the Spackman–Stein–Moore method.[24]

The abbreviations for amino acids and protecting groups are those of the IUPAC-IUB Commission on Biochemical Nomen-

(22) R. H. Mazur, B. W. Ellis, and P. Cammarata, *J. Biol. Chem.*, **237**, 1619 (1962).

(23) D. P. Schwartz and M. J. Pallansch, *Anal. Chem.*, **30**, 219 (1958).

(24) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

clature [*Biochemistry*, 5, 1445, 2485 (1966); 6, 362 (1967); *J. Biol. Chem.* 241, 2491 (1966); 247, 977 (1972)]. Furthermore, DCC was used for dicyclohexylcarbodiimide, DCU for *N,N'*-dicyclohexylurea, TFA for trifluoroacetic acid, DMF for dimethylformamide, Z for benzyloxycarbonyl, INOC for isonicotinyloxycarbonyl, DCZ for 2,6-dichlorobenzyloxycarbonyl, Boc for *tert*-butyloxycarbonyl, ONP for *p*-nitrophenyloxy, and ONO for *o*-nitrophenyloxy groups.

***tert*-Butyloxycarbonyl-*O*-benzyl-L-serine *o*-Nitrophenyl Ester.**[25]—Boc-L-Ser(Bzl) (1.62 g, 5.5 mmol) and *o*-nitrophenol (1.39 g, 10 mmol) were dissolved in pyridine (5 ml) and cooled in an ice–water bath. DCC (1.03 g, 5 mmol) was added to the stirred solution and rinsed in with more pyridine (5 ml). After 30 min, the ice bath was replaced with a bath at room temperature. After 5 hr the DCU was removed by filtration and the pyridine was removed by evaporation *in vacuo*. The oil was taken up in ether and filtered to remove more DCU. The solvent was evaporated and the residue was dissolved in $CHCl_3$ (100 ml). The solution was extracted with 5% citric acid (50 ml in two portions) and 0.1 *N* NaOH (300 ml in four portions). The organic layer was washed with water (100 ml), dried over $MgSO_4$, and filtered, and the solvent was removed *in vacuo*. The residue was taken up in $CHCl_3$ (1.5 ml) and chromatographed on a column of silica gel (25 g) with $CHCl_3$. The fractions shown to be homogeneous by tlc were pooled and evaporated to give 1.95 g of oil. The product was crystallized from hot petroleum ether (150 ml, bp 38–47°), filtered, washed with cold petroleum ether (50 ml), and dried *in vacuo* over P_2O_5 to give 1.32 g (63%), mp 49–52°. A second crop (223 mg, mp 49–52°) and third crop (88 mg, mp 49–52°) were recovered from the mother liquor, total yield 78%. For specific rotation, R_f values on tlc, and analytical data, *cf.* Table I.

***tert*-Butyloxycarbonyl-L-alanine *o*-nitrophenyl ester** was prepared according to the method described above, with a reaction time of 6 hr. The crude, crystalline product (5.2 g, 61%) was recrystallized from warm EtOH to give a total of 3.8 g (49%) in successive crops, mp 86–87°.

***tert*-Butyloxycarbonyl-L-isoleucine *o*-nitrophenyl ester** was prepared according to the procedure described for Boc-L-Ser(Bzl)-ONO. The crude product from a 5-mmol preparation was taken up in $CHCl_3$ (1 ml) and chromatographed on a column of silica gel (20 g) with $CHCl_3$. The material running with the front was collected (20 ml) and shown to be homogeneous by tlc. The solvent was removed *in vacuo* to give 1.76 g (99%) of an oil which has thus far resisted attempts at crystallization.

***tert*-Butyloxycarbonyl-L-valine *o*-nitrophenyl ester** was prepared according to the procedure described for Boc-L-Ser(Bzl)-ONO with a reaction time of 3 hr. The crude product from a 50-mmol preparation was taken up in ether and filtered to remove more DCU. The solvent was removed by evaporation and the oily residue was dried *in vacuo* over P_2O_5 to give the desired product in quantitative yield. The purified material crystallized in the refrigerator after many weeks, mp 53–56°.

***tert*-Butyloxycarbonyl-L-aspartic acid α-*o*-nitrophenyl ester β-benzyl ester** was prepared according to the procedure described for Boc-L-Ser(Bzl)-ONO. The crude crystalline product from a 5-mmol preparation was dried *in vacuo* over P_2O_5 to give 2.12 g. It was recrystallized from hot 95% EtOH (50 ml), filtered, washed with cold 95% EtOH (30 ml in three portions), and dried *in vacuo* to give 1.35 g (51%), mp 90–93°. A second crop (0.51 g, mp 90–93°) was recovered from the mother liquor, total yield 84%. A sample (1.25 g) was dissolved in hot 95% EtOH (15 ml) and allowed to crystallize at room temperature. The crystals were filtered, washed with cold 95% EtOH (15 ml), and dried. The recovered material (1.09 g) melts at 94–95°.

***tert*-Butyloxycarbonyl-L-glutamic acid α-*o*-nitrophenyl ester γ-benzyl ester** was prepared according to the procedure described for Boc-L-Ser(Bzl)-ONO. The crude crystalline product from a 5-mmol preparation was dried *in vacuo* over P_2O_5 to give 2.18 g. The product was crystallized from hot 95% EtOH (35 ml), filtered, washed with cold 95% EtOH (30 ml in three portions), and dried *in vacuo* to give 1.96 g (86%), mp 124–125°. A sample (1.25 g) was dissolved in hot 95% EtOH (20 ml) and allowed to crystallize at room temperature. The crystals were filtered, washed with cold 95% EtOH (15 ml), and dried. The purified material (1.19 g) melts at 123–125°.

***tert*-Butyloxycarbonyl-L-methionine *o*-nitrophenyl ester** was prepared on a 4-mmol scale, with a reaction time of 3 hr, according to the procedure described for Boc-L-Ser(Bzl)-ONO. The crude product was recrystallized from warm 95% EtOH containing 0.1% AcOH, yield 1.15 g (78%), mp 104–105°.

***tert*-Butyloxycarbonyl-*O*-benzyl-L-tyrosine *o*-nitrophenyl ester** was prepared according to the procedure described for Boc-L-Ser(Bzl)-ONO. The reaction was carried out on a 6-mmol scale and was complete after 3 hr. The crude oil was dissolved in 95% EtOH containing 0.1% AcOH. The crystals which separated on cooling were collected, washed with cold 95% EtOH, and dried *in vacuo* to give 2.3 g (78%) of product, mp 139–140°.

***tert*-Butyloxycarbonyl-L-tryptophan *o*-nitrophenyl ester** was prepared according to the procedure described for *p*-nitrophenyl esters.[20] The reaction was carried out in EtOAc as solvent on a 1-mmol scale. The crude product was recrystallized from warm 95% EtOH containing 0.1% AcOH to give 0.23 g (53%), mp 155–156°. A second crop (0.12 g, 28%, mp 155–156°) was recovered from the mother liquor.

***tert*-Butyloxycarbonyl-L-phenylalanine *o*-nitrophenyl ester** was prepared according to the method used for the tryptophan derivative described above. The crude product from a 51.5-mmol preparation was recrystallized from warm 95% EtOH containing 0.1% AcOH (60 ml) to give 6.8 g (34%), mp 146–146.5°. A second crop from the mother liquor (4.65 g, mp 145–146°) raised the total yield to 57%.

***N*α-*tert*-Butyloxycarbonyl-*N*ε-2,6-dichlorobenzyloxycarbonyl-L-lysine *o*-Nitrophenyl Ester.**—Phosgene (12.5% in benzene, 130 ml) was cooled to 0° in an ice–water bath. 2,6-Dichlorobenzyl alcohol (24 g, 136 mmol) was added to the cooled solution with vigorous stirring. After 30 min, the ice–water bath was replaced with a bath at room temperature. The 2,6-dichlorobenzyl alcohol dissolved when the solution warmed to room temperature. After 4 hr, the benzene was removed by evaporation *in vacuo* at 40° bath temperature, giving an oil that in part crystallized in the cold room overnight. To complete the conversion, the product was again treated with phosgene (12.5% in benzene, 130 ml) and stirred overnight. The benzene was removed by evaporation at 40° *in vacuo* to give 34 g of 2,6-dichlorobenzyl chloroformate, an oil.

Lysine hydrochloride (12.2 g, 67 mmol) was dissolved in water (100 ml). Sodium hydroxide (4 *N*, 33.5 ml) was added, followed by a solution of $CuSO_4 \cdot 5H_2O$ (8.4 g, 33.5 mmol) in water (100 ml). Sodium carbonate (14.2 g, 134 mmol) was added to the deep blue solution, followed immediately by 2,6-dichlorobenzyl chloroformate (19.4 g, 81 mmol). The reaction mixture was stirred vigorously for 4 hr. The blue precipitate was filtered and washed with water (500 ml), 95% ethanol (250 ml), acetone (200 ml), and ether (200 ml). The copper complex was air dried to give 20.2 g. It was suspended in water (300 ml) and H_2S was bubbled through the vigorously stirred suspension for 1 hr. Cupric sulfide and the desired product precipitated out rapidly, causing thickening and foaming. Water (300 ml) was added to aid stirring. The flask was stoppered and the mixture was allowed to stand overnight. After brief boiling, charcoal (3 g) and Celite (6 g) were added. The mixture was diluted with water (700 ml), 95% ethanol (800 ml), and acetic acid (60 ml), and heated to boiling to dissolve the white, crystalline product. The solution was filtered through a steam-heated funnel and the cake was washed with a mixture of hot water (300 ml), 95% ethanol (300 ml), and acetic acid (25 ml). The Nε-protected lysine crystallized in the cold room overnight. The crystals were filtered, washed with water (100 ml) and acetone (100 ml), and dried *in vacuo* over P_2O_5 to give 14.9 g, mp 245–248°. The filtrate was concentrated *in vacuo* to a volume of 150 ml. The product that separated was filtered, washed with water (30 ml), and dried to give 2.1 g, mp 245–246.5°. A third crop (0.8 g) was recovered in a similar manner.

*N*ε-2,6-Dichlorobenzyloxycarbonyl-L-lysine[26] (1.7 g, 5 mmol) was dissolved in a mixture of dioxane (4 ml), water (1 ml), and 2 *N* sodium hydroxide (3 ml). *tert*-Butyl azidoformate (0.9 g, 5.5 mmol) was added with vigorous stirring. The pH was maintained at 10.2 for 24 hr by the addition of 2 *N* sodium hydroxide

(25) The esterification of Boc-L-Thr, unprotected on the OH group, with *o*-nitrophenyl was attempted both in EtOAc and in pyridine solution. In pyridine, the formation of the desired active ester was observed by ir and by tlc, but the material was impure even after chromatography on silica gel [*cf.* M. Bodanszky and M. A. Ondetti, *Chem. Ind.* (*London*), 26 (1966)].

(26) B. W. Erickson and R. B. Merrifield "in Chemistry and Biology of Peptides," J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 191.

in small portions.[27] A viscous white gum separated, making stirring difficult. Dioxane–water (50%, 25 ml) was added to dissolve it. After 2 more days of stirring, no more base was consumed. The reaction mixture was diluted with 50% dioxane–water (50 ml) and extracted with ether (100 ml in two portions). The aqueous layer was filtered and acidified to pH 3.1 with 20% citric acid. The product deposited as a viscous gum on the walls of the flask. The supernatant liquid was decanted, and the product was rinsed with water (100 ml), dissolved in ether (25 ml), and filtered from a small amount of an impurity. The solvent was removed *in vacuo* to give 1.6 g (69%) of a fluffy material: mp 55–60°; $[\alpha]^{25}D$ −8° (*c* 2, AcOH); tlc R_fA 0.74.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysine (989 mg, 2.2 mmol) and *o*-nitrophenol (556 mg, 4 mmol) were dissolved in pyridine (5 ml) and stirred in an ice–water bath. Dicyclohexylcarbodiimide (412 mg, 2 mmol) was added. After 30 min, the ice bath was replaced with a bath at room temperature. After a total of 7.5 hr, DCU was removed by filtration and washed with pyridine (5 ml) and ether (5 ml). The solvent was removed by evaporation *in vacuo* and the crude oily product was triturated with ether (25 ml). The crystals were filtered, washed with ether (20 ml), and dried to give 888 mg (78%), mp 131–135°. More crystals separated from the mother liquor on standing. These were collected, washed with ether (15 ml), and dried to give 118 mg, mp 131–135°, a total yield of 88%. For analysis, a sample (100 mg) was dissolved in $CHCl_3$ (1 ml) and chromatographed on a column of silica gel (2 g). The purified active ester had a melting point of 135–137°.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-isonicotinyloxycarbonyl-L-lysine *o*-nitrophenyl ester was prepared according to the method described for Boc-L-Ser(Bzl)-ONO with a reaction time of 7 hr. The crude oil from a 0.9-mmol preparation crystallized on standing at room temperature to give 447 mg. A sample (60 mg) was dissolved in warm 95% EtOH containing 0.1% AcOH (0.75 ml) and centrifuged to remove a small amount of an impurity. The product crystallized in the freezer. It was filtered, washed with cold 95% EtOH, and dried *in vacuo* to give 23 mg (38%). The remaining crude product was dissolved in $CHCl_3$ (0.5 ml) and chromatographed on a column of silica gel (10 g) with $CHCl_3$, followed by 1, 3, and 5% MeOH in $CHCl_3$. The fractions containing the purified product were pooled and the solvent was removed by evaporation to give 339 mg of oil which was crystallized from 95% EtOH containing 0.1% AcOH in two crops of equal purity to give 204 mg (60%), mp 94–98°.

***tert*-Butyloxycarbonyl-L-valinamide (I).**—A stream of dry NH_3 was led over a solution of Boc-L-Val-ONO (16.77 g, 49.6 mmol) in THF (100 ml) for 3 hr. The flask was stoppered and allowed to stand for an additional 1 hr. The ammonium salt of *o*-nitrophenol separated on standing and was removed by filtration. The THF was removed *in vacuo*, and the yellowish-white crystalline residue was triturated with ether (100 ml), filtered, washed with cold ether (100 ml), and dried *in vacuo* over P_2O_5 to give 8.93 g (83%), mp 157–158° (lit.[28] mp 156–157°). Additional amounts of the same product were isolated from the mother liquor, increasing the total yield to 86%. Thin layer chromatography revealed a few per cent of DCU contamination. This impurity was removed by countercurrent distribution (60 transfers) in a $CHCl_3$–toluene–MeOH–H_2O (5:5:8:2) system.

***tert*-Butyloxycarbonyl-L-leucyl-L-valinamide (II).**—A sample of compound I (6.9 g, 32 mmol) was dissolved in TFA (32 ml). After 15 min at room temperature, the excess TFA was removed *in vacuo* and the trifluoroacetate salt was triturated with ether (100 ml), filtered, washed with ether (50 ml), and dried *in vacuo* over P_2O_5: 7.3 g (99%); mp 123.5–125.5°; $[\alpha]^{25}D$ +55° (*c* 1, DMF). The salt (5.8 g, 25 mmol) was dissolved in DMF (40 ml). Triethylamine (3 ml) was added to the solution, followed by Boc-L-Leu-ONO (10.6 g, 30 mmol), and TEA (0.6 ml) was added in small portions to maintain alkalinity. The next day, the semisolid mass of crystals was filtered and washed with DMF (6 ml) and EtOAc (20 ml). The product, dried *in vacuo* over P_2O_5, weighed 3.2 g (39%): mp 187–188°; $[\alpha]^{25}D$ −47° (*c* 2, AcOH). The filtrate and washings were evaporated *in vacuo*, and the crystalline residue was triturated with EtOAc (50 ml), filtered, and washed with EtOAc (50 ml) to give an additional 3.65 g (44%), mp 187–189°. A third crop (0.91 g), mp 187–189°, was recovered from the mother liquor, raising the total yield to 94%. The crops are identical on tlc, R_fB 0.44. Amino acid analysis: Val, 1.00; Leu, 0.94.

Anal. Calcd for $C_{16}H_{31}N_3O_4$ (329.4): C, 58.3; H, 9.5; N, 12.8. Found: C, 58.6; H, 9.2; N, 12.8.

***tert*-Butyloxycarbonylglycyl-L-leucyl-L-valinamide (III).**—The *tert*-butyloxycarbonyl group was removed from compound II (7.4 g, 22.5 mmol) with TFA (30 ml) as described in the previous paragraph. The trifluoroacetate salt was dissolved in DMF (40 ml), and TEA (11 ml) was added, followed by Boc-Gly-ONO (8.3 g, 28 mmol). After the acylation was complete, the DMF was removed *in vacuo* at 35°, and the yellow oily residue was triturated with EtOAc (100 ml), filtered, and washed with EtOAc (200 ml). The crystalline product was dried *in vacuo* over P_2O_5 to give 7.65 g (88%): mp 205–206.5°; $[\alpha]^{25}D$ −32.5° (*c* 2, AcOH); tlc R_fB 0.32. Amino acid analysis: Gly, 1.00; Val, 0.95; Leu, 0.95. Additional material (0.75 g, 9%) of the same purity was obtained from the mother liquors.

Anal. Calcd for $C_{18}H_{34}N_4O_5$ (386.5): C, 55.9; H, 8.9; N, 14.5. Found: C, 55.8; H, 8.7; N, 14.4.

***tert*-Butyloxycarbonyl-L-glutaminylglycyl-L-leucyl-L-valinamide (IV).**—The *tert*-butyloxycarbonyl group was removed from compound III (7.7 g, 20 mmol) with TFA (20 ml) as described. The trifluoroacetate salt was dissolved in DMF (35 ml) and the solution was made basic with TEA (6.5 ml). Boc-L-Gln-ONO (8.8 g, 24 mmol) was added and rinsed in with DMF (15 ml). After 3 hr, DMF (35 ml) was added to the semisolid mass of crystals to aid homogenization. Acylation appeared complete in 24 hr. The DMF was removed *in vacuo* at 35° and the crude product was triturated with EtOAc (75 ml), filtered, washed with EtOAc (175 ml in small portions), and dried *in vacuo* at 46° for 4 hr to give 10.0 g (97%): mp 219–220°; $[\alpha]^{25}D$ −31° (*c* 2, AcOH); tlc R_fA 0.62. Amino acid analysis: Glu, 1.00; Gly, 1.00; Val, 1.02; Leu, 1.13.

Anal. Calcd for $C_{23}H_{42}N_6O_7$ (514.6): C, 53.7; H, 8.2; N, 16.3. Found: C, 53.8; H, 8.3; N, 16.1.

***tert*-Butyloxycarbonyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide (V).**—The *tert*-butyloxycarbonyl group was removed from a sample (5.1 g, 10 mmol) of compound IV with TFA (15 ml) as described above. The trifluoroacetate salt was suspended in DMF (25 ml); a thick gel formed. Triethylamine (4.5 ml) was added, followed immediately by Boc-L-Leu-ONO (7.0 g, 20 mmol). Subsequently the mixture was diluted with DMF (25 ml). Acylation was complete in 20 hr. The DMF was removed *in vacuo* at 35° bath temperature, and the crude product was triturated with EtOAc (100 ml), filtered, washed with EtOAc (150 ml), and dried *in vacuo* over P_2O_5 to give 6.1 g (96%): mp 240–242°; $[\alpha]^{25}D$ −40° (*c* 2, AcOH); tlc R_fA 0.67. Amino acid analysis: Glu, 0.97; Gly, 1.00; Val, 0.97; Leu, 1.98.

Anal. Calcd for $C_{29}H_{53}N_7O_8$ (627.8): C, 55.5; H, 8.5; N, 15.6. Found: C, 55.7; H, 8.6; N, 15.4.

***tert*-Butyloxycarbonyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide (VI).**—The *tert*-butyloxycarbonyl group was removed from compound V (5.8 g, 9.3 mmol) with TFA (15 ml) as described above. The trifluoroacetate salt was dissolved in DMF (40 ml). Triethylamine (2.8 ml) and Boc-L-Leu-ONO (4.9 g, 13.9 mmol) were added with vigorous mixing. Since the reaction mixture thickened to a semisolid mass of crystals in 30 min, DMF (20 ml) was added to aid homogenization. After 3 days the solvent was removed *in vacuo* at 35°, and the crude product was triturated with EtOAc (50 ml), filtered, and washed with EtOAc (50 ml). The product was dried in air, powdered, and washed again with EtOAc (150 ml). The protected hexapeptide amide was dried *in vacuo* to give 6.75 g (98%). The crystals sinter at 255° and melt with decomposition at 263–265°; $[\alpha]^{25}D$ −48° (*c* 2, AcOH); tlc R_fA 0.75. Amino acid analysis: Glu, 1.00; Gly, 1.00; Val, 0.99; Leu, 3.10.

Anal. Calcd for $C_{35}H_{64}N_8O_9$ (740.95): C, 56.7; H, 8.7; N, 15.1. Found: C, 56.6; H, 8.6; N, 14.9.

L-Leucyl-L-glutaminyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide Trifluoroacetate (IXa).—All the following operations were carried out in a 40-ml centrifuge tube fitted with a 24/40 ground glass joint to allow its attachment to a rotary evaporator. The intermediates were not removed from the vessel at any time during the chain-lengthening steps. Trifluoroacetic acid was used for the (partial) deprotection of the peptides and TEA for the liberation of the amines from their trifluoroacetate salts. Stepwise acylation was accomplished with a gradual increase from 20 to 50% excess of the respective protected amino acid *o*-nitrophenyl esters, except in the preparation of the tetrapeptide,

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where, to suppress pyroglutamyl peptide formation, a 100% excess was applied. The acylation of the N-terminal leucyl residue of the pentapeptide amide with Boc-L-Leu-ONO was observed to proceed with a slower than desirable rate; this probably could be increased by the application of a larger excess of the active ester.[29]

A sample of Boc-L-Val-NH_2 (I, 400 mg, 1.85 mmol) was placed in the centrifuge tube and dissolved in TFA (1 ml). After 15 min at room temperature, the excess TFA was removed *in vacuo*. The trifluoroacetate salt was triturated with ether, the solution was removed after centrifugation, and the solid was washed with ether (45 ml in three portions) and dried *in vacuo* to give compound Ia (416 mg, 98%). The amide trifluoroacetate was dissolved in DMF (2 ml), and TEA (270 μl) was added followed by Boc-L-Leu-ONO (763 mg, 2.2 mmol). After 24 hr the DMF was removed *in vacuo* at 35°. The residue was triturated and washed with EtOAc (15 ml in five portions). The dry product II weighed 534 mg (90%). Melting points and R_f values were similar to those of the respective compounds reported above. No attempt was made to secure additional material from the mother liquors and washings.

Following this procedure, the protected tripeptide amide III was secured in 82% yield (514 mg). The tetrapeptide IV and all subsequent peptides were triturated and washed with EtOAc (90 ml in six portions). Compound IV was obtained in quantitative yield, 550 mg. The pentapeptide V (610 mg, 97%) showed a trace of a slower moving ninhydrin-negative material on tlc which is probably pyroglutamyltetrapeptide amide. The hexapeptide VI (701 mg, 97%), with the trace impurity still noticeable, gave a satisfactory amino acid analysis: Glu, 1.01; Gly, 1.00; Val, 1.00; Leu, 2.96.

tert-Butyloxycarbonyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide (VII) was isolated in a yield of 948 mg (98%): sintering at 263°, mp 270–273° dec; $[\alpha]^{25}D$ −42° (*c* 1, AcOH); tlc R_fA 0.76, R_fC 0.83. Amino acid analysis: Lys, 0.97; Glu, 1.02; Gly, 1.00; Val, 1.00; Leu, 2.98; NH_3, 2.10.

Anal. Calcd for $C_{49}H_{80}N_{10}O_{12}Cl_2$ (1072.1): C, 54.9; H, 7.5; N, 13.1. Found: C, 54.7; H, 7.4; N, 12.8.

tert-Butyloxycarbonyl-L-glutaminyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide (VIII) was secured in a yield of 919 mg (96%): sinters at 266°, mp 267–269° dec; tlc R_fA 0.69, R_fC 0.64. A sample (20 mg) was removed from the reaction vessel, deprotected with TFA (0.5 ml) and filtered to remove mechanical impurities, precipitated, washed with ether, and dried for analysis; VIIIa sinters at 220°, darkens at 260°, mp 270–273° dec, tlc R_fA 0.49. Amino acid analysis: Lys, 1.05; Glu, 1.96; Gly, 1.00; Val, 1.01; Leu, 3.10; NH_3, 3.40.

Anal. Calcd for $C_{56}H_{89}N_{12}O_{16}Cl_2F_3$ (1214.2): C, 50.4; H, 6.7; N, 13.8. Found: C, 50.5; H, 6.8; N, 13.6.

tert-Butyloxycarbonyl-L-leucyl-L-glutaminyl-N^{ϵ}-2,6-dichlorobenzyloxycarbonyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide (IX) was prepared as described above. A 100% excess of Boc-L-Leu-ONO was applied, followed later by an additional 65%.[29] The yield of compound IX was 955 mg (98%): sinters at 275°, mp 283–286° dec; tlc R_fA 0.70, R_fC 0.63. A sample (10 mg) was deprotected and prepared for analysis as described for VIIIa. The trifluoroacetate salt IXa sinters at 200° and darkens at 260°, mp 278–279° dec, tlc R_fA 0.51. Amino acid analysis: Lys, 1.04; Glu, 1.94; Gly, 1.00; Val, 1.00; Leu, 4.06; NH_3, 3.2.

Anal. Calcd for $C_{62}H_{100}N_{13}O_{17}Cl_2F_3$ (1327.3): C, 51.6; H, 7.0; N, 13.7. Found: C, 50.0; H, 6.6; N, 13.0.

These values suggest that the sample contains more than 1 mol of TFA, even though it was dried at 40° *in vacuo* for 2.5 hr. Attempts to dry the sample at higher temperatures resulted in decomposition.

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Registry No.—I, 35150-08-4; II, 33900-16-2; II TFA salt, 41641-83-2; III, 41120-77-8; IV, 41120-78-9; V, 33529-91-8; VI, 7802-00-8; VII, 41120-80-3; VIII, 41594-22-3; VIII TFA salt, 41120-82-5; IX, 41120-83-6; IX TFA salt, 41594-23-4; Boc-L-Ser(Bzl), 23680-31-1; o-nitrophenol, 88-75-5; 2,6-dichlorobenzyl alcohol, 15258-73-8; *tert*-butyl azidoformate, 1070-19-5; dicyclohexylcarbodiimide, 538-75-0; triethylamine, 121-44-8.

(29) The completion of the coupling reaction required 1 week. Similar difficulties encountered in the preparation of the protected nonapeptide IX were overcome by the application of the active ester in 100% excess and by catalysis with 1-hydroxybenzotriazole used in an amount equimolar to the active ester (W. König and R. Geiger in "Chemistry and Biology of Peptides," J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 343). Under these conditions, acylation was complete in less than 1 day.

New Convenient Syntheses of α-C-Acylamino Acids and α-Amino Ketones[1]

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α-C-Acylamino acid esters (3-oxo-2-amino acid esters, **6**) were prepared in good yields by the acid hydrolysis of α-acyl-α-isocyanoacetate analogs (**5**) and oxazole-4-carboxylate derivatives (**4**), which were easily obtained by the reaction of α-isoeyanoacetate analogs (**1**) with acyl halides (**2**) or acid anhydrides (**3**) in the presence of metallic or organic bases. Further, the hydrolysis of **6** and **4** gave the α-amino ketones (**7**) in high yields.

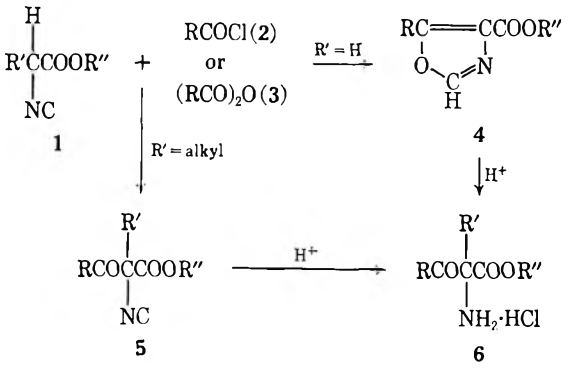
α-C-Acylamino acids are pharmaceutically interesting compounds and important intermediates for the synthesis of β-hydroxyamino acids.[2-5] Most recently, α-C-acylamino acids have been used for the preparation of β-keto esters.[6]

A few methods for the synthesis of α-C-acylamino acids have been reported. Bolhofer[2] and Sallay, *et al.*,[3] described a partial reduction of acyldiazoacetates which were prepared by the diazotization of β-keto esters and by the acylation of diazoacetates, respectively. Pines, *et al.*, reported the synthesis of *N*-acetyl-α-benzoylglycine derivatives by a reaction of azlactone with Grignard reagents in about 30% yield.[4] However, these methods require various limiting conditions.

In the course of our studies on the synthesis of amino acids, we have reported the reaction of isocyano compounds with various electrophiles,[5,7-9] among which the synthesis of aroylamino acids has been published in a preliminary communication.[8] In the present paper, we wish to report in detail a new convenient synthesis of various α-C-acylamino acid esters (**6**), using the reaction of isocyano compounds (**1**) with acyl halides (**2**) or acid anhydrides (**3**) as shown in Scheme I.

The reaction of α-isocyanoacetate[10] (**1**, R′ = H) with benzoyl chloride analogs (**2**, R = aromatic group) in the presence of triethylamine to produce oxazole-4-carboxylates (**4**) (method A) (Table I, **4g-k**) was previously described.[8] Schöllkopf and Schröder also reported that the reactions of α-isocyanoacetate with acyl halides and acyl amides in the presence of metallic bases gave oxazole (**4**).[11] Furthermore, we have studied reactions using acylating reagents other than acyl halides and acyl amides. We have found that reaction of α-isocyanoacetate with various acid anhydrides

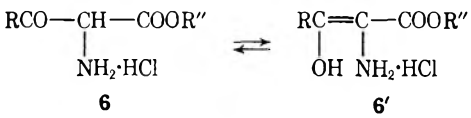
Scheme I



(**3**) proceeds easily in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[12] which is a very strong organic base,[13] and consequently various oxazole-4-carboxylates (**4**) are obtained in good yields as listed in Table I (method B). The same reaction took place also in the case of cyclic acid anhydrides such as succinic anhydride or glutaric anhydride and subsequently yielded dicarboxylic acid oxazole compounds (**4e** and **4f**) which are new and interesting substances, in 65 and 60% yields, respectively.

It was also found that the oxazole compounds prepared according to method A or B were readily converted to α-C-acylamino acid derivatives (**6**, R′ = H) by heating at 40–50° in 3 *N* HCl–MeOH for 4 hr in high yields. These results are listed in Table II. The conversion of the oxazole compounds (**4e** and **4f**) to α-C-acylamino acid esters was accompanied by esterification of the ω-carboxylic acid group; the corresponding esters were identified as 2-amino-3-oxyhexanedioic acid dimethyl ester hydrochloride (**6e**) and 2-amino-3-oxyheptanedioic acid dimethyl ester hydrochloride (**6f**).

The α-C-acylamino acid ester hydrochlorides (**6**, R′ = H) prepared by the hydrolysis of the oxazole compounds (**4**) may exist in keto–enol tautomeric forms as shown in the following equation.



For example, the ir spectrum (KBr disk) of α-(3,4-dichloro)benzoylglycine (**6j**) showed the characteristic

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TABLE I

FORMATION OF OXAZOLE COMPOUNDS (4)

Compd	R	R''	Method[a]	Yield, %	Mp, °C [bp, °C (mm)]	Formula	Analysis, % C	H	N
4a	CH_3	Me	B	78	46–48 [55–57 (0.1)]	$C_6H_7O_3N$	51.06[f] 51.28[g]	5.00 4.99	9.93 9.85
4b	$CH_3CH_2CH_2$	Et	B	85	[85–88 (1.2)]	$C_9H_{13}O_3N$	59.00 59.27	7.15 7.00	7.65 7.56
4c	$(CH_3)_2CHCH_2$	Me	A	25	[78–80 (0.35)]	$C_9H_{13}O_3N$	59.00	7.15	7.65
			B	75			58.87	7.32	7.60
4d	$C_6H_5CH_2$	Et	B	70	[125–128 (0.1)[b]]	$C_{13}H_{13}O_3N$	67.52 67.18	5.67 5.52	6.06 5.99
4e	$HOOCCH_2CH_2$[c]	Me	B	65	121–123	$C_8H_9O_5N$	48.24 48.39	4.56 4.40	7.03 6.83
4f	$HOOCCH_2CH_2CH_2$[d]	Me	B	60	84–85	$C_9H_{11}O_5N$	50.70 50.96	5.20 5.17	6.57 6.38
4g	C_6H_5	Me	A	90	91–93	$C_{11}H_9O_3N$	65.02	4.46	6.89
			B	85			64.86	4.40	6.89
4h	3,4-Methylenedioxy Ph	Me	A	92	130–132	$C_{12}H_9O_5N$	58.30 58.17	3.67 3.67	5.67 5.52
4i	3,4,5-Trimethoxy Ph	Me	A	79	137–139	$C_{14}H_{15}O_6N$	57.33 57.56	5.16 5.26	4.78 4.96
4j	3,4-Dichloro Ph	Me	A	88	142–143	$C_{11}H_7O_3NCl_2$	48.55 48.37	2.59 2.63	5.14 5.10
4k	2-Naphthalene[e]	Me	A	85	111–113	$C_{15}H_{11}O_3N$	71.14 70.74	4.37 4.50	5.53 5.44

[a] Method A, from acyl halides; method B, from acid anhydrides. [b] Lit.[11] bp 135° (0.1 mm). [c] Reaction using succinic anhydride. [d] Reaction using glutaric anhydride. [e] Reaction using β-naphthoyl chloride. [f] Calculated. [g] Found.

TABLE II

FORMATION OF α-C-ACYLAMINO ACID DERIVATIVES (6, R' = H)

Compd	R	R''	Yield, %	Mp, °C[b] dec	Formula	Analysis, % C	H	N
6a	CH_3	Me	73	146–148	$C_5H_{10}O_3NCl$	35.83[c] 35.89[d]	6.01 6.00	8.35 8.44
6b	$CH_3CH_2CH_2$	Et	84	125–126	$C_8H_{16}O_3NCl$	45.82 45.64	7.69 7.66	6.68 6.79
6c	$(CH_3)_2CHCH_2$	Me	77	110–113	$C_8H_{16}O_3NCl$	45.82 45.77	7.69 7.52	6.68 6.80
6d	$C_6H_5CH_2$	Et	80	144–146	$C_{12}H_{16}O_3NCl$	55.92 55.79	6.25 6.14	5.43 5.58
6e	$MeOOCCH_2CH_2$	Me	83	143–146	$C_8H_{14}O_5NCl$	40.09 40.17	5.88 5.69	5.84 5.88
6f	$MeOOCCH_2CH_2CH_2$	Me	87	Oil[a]				
6g	C_6H_5	Me	84	185–186	$C_{10}H_{12}O_3NCl$	52.29 52.26	5.28 5.39	6.10 6.11
6h	3,4-Methylenedioxy Ph	Me	85	170–171	$C_{11}N_{12}O_5NCl \cdot H_2O$	45.29 45.20	4.80 4.90	4.79 4.83
6i	3,4,5-Trimethoxy Ph	Me	80	174–175	$C_{13}H_{18}O_6NCl$	48.82 48.63	5.67 5.56	4.38 4.30
6j	3,4-Dichloro Ph	Me	80	165–167	$C_{10}H_{10}O_3NCl_3 \cdot {}^3/_2H_2O$	36.58 36.86	4.02 3.96	4.29 4.56
6k	2-Naphthalene	Me	85	169–170	$C_{14}H_{14}O_3NCl$	60.11 60.28	5.04 5.38	5.00 4.81

[a] Identified by ir and nmr spectra. [b] Recrystallization from ethyl acetate–methanol. [c] Calculated. [d] Found.

absorption of the ester group at 1750 cm^{-1} and of the ketone group at 1690 cm^{-1}, respectively. These results suggested that the keto form (**6**) should be preferred. On the other hand, the nmr spectrum (DMSO-d_6) of compound **6j** showed one proton signal for the hydroxy at δ 6.35 which disappeared on deuterium exchange and obtained no signal for the methine proton. From these results, the stability of the enol form (**6'**) was high in solution. Similar behavior was also shown by other various α-*C*-acylamino acid ester hydrochlorides (**6**, R' = H).

In the reaction of α-alkylisocyano compounds [**1**, R' = CH_3, CH_2CH_3, $CH(CH_3)_2$] with various acyl halides in the presence of metallic base such as NaH or organic base such as DBU, the oxazoles were not formed, but α-acyl-α-isocyano compounds (**5**) were obtained. Part of the products (**5**, R = C_6H_5, R' = CH_3, R'' = Me) was distilled for purification and identified by the ir spectrum, which exhibited bands at 2120, 1750, and 1700 cm^{-1} due to the NC, COOMe, and CO, respectively, and by the nmr spectrum. The other compounds (**5**) were subsequently hydrolyzed without purification with 2 *N* HCl–MeOH for 1 hr at 40° to afford the various α-alkyl-α-*C*-acylamino acid methyl ester hydrochlorides (**6**, R' = alkyl) in 50–65% yields as summarized in Table III.

Table III
Formation of α-Alkyl-α-aroylamino Acid Derivatives (6, R'' = Me)

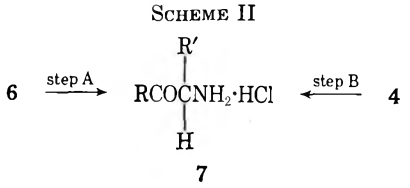
Compd	R	R'	Yield,[a] %	Mp, °C[c] dec	Formula	Analysis, % C	H	N
6l	C_6H_5	CH_3	50 (65[b])	154–155	$C_{11}H_{14}O_3NCl$	54.21[d]	5.79	5.74
						53.95[e]	5.82	5.71
6m	3,4-Methylenedioxy Ph	CH_3	58	146–147	$C_{12}H_{14}O_5NCl \cdot H_2O$	47.15	5.28	4.58
						46.85	5.26	4.58
6n	3,4,5-Trimethoxy Ph	CH_3	62	155–157	$C_{14}H_{20}O_6NCl \cdot H_2O$	47.79	6.30	3.98
						47.51	6.42	3.99
6o	C_6H_5	CH_2CH_3	52	166–167	$C_{12}H_{16}O_3NCl$	55.93	6.08	5.44
						55.98	6.31	5.41
6p	3,4-Methylenedioxy Ph	CH_2CH_3	58	163–164	$C_{13}H_{16}O_5NCl$	51.75	5.35	4.64
						51.41	5.53	4.44
6q	3,4,5-Trimethoxy Ph	CH_2CH_3	53	142–145	$C_{15}H_{22}O_6NCl \cdot H_2O$	49.24	6.61	3.83
						49.04	6.68	3.85
6r	C_6H_5	$CH(CH_3)_2$	65	167–168	$C_{13}H_{18}O_3NCl$	57.46	6.68	5.15
						57.42	6.81	5.23
6s	3,4-Methylenedioxy Ph	$CH(CH_3)_2$	55	152–153	$C_{14}H_{18}O_5NCl \cdot H_2O$	50.37	6.04	4.20
						50.08	6.07	4.20
6t	3,4,5-Trimethoxy Ph	$CH(CH_3)_2$	60	132–134	$C_{16}H_{24}O_6NCl \cdot H_2O$	50.59	6.89	3.68
						50.81	6.58	3.70
6u	2-Naphthalene	$CH(CH_3)_2$	55	142–143	$C_{17}H_{20}O_3NCl \cdot H_2O$	60.00	6.52	4.12
						59.81	6.47	4.38

[a] Reaction of isocyano compounds with acyl halides in the presence of NaH. [b] Reaction of isocyano compounds with benzoic anhydride in the presence of DBU. [c] Recrystallization from ethyl acetate–methanol. [d] Calculated. [e] Found.

On the other hand, α-amino ketones are also useful compounds for the synthesis of amino alcohols, which include such physiologically interesting substances as ephedrine and adrenaline. Several methods for the preparations of amino ketones have been reported.[14] For example, the hydrolysis of the quaternary salt obtained from phenacyl bromide and hexamethylenetetramine,[15] the reduction of α-oximino acetone derivatives[16] or α-nitroacetone derivatives,[17] the Neber rearrangement of the tosylate of acetophenone oxime derivatives,[18] and the rearrangement of *N,N*-dichloro-*sec*-alkylamine[19] are generally known.

We previously reported a method for the preparation of phenacylamine derivatives from aroylamino acids and oxazoles as shown in Scheme II.[8] In the

Scheme II



present study, the method is extended to various aliphatic α-*C*-acylamino acid esters and oxazoles.

When the α-*C*-acylamino acid ester hydrochlorides (6) were treated with 6 *N* hydrochloric acid under heating at 90–95° for 4 hr, the corresponding α-amino ketone hydrochlorides (7) were obtained in high yields by decarboxylation (step A). Furthermore, hydrolysis of the oxazoles (4) carried out under conditions similar to the method of step A afforded the corresponding α-amino ketone hydrochlorides (7, R' = H) (step B). These results are summarized in Table IV.

It appears that these synthetic methods will be generally useful for the preparation of α-*C*-acylamino acids and α-amino ketones.

Experimental Section[20]

Typical Procedures for Preparation of Oxazoles (4). Method A.—This method has been described previously.[8] Various oxazoles (4g–k) were prepared in the same way. The yields, melting points, and elemental analyses of the compounds are shown in Table I.

Method B. Methyl 5-Methyloxazole-4-carboxylate (4a).—To a mixture of methyl α-isocyanoacetate (2.97 g, 0.03 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.5 g, 0.03 mol) in THF (40 ml) was added a mixture of acetic anhydride (3, R = CH_3, 3.06 g, 0.03 mol) and THF (10 ml) at 10° with stirring. After the solution was stirred for 10 hr at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and the solution was washed with water. The solution was dried over magnesium sulfate and the solvent was evaporated *in vacuo*. The residual oil was distilled under reduced pressure, bp 55–57° (0.1 mm), yield 3.3 g (78%). The product solidified on standing and was recrystallized from a mixture of isopropyl ether and *n*-hexane: mp 46–48°; ir (Nujol) 3100 (CH), 1695 (COOMe), 1600 (C=N), 1510 cm^{-1} (C=C); nmr (CCl_4) δ 7.84 (s, 1, CH), 3.92 (s, 3, OCH_3), 2.65 (s, 3, CH_3).

Other oxazole compounds (4b–d and 4g) were prepared in a similar way. The results are summarized in Table I.

4-Methoxycarbonyl-5-oxazolepropionic Acid (4e).—A mixture of succinic anhydride (3.0 g, 0.03 mol) and THF (30 ml) was gradually added to a solution of methyl α-isocyanoacetate (2.97 g, 0.03 mol) and DBU (9.0 g, 0.06 mol) in THF (40 ml) for a period of 30 min at 30–33° with vigorous stirring. After stirring was continued for 4 hr at room temperature, the reaction mixture was neutralized with acetic acid under cooling and evaporated to remove the solvent under reduced pressure. The residue was dissolved in water (70 ml) and the solution was washed out with benzene. The separated aqueous layer was acidified with concentrated hydrochloric acid (15 ml) and then saturated with sodium chloride. The solution was sufficiently

(14) W. E. Parham, N. Newman, and R. M. Dobson, *Org. Syn.*, **41**, 88 (1961).
(15) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911)
(16) H. O. House and E. F. Grubbs, *J. Amer. Chem. Soc.*, **81**, 4733 (1959).
(17) J. Thiele and S. Haeckel, *Justus Liebigs Ann. Chem.*, **325**, 13 (1886).
(18) F. W. Neber and G. Huh, *Justus Liebigs Ann. Chem.*, **515**, 283 (1935).
(19) H. E. Baumgarten and F. A. Bower, *J. Amer. Chem. Soc.*, **76**, 4561 (1954).

(20) All the melting points and the boiling points were uncorrected. All the melting points were measured by the use of the Yamato melting point apparatus. The infrared spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The nmr spectra were obtained using a Hitachi Perkin-Elmer R-20A high resolution nmr spectrometer with tetramethylsilane as internal standard.

TABLE IV
FORMATION OF α-AMINO KETONE HYDROCHLORIDES (7)

Compd	R	R′	Yield, %[a]	Yield, %[b]	Mp, °C[c] dec	Formula	Analysis, % C	H	N
7a	CH_3	H	75	70	70–72[d]	C_3H_8ONCl	32.88[j]	7.36	12.78
							33.01[k]	7.19	12.50
7b	$CH_3CH_2CH_2$	H	90	85	172–174[e]	$C_5H_{12}ONCl$	43.63	8.78	10.17
							43.71	8.58	10.22
7c	$(CH_3)_2CHCH_2$	H	85	80	177–178[f]	$C_6H_{14}ONCl$	47.52	9.30	9.23
							47.34	8.97	9.19
7d	$C_6H_5CH_2$	H	95	93	200–202[g]	$C_9H_{12}ONCl$	58.22	6.51	7.54
							58.47	6.46	7.49
7g	C_6H_5	H	90	92	190–191[h]	$C_8H_{10}ONCl$	55.98	5.87	8.16
							56.32	5.93	8.37
7h	3,4-Methylenedioxy Ph	H	93	94	187–191[i]	$C_9H_{10}O_3NCl$	50.12	4.67	6.49
							50.19	4.68	6.48
7i	3,4,5-Trimethoxy Ph	H	91	94	243–244	$C_{11}H_{16}O_4NCl$	50.48	6.16	5.73
							50.24	6.06	5.41
7k	2-Naphthalene	H	91	90	256	$C_{12}H_{12}ONCl$	65.01	5.45	6.31
							64.88	5.46	6.41
7m	3,4-Methylenedioxy Ph	CH_3	93		206	$C_{10}H_{12}O_3NCl$	52.30	5.27	6.10
							52.11	5.30	6.31
7n	3,4,5-Trimethoxy Ph	CH_3	95		237	$C_{12}H_{18}O_4NCl$	52.27	6.58	5.08
							51.90	6.57	5.10
7r	C_6H_5	$CH(CH_3)_2$	87		198–199	$C_{11}H_{16}ONCl$	61.82	7.54	6.55
							61.73	7.42	6.60
7t	3,4-Methylenedioxy Ph	$CH(CH_3)_2$	86		227–229	$C_{12}H_{16}O_3NCl$	55.92	6.26	5.44
							55.68	6.21	5.63

[a] From step A in Scheme II. [b] From step B in Scheme II. [c] Recrystallization from ethyl acetate–methanol. [d] Lit. mp 75° dec: S. Gabriel and G. Pinkus, *Ber.*, **35**, 3806 (1902). [e] Lit. mp 163–164° dec: M. Jackman, M. Klenk, B. Fishburn, B. F. Tuller, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 2884 (1948). [f] Lit.[e] mp 179–180°. [g] Lit.[e] mp 190–193° dec. [h] Lit.[19] mp 185–186° dec. [i] Lit. mp 193° dec: P. W. Neber, A. Burgard, and W. Thier, *Justus Liebigs Ann. Chem.*, **526**, 277 (1936). [j] Calculated. [k] Found.

extracted with ethyl acetate (50 ml) three times and the combined extract was dried over magnesium sulfate and then evaporated *in vacuo*. The obtainable crystals were washed with ether and collected by filtration. Recrystallization from ethyl acetate gave **4e** as colorless needles: yield 3.9 g (65%); mp 121–123°; ir (Nujol) 3120 (CH), 1728 (COOMe), 1708 (COOH), 1608 (N=C), 1525 cm^{-1} (C=C); nmr ($CDCl_2$) δ 10.37 (s, 1, COOH), 7.85 (s, 1, CH), 3.90 (s, 3, OCH_3), 3.45 (t, 2, CH_2), 2.75 (t, 2, CH_2).

4-Methoxycarbonyl-5-oxazolebutyric Acid (4f).—A mixture of glutaric anhydride (3.42 g, 0.03 mol) and THF (20 ml) was added dropwise to a solution of methyl α-isocyanoacetate and DBU (9.0 g, 0.06 mol) in THF (40 ml) for a period of 20 min at 30–33° with vigorous stirring. After additional stirring was continued for 1 hr at room temperature, the same treatment as described above was carried out to afford the oxazole compound **4f**. Recrystallization from ethyl acetate gave colorless needles: yield 3.8 (60%); mp 83–85°; ir (Nujol) 3150 (CH), 1722 (COOMe), 1710 (COOH), 1625 (N=C), 1515 cm^{-1} (C=C); nmr ($CDCl_3$) δ 11.08 (s, 1, COOH), 7.87 (s, 1, CH), 3.90 (s, 3, OCH_3), 3.16 (t, 2, CH_2), 2.90 (t, 2, CH_2), 2.10 (m, 2, CH_2).

General Procedure for Preparation of α-*C*-Acylamino Acid Derivatives (6a–k) *via* Oxazole Compounds (4a–k).—Oxazole compound **4** (0.01 mol) was dissolved in a mixture of concentrated hydrochloric acid (5 ml) and methanol (15 ml) and the solution was heated at 45–50° for 4 hr. After the reaction was complete, methanol was removed under reduced pressure below 30°. To the residue was added water (10 ml) and the acidic solution was washed with ether (10 ml). The separated aqueous layer was treated with activated charcoal and was concentrated to dryness *in vacuo* below 30°. The residue was dissolved in methanol and the mixture was then evaporated *in vacuo*. Such a treatment was repeated more than five times to remove completely excess hydrochloric acid. The resulting precipitates were washed with ether and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol gave various α-acylamino acid derivatives in good yields. The yields, physical properties, and elemental analyses of these compounds are listed in Table II.

Preparation of α-Benzoyl Alanine Methyl Ester Hydrochloride (6l).—To a mixture of DBU (6.0 g, 0.04 mol) and dimethylformamide (DMF, 40 ml) was added a mixture of methyl α-isocyanopropionate (3.39 g, 0.03 mol) and DMF (10 ml) at room temperature with stirring for a period of 10 min. After stirring was continued for 3 hr at the same temperature, benzoic anhydride (6.78 g, 0.03 mol) dissolved in DMF (10 ml) was added dropwise to the mixture for a period of 30 min at 30° with vigorous stirring. After the reaction mixture was stirred for 3 hr, water (100 ml) was added to the mixture under cooling and the solution was extracted with ethyl acetate (100 ml). The extract was washed with water (2 × 50 ml) and 10% sodium bicarbonate (2 × 30 ml) and dried over magnesium sulfate. After the solvent was removed, the residual oil was distilled under reduced pressure to afford methyl α-benzoyl-α-isocyanopropionate (**5**, R = Ph; R′ = CH_3; R″ = Me): bp 95–97° (0.15 mm); yield 4.2 g (65%); ir (film) 2120 (NC), 1750 (COOMe), 1700 cm^{-1} (CO); nmr (CCl_4) δ 8.10–7.70 (m, 5, aromatic H), 3.75 (s, 3, OCH_3), 1.88 (s, 3, CH_3).

Subsequently, the isocyano compound (2.17 g, 0.01 mol) was dissolved in 2 *N* methanolic hydrochloric acid solution (30 ml) and the solution was heated at 40° for 1 hr. After the reaction was over, the solvent and the excess hydrochloric acid were removed under reduced pressure below 30°. The obtainable crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol gave α-benzoylalanine methyl ester hydrochloride (**6l**): yield 2.4 g (quantitative); mp 154–155° dec; ir (Nujol) 1750 (COOMe), 1690 cm^{-1} (CO); nmr (DMSO-d_6) δ 9.50 (br, 3, $NH_2 \cdot HCl$), 8.00–7.50 (m, 5, aromatic H), 3.80 (s, 3, OCH_3), 1.90 (s, 3, CH_3).

A method using NaH was reported previously.[8] In a similar manner, several α-alkyl-α-*C*-acylamino acid ester hydrochlorides (**6l–u**) were prepared and these results are shown in Table III.

Typical Hydrolysis of α-*C*-Acylamino Acid Ester 6b to α-Amino Ketone Hydrochloride 7b (Step A).—α-Butyrylglycine ester hydrochloride (**6b**, 0.5 g, 0.0024 mol) was dissolved in 6 *N* hydrochloric acid (20 ml) and the solution was heated at 90–95° for 4 hr. After the reaction was over, the solution was removed under reduced pressure. The crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol afforded colorless leaflets: yield 0.29 g (90%); mp 172–174° dec; ir (Nujol) 1720 cm^{-1} (CO); nmr (DMSO-d_5) δ 8.50 (br, 3, $NH_2 \cdot HCl$), 3.88 (s, 2, CH_2), 2.52 (t, 2, CH_2), 1.50 m, 2, CH_2), 0.88 (t, 3, CH_3).

In a similar way, other α-amino ketone hydrochlorides (**7**) were prepared and these results are summarized in Table IV.

General Procedure for Preparation of α-Amino Ketone Hydrochlorides (7, R′ = H) from Oxazole Compounds (4) (Step B).—After a mixture of the oxazole compounds (**4**, 0.01 mol) and 6 *N* hydrochloric acid (30 ml) was heated at 95–100° for 5 hr, the solution was washed with benzene, treated with activated charcoal, and then evaporated *in vacuo*. The obtainable crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol afforded various α-amino ketone hydrochlorides (**7a–k**, R′ = H) in good yields as listed in Table IV. The physicochemical properties of the resulting products in this way agreed with those obtained by step A.

Acknowledgment.—We wish to express our thanks to Drs. T. Takayanagi and I. Chibata for their encouragement in this study.

Registry No.—**1** (R′ = H; R″ = Me), 105-34-0; **1** (R′ = H; R″ = Et), 105-56-6; **3** (R = Me), 108-24-7; **3** (R = Pr), 106-31-0; **3** (R = *i*-Bu), 1468-39-9; **3** (R = CH_2Ph), 1555-80-2; **3** (R = Ph), 93-97-0; **4a**, 41172-57-0; **4b**, 41172-58-1; **4c**, 41172-59-2; **4d**, 32998-96-2; **4e**, 41172-61-6; **4f**, 41172-62-7; **4g**, 38061-18-6; **4h**, 38061-19-7; **4i**, 38061-20-0; **4j**, 38061-21-2; **4k**, 38061-22-2; **5** (R = Ph; R′ = Me; R″ = Me), 41172-68-3; **5** (R = 3,4-methylenedioxy Ph; R′ = Me; R″ = Me), 41265-39-8; **5** (R = 3,4,5-trimethoxy Ph; R′ = Me; R″ = Me), 41172-69-4; **5** (R = Ph; R′ = Et; R″ = Me), 41172-70-7; **5** (R = 3,4-methylenedioxy Ph; R′ = Et; R″ = Me), 41172-71-8; **5** (R = 3,4,5-trimethoxy Ph; R′ = Et, R″ = Me), 41172-72-9; **5** (R = Ph; R′ = *i*-Pr; R″ = Me), 41172-73-0; **5** (R = 3,4-methylenedioxy Ph; R′ = *i*-Pr; R″ = Me), 41172-74-1; **5** (R = 3,4,5-trimethoxy Ph; R′ = *i*-Pr; R″ = Me), 41172-75-2; **5** (R = 2-naphthalene; R′ = *i*-Pr; R″ = Me), 41172-76-3; **6a**, 41172-77-4; **6b**, 41172-78-5; **6c**, 41172-79-6; **6d**, 38603-81-5; **6e**, 6317-41-5; **6f**, 41172-82-1; **6g**, 38061-23-3; **6h**, 38061-24-4; **6i**, 38061-25-5; **6j**, 38061-26-6; **6k**, 38061-27-7; **6l**, 40846-67-1; **6m**, 38061-28-8; **6n**, 38061-29-9; **6o**, 40846-68-2; **6p**, 40846-71-7; **6q**, 40846-74-0; **6r**, 38061-30-2; **6s**, 38061-31-3; **6t**, 40846-73-9; **6u**, 38061-32-4; **7a**, 7737-17-9; **7b**, 41172-98-9; **7c**, 21419-26-1; **7d**, 41173-00-6; **7g**, 5468-37-1; **7h**, 38061-34-6; **7i**, 38061-35-7; **7k**, 38061-36-8; **7m**, 38061-37-9; **7n**, 38061-38-0; **7r**, 33119-73-2; **7t**, 38061-40-4; succinic anhydride, 108-30-5; glutaric anhydride, 108-55-4; DBU, 6674-22-2.

Selective Hydrolysis of Dihydrocinnamate Ester Protecting Groups by α-Chymotrypsin. Further Studies on the Scope and Limitations of the Method

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Further examples of the preparative feasibility of exploiting the aromatic acyl group specificity of α-chymotrypsin as a useful addition to the methods of protecting group chemistry have been provided by studies on representative decalin and tropane acetate–dihydrocinnamate diesters. When the hydroxide-ion susceptibility of both ester functions is approximately equal, α-chymotrypsin catalysis exposes only the hydroxyl group protected as its dihydrocinnamate ester. On the other hand, when hydroxide-ion selectivity of hydrolysis is possible, enzymic hydrolysis of the dihydrocinnamate function can be used to complement or reverse the chemical specificity. The alcohol moiety binding site of the enzyme is hydrophobic in character and tolerates wide structural variations and the method appears applicable to a broad range of organic compounds provided that a marginal solubility in aqueous solutions is preserved. The approach seems most appropriate for alkaloids where partial conjugate acid formation can enhance the water solubility of the substrate. The mild, pH 7.8, conditions used are synthetically attractive since they minimize the problems of epimerization, isomerization, racemization, rearrangement, etc., often encountered during acid- or base-mediated hydrolyses of ester protecting groups.

In view of the increasing availability of purified enzymes and their immobilized derivatives, there can be little doubt that preparative exploitations of enzymes as selective and/or stereospecific catalysts of organic reactions will become far more widespread in the future. One of the areas in which the synthetic advantages of enzymatic catalysis has already been recognized is in the use of α-chymotrypsin to effect selective removal of aromatic amino acid and related acyl protecting groups from hydroxyl and amino functions of nucleosides.[1–4] Our preliminary studies[5] indicated that the method might be generally applicable and this communication provides further data on the scope and limitations of the technique when extended to mixed esters of other classes of organic compounds.

Choice and Syntheses of Some Representative Diols and their Esters.—In our initial survey,[5] it was found that, whereas simple acetate and dihydrocinnamate esters were hydrolyzed at almost equivalent rates by hydroxide ion,[6] α-chymotrypsin-catalyzed cleavage of the dihydrocinnamoyl moiety was achieved with complete specificity with acyclic acetate–dihydrocinnamate diesters. Accordingly, mixed diesters of this type were used to evaluate the preparative selectivity of α-chymotrypsin toward the dihydrocinnamoyl group in molecules of more general structural interest to organic chemists.

It was desired to evaluate the feasibility of achieving preferential removal of the α-chymotrypsin-sensitive acyl group from acetate dihydrocinnamates for which differences in the rates of chemical hydrolysis of each ester function were small or nonexistent. Alternatively, for compounds where preferential chemical cleavage of one ester group was possible, exploitation of α-chymotrypsin's specificity to reverse the chemical selectivity was the goal. Mixed esters of *trans*-decalin-1,6-diols and of tropane-3α,6β-diol appeared to satisfy most of the requirements for such evaluation and selected mixed ester derivatives were prepared as described below.

(1) Z. A. Shabarova, N. I. Sokolova, and M. A. Prokov'ev, *Dokl. Akad. Nauk SSSR*, **128**, 740 (1959).

(2) N. I. Sokolova, L. A. Borkova, and M. A. Prokov'ev, *Zh. Obshch. Khim.*, **29**, 2917 (1959).

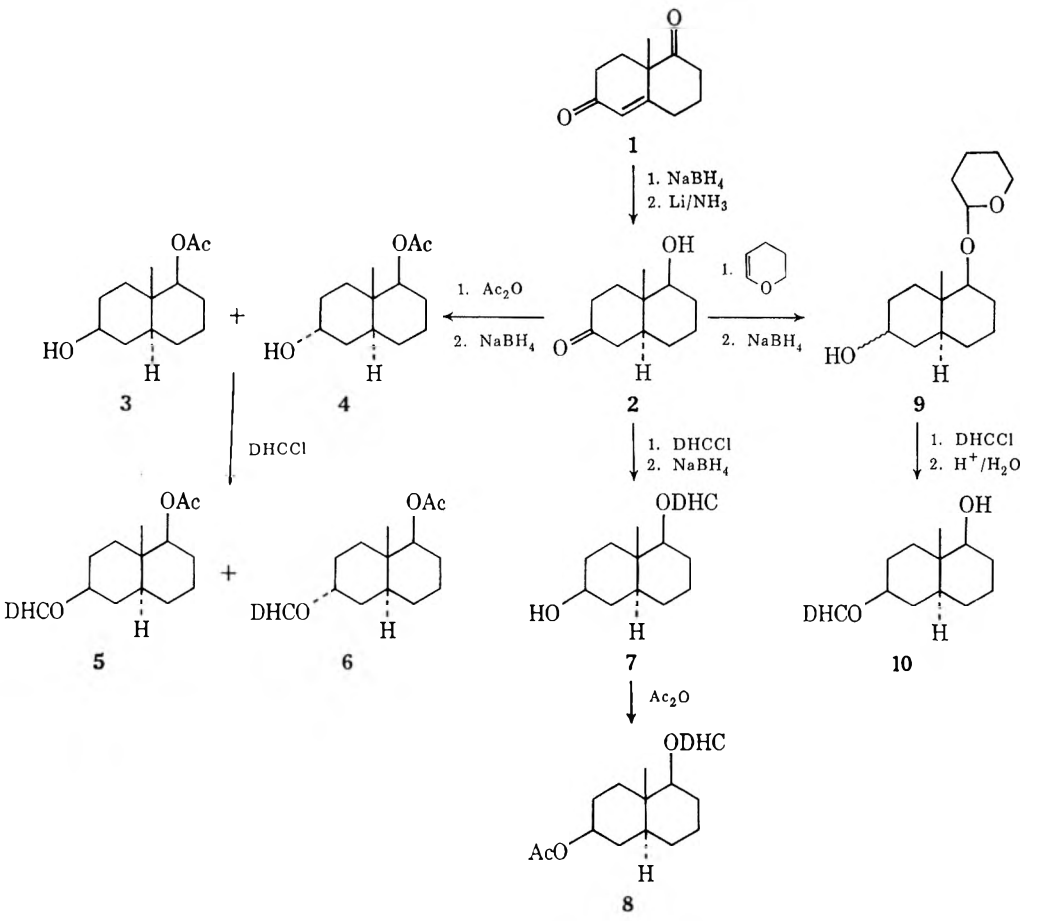
(3) D. H. Rammler and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 1997 (1963).

(4) H. S. Sachdev and N. A. Starkovsky, *Tetrahedron Lett.*, 733 (1969); A. Taunton-Rigby, *J. Org. Chem.*, **38**, 977 (1973).

(5) J. B. Jones and Y. Y. Lin, *Can. J. Chem.*, **50**, 2053 (1972).

(6) M. L. Bender, F. J. Kezdy, and C. R. Gunter, *J. Amer. Chem. Soc.*, **86**, 3714 (1964).

SCHEME I



The synthetic pathways leading to the desired *trans*-decalin esters are outlined in Scheme I.[7] Sodium borohydride reduction of 9-methyl-$\Delta^{5(10)}$-octalin-1,6-dione (**1**) followed by lithium in liquid ammonia treatment of the resulting 1β-alcohol gave the 1β-hydroxy-6-ketone **2** in good yield.[8] 1β Acetylation of **2** followed by a second sodium borohydride reduction proceeded smoothly to yield a difficult-to-separate mixture of the C-6 epimeric alcohols **3** and **4** in which glc analysis showed the equatorial 6β-hydroxy compound to predominate to the extent of ~85%. Esterification of the mixture of **3** and **4** with dihydrocinnamoyl chloride afforded the corresponding mixture of diesters **5** and **6** from which the 6β epimer **5** was fairly readily isolable. In contrast, exhaustive chromatography was required before a small sample of the pure 6α-dihydrocinnamate **6** could be obtained.[9] The 6β-acetoxy-1β-dihydrocinamate **8** was obtained from **2** in a similar manner by reversing the order of the esterification steps. Conversion of **2** into the 6β-dihydrocinnamate **10**, while retaining the β-hydroxyl function at C-1, was accomplished *via* the 1β-tetrahydropyranyloxy derivative **9**. The C-1 and C-6 configurational assignments of the compounds prepared were confirmed by the characteristic shape and relative chemical shifts of the 1α- and 6α- and β-proton peaks in the nmr spectra.[10]

The synthetic steps carried out in the tropane series are summarized in Scheme II. 6β-Hydroxytropinone (**11**)[11] was stereospecifically reduced[12] to the 3α,6β-diol **12**, which was then esterified with dihydrocinnamoyl chloride to give the bisdihydrocinnamate **13**. Selective[13] hydrolysis of the 6β-ester function of **13** proceeded smoothly and the 3α-dihydrocinnamate **14** obtained was converted into the mixed diester **15** by treatment with acetic anhydride. Conversion of 6β-hydroxytropinone (**11**) into the 6β-acetoxy ketone **16** followed by hydrogenation over Raney nickel to the 3α-hydoxy-6β-acetate **17** and then treatment with dihydrocinnamoyl chloride provided a convenient alternative synthesis of **15**. The C-3 and C-6 configurations assigned[14] to the compounds of Scheme II were supported by the chemical shifts and multiplicities observed for the protons at these positions. In the spectra of the 3-oxotropanes **11** and **16** the C-6α protons appeared as triplets. However, when 3α-hydroxy or ester functions were present, the multiplicity of this peak changed to a doublet of doublets. In contrast, the C-3β protons were consistently observed as triplets.

(7) In all schemes, the dihydrocinnamoyl function is represented as DHC.

(8) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

(9) Similar separation difficulties were encountered during all subsequent attempts to obtain pure samples of each of the minor (<15% in each case) 6α axially substituted derivatives encountered in Scheme I. Accordingly, all work carried out following the separation of **5** and **6** was concentrated on the predominant and more readily purified 6β-equatorial compounds.

(10) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

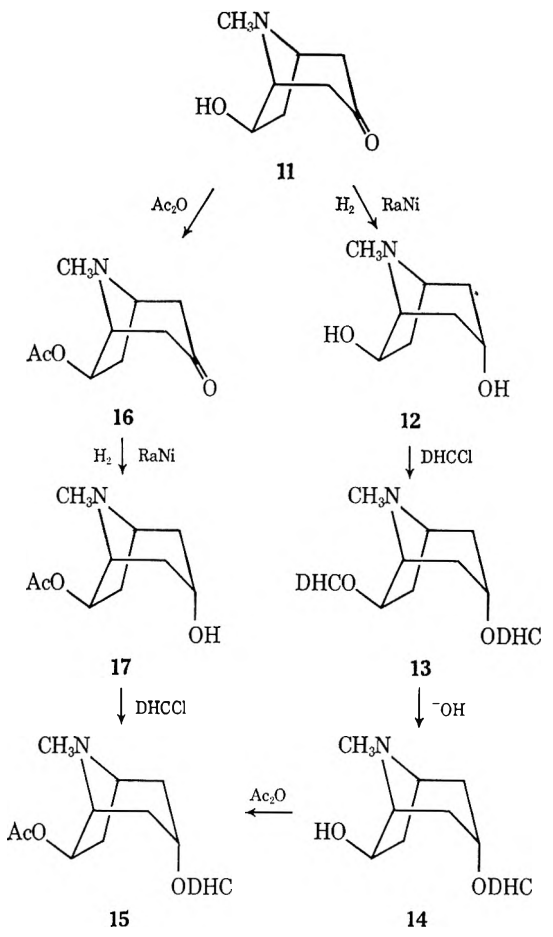
(11) P. Nedenskov and N. Clauson-Kaas, *Acta Chem. Scand.*, **8**, 1295 (1954).

(12) A. Stoll, B. Becker, and E. Jacker, *Helv. Chim. Acta*, **35**, 1263 (1952).

(13) G. Folder, I. W. Vinege, and J. Toth, *J. Chem. Soc.*, 3219 (1961); G. Folder, S. Kiss, and J. Rakoczi, *Chem. Ind. (London)*, **90**, 225 (1963).

(14) G. Fodor in "Chemistry of the Alkaloids," S. W. Pelletier, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, p 449.

Scheme II



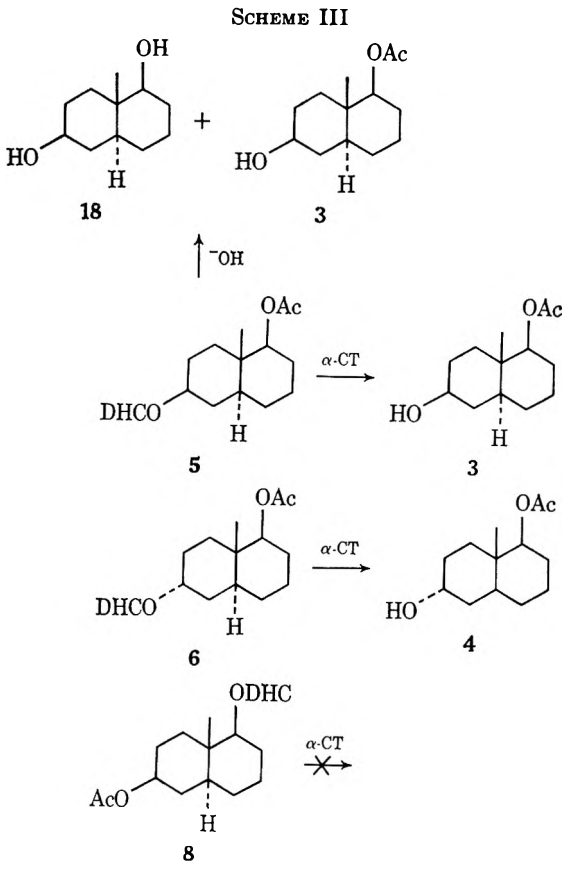
Results

On the basis of literature data on the hydrolysis of *trans*-decalin[15] and analogous steroid[16] diesters, some preferential hydrolysis of the 6β function of the diester **5** by hydroxide ion was expected. However, that this degree of chemical selectivity was of limited preparative utility on a routine basis was demonstrated by the product distribution observed when **5** was treated with 1 equiv of sodium hydroxide in aqueous methanol at 25°. Only 53% of the 1β-acetate **3** was isolated, and furthermore, 35% of the 1β,6β-diol product **18** of complete hydrolysis was also formed. In contrast, α-chymotrypsin-catalyzed hydrolysis of **5** resulted in completely specific removal of the 6β-dihydrocinnamoyl group, and quantitative conversion into the 1β-acetate **3** was achieved (Scheme III) with none of the 6β-dihydrocinnamoyloxy-1β-alcohol **10** being formed. Although the rate of hydrolysis of the epimeric 6α-dihydrocinnamate **6** was significantly slower, its selective enzymic conversion into the 6α-hydroxy-1β-acetate **4** also occurred to the extent of 96%. For the isomeric, but much less soluble, 1β-dihydrocinnamate-6β-acetate diester **8**, the enzyme-mediated reaction was much more sluggish than for **5** or **6** and α-chymotrypsin-catalyzed hydrolysis was not preparatively feasible for this compound.

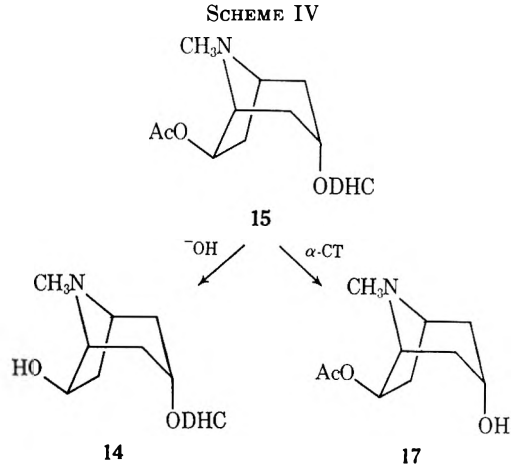
On treatment of diesters, such as the acetates or isovalerates, of 3α,6β-dihydroxytropane with hydroxide ion under controlled conditions, hydrolysis of only the 6β function can be achieved.[13] The mixed 6β-acetate–3α-dihydrocinnamate diester **15** was therefore synthesized in order to evaluate the ability of α-chymotrypsin to reverse the hydroxide ion selectivity by effecting specific cleavage at the 3α position.

The results obtained are represented in Scheme IV.

Scheme III



Scheme IV



That selective hydroxide ion mediated cleavage of the 6β-ester function could be effected was confirmed by the hydrolysis of **15** and of the bisdihydrocinnamate **13** to the 6β-hydroxy-3α-cinnamate **14** in 65–70% yields. The hydrochloride salt of **15** was used as the substrate for the α-chymotrypsin experiments, and consequently, addition of ~0.5 equiv of sodium hydroxide was required in order to bring the reaction solution up to the pH optimum of 7.8 prior to the addition of the enzyme. When the enzyme-catalyzed

(15) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 237.

(16) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 513.

hydrolysis ceased, a further 0.5 equiv of base had been consumed and the desired product of 3α hydrolysis, 6β-acetoxy-3α-hydroxytropane (**17**), was obtained in quantitative yield.[17]

The relative rates of hydrolysis under preparative conditions of all the compounds studied, and, where relevant, the degree of selectivity of the desired α-chymotrypsin-catalyzed cleavage, are summarized in Table I. For **15** and the two most soluble dihydrocinnamate esters of the decalin series, **7** and **10**, quantitative kinetic data were obtainable under homogeneous conditions. The kinetic parameters obtained are recorded in Table II.

TABLE I

PRODUCT ANALYSES AND RELATIVE RATE DATA FOR PREPARATIVE-SCALE α-CHYMOTRYPSIN-CATALYZED HYDROLYSES OF DIHYDROCINNAMATE ESTERS[a]

Compd	Product(s) (% selectivity)[b]	Relative hydrolysis rates[c]
$C_6H_5(CH_2)_2COOCH_3$		1.0
5	**3** (100)	0.51
6	**4** (96)	0.11
8[d]		0.03
7	**18**	0.16
10	**18**	2.02
15	**17** (100)	0.49

[a] The preparative-scale enzyme-catalyzed hydrolyses were carried out on heterogeneous suspensions of up to 2 g of the substrates in 0.1 *M* aqueous KCl at 25° and pH 7.8. Concentrations of α-chymotrypsin of 1 mg/ml of reaction volume were used. [b] By glc analysis; each product was also isolated and characterized. [c] Determined from initial velocities of hydrolyses carried out under standardized conditions in solutions containing 5% acetonitrile. [d] Too slow to be preparatively viable.

TABLE II

KINETIC DATA FOR THE α-CHYMOTRYPSIN-CATALYZED HYDROLYSES OF THE DIHYDROCINNAMATE ESTERS **7**, **10**, AND **15**[a]

Substrate	k_{cat}, sec^{-1}	K_m, $M \times 10^3$	k_{cat}/K_m, M^{-1} sec^{-1}
$C_6H_5(CH_2)_2COOCH_3$	0.13	8.46	15.4
7[b]	0.009	0.4	22.5
10[b]	0.085	0.7	121.4
15	0.09	2.95	30.5

[a] Kinetic determinations were carried out with a pH-Stat at 25° at pH 7.8 in aqueous 0.1 *M* KCl solutions containing 20% acetonitrile for all substrates except **15**. For the latter, no organic cosolvent was required. [b] Under the same conditions k_{OH} (M^{-1} sec^{-1} × 10^3) values for **7** and **10** are 0.7 and 1.6, respectively.

The overall data obtained show that the structure of the alcohol moiety, and also the solubility of the overall molecule in aqueous solutions, have a considerable influence on the hydrolysis process.

Discussion

All of the α-chymotrypsin-catalyzed hydrolyses were carried out at the pH 7.8 optimum of the enzyme. At this pH, no nonenzymic hydrolysis of the ester groups could be detected. Since the diesters evaluated were of limited solubility in water, the reactions were carried out on heterogeneous mixtures. For the most hydrophobic and more slowly hydrolyzed compounds, such as **5**, **6**, and **8**, a small percentage of acetonitrile was sometimes added to increase the water solubility of the potential substrate. However, owing to the inactivation of the enzyme which occurs on addition of an organic cosolvent of this type,[18] the acetonitrile content was kept below 5% for the preparative-scale experiments. The rates of hydrolyses were also significantly reduced when other aprotic solvents, such as tetrahydrofuran and dioxane, were used to increase the solubility of the more hydrophobic substrates. The adverse influence of dimethyl sulfoxide on the enzyme was less marked,[19] but, unfortunately, its effect on the water solubility of the decalin substrates was small. Attempted hydrolyses in the presence of the nonionic surfactants Tween-80 and Brij-35, and in biphasic benzene–water systems, were also unsatisfactory. In fact, in spite of the heterogeneous nature of most of the reaction mixtures, the most rapid hydrolyses were observed when no cosolvent or other additives were present. As the reactions proceeded and the extent of dihydrocinnamate cleavage increased, the solutions often became homogeneous. The pH was maintained at 7.8 by pH-Stat-controlled[20] addition of aqueous sodium hydroxide. For the better substrates, such as **5** and **15**, the hydrolysis virtually ceased soon after the uptake of 1 equiv of base. However, owing to slow autolysis of the enzyme during the reaction periods (up to 24 hours) of the other substrates such as **6**, the addition of 1 equiv of sodium hydroxide did not always signify the end of the desired selective cleavage. In such cases, some starting material was recovered. Concentrations of enzyme of 1 mg/ml were generally found to be the most satisfactory. At this level, the activity of the enzyme remained relatively constant for up to 24 hr at 25°. The desired products of selective hydrolysis were very readily isolated by simple extraction and chromatographic procedures. Dihydrocinnamic acid was also isolable from the acidified aqueous solutions.

The *trans*-decalin acetate–dihydrocinnamates **5**, **6**, and **8** were selected as representative diesters for which the differences in the rates of hydroxide attack of the different acyl functions were unlikely to be large enough to be generally exploitable for preparative purposes.[15] The validity of this supposition was confirmed by the relative lack of selectivity exhibited during the hydroxide ion hydrolysis of **5**. In contrast, α-chymotrypsin-catalyzed hydrolyses of the dihydrocinnamate functions of **5** and **6** were completely stereospecific and the desired monoacetates **3** and **4**, respectively, were produced to the extent of ≥96%. Unfortunately, no significant enzymic catalysis could be demonstrated for the isomeric acetate, dihydrocinnamate **8**. The extreme insolubility of this compound in the aqueous reaction media was considered one of the major factors responsible for the inability of α chymotrypsin to catalyze its hydrolysis. A semi-

(17) A small proportion of **17** was isolated as its dihydrocinnamate salt. However, this was readily reconverted to the free base with aqueous potassium carbonate.

(18) G. E. Clement and M. L. Bender, *Biochemistry*, **2**, 836 (1963).

(19) U. I. Khurgin, V. Y. Koslyakov, U. M. Azizov, and E. D. Kaverzneva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2840 (1968).

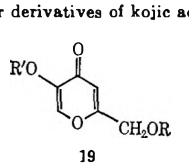
(20) As described previously,[5] addition of base from a buret is also satisfactory for good substrates. Use of buffered solutions should also be satisfactory.

quantitative evaluation of the adverse influence on the hydrolysis rate of the low water solubility of the hydrophobic decalin diesters was provided by a comparison (Table I) of the ease of dihydrocinnamate cleavage from **5** and **8** with those of their hydroxy analogs **10** and **7**, respectively. The rates of enzymic hydrolysis of the latter more hydrophilic substrates are four to five times greater than those of the corresponding diesters. Addition of the organic cosolvents acetonitrile, tetrahydrofuran, dioxane, and dimethyl sulfoxide to increase the water solubility of the hydrophobic decalin substrates was somewhat self-defeating, since aprotic dipolar solvents are believed to compete with substrate binding at the active site.[18]

As indicated above, selective hydroxide-ion cleavage is unlikely to be of much preparative value for decalin diesters such as **5**, **6**, and **8**. However, for di- or polyesters where one or more functions can be selectively cleaved in this way, the use of an appropriate combination or sequence of chemical and enzymic hydrolysis could be advantageous in a synthetic sequence using ester protecting groups. The controlled hydrolysis of 3α,6β-dihydroxytropane diesters was used to exemplify this type of application.

The starting material used, 6β-hydroxytropinone (**11**), permits two illustrations of how the method can be applied to a diol or a keto alcohol. Esterification of the diol **12** with dihydrocinnamoyl chloride gave the 3α,6β-bisdihydrocinnamate **13**. This, on treatment with 1 equiv of sodium hydroxide under controlled conditions, afforded 3α-dihydrocinnamoyl-6β-hydroxytropane (**14**) in 65% yield. Reprotection of the 6β-hydroxyl group as the α-chymotrypsin-insensitive acetate gave the mixed diester **15**. On being subjected to enzymic hydrolysis conditions, **15** underwent specific dihydrocinnamate hydrolysis at the chemically less accessible 3α position to give the 6β-acetoxy-3α-alcohol **17** in quantitative yield. Alternatively, starting from a compound of mixed functionalization such as **11**, the 6β-alcohol can be protected directly as the acetate, and the 3-ketone then transformed into the 3α-dihydrocinnamate. The mixed diester **15** so obtained could then be selectively hydrolyzed (Scheme IV) by hydroxide ion to give the 3α-dihydrocinnamate-6β-ol **14** in 70% yield or specific and quantitative 3α cleavage could be induced by α-chymotrypsin as described above.[21]

(21) All of the esters discussed in this communication were unaffected by pH 7.8 aqueous conditions in the absence of enzyme. In order to provide a more severe test of the scope of the method with respect to more sensitive esters, enol and allylic ester derivatives of kojic acid (**19**, R = R′ = H), for



19

which piperidine-catalyzed chemical hydrolysis at the 5 position is possible,[22] were evaluated. The desired selective hydrolysis of the bisdihydrocinnamate **19**, R = R′ = DHC, was readily achieved and the allylic dihydrocinnamate **19**, R = DHC, R, = H, obtained was reesterified with acetic anhydride. Disappointingly, it was found that, at pH 7.8, hydrolysis of *both* ester functions of **19**, R = DHC. R′ = Ac, were facile and that, although addition of α-chymotrypsin accelerated the reaction, the susceptibility of the enol acetate function to hydrolysis overwhelmed the DHC specificity of the enzyme. No reversal of the chemical selectivity was achievable within the pH range 4–9 surveyed. Use of aromatic amino acid acyl protecting groups for which the α-chymotrypsin specificity is much greater[2,3] might help to surmount this problem.

(22) M. G. Brown, *J. Chem. Soc.*, 2558 (1956).

As would have been predicted,[23] the more sterically hindered of the dihydrocinnamate esters are hydrolyzed the least rapidly by α-chymotrypsin (Table I). Although this is also true for the corresponding hydroxide-ion cleavages, the enzyme-catalyzed reactions generally expand the rate differences. For example, the rate constants for hydroxide hydrolysis of the 6β-dihydrocinnamate **10** and 1β-dihydrocinnamate **7** differ by a factor of 2:1 (Table II). In contrast, for the α-chymotrypic cleavages of the same esters, an ~13-fold rate difference is observed. Not unexpectedly, variations in the relative rates of hydroxide and enzymic hydrolyses of axial and equatorial esters are less dramatic. The 3:1 ratio of hydrolysis rates expeced[24] for the 6β- and 6α-dihydrocinnamates **5** and **6** is somewhat enhanced by α-chymotrypsin with the 6β-equatorial epimer **5** being cleaved five times faster than **6**.

Further analysis of the data of Table I, and particularly of Table II, enables more quantitative deductions to be drawn regarding the influence of the alcohol structure on the enzyme-catalyzed hydrolysis and on the preparative viability of such selective dihydrocinnamate cleavages. For methyl dihydrocinnamate the overall rate constant k_{cat} is markedly influenced by the acylation rate constant k_2,[25] since the latter is significantly smaller than that for deacylation, k_3. The lower k_{cat} values (Table II) for **7**, **10**, and **15** are attributed to a further slowing of the acylation rate relative to methyl dihydrocinnamate[27] owing to less favorable orientations of the bulky ester moieties at the active site. On the other hand, the decreased K_m values (compared with methyl dihydrocinnamate) of **7** and **10** show that the hydrophobic decalin moieties contribute significantly to binding[28] in the ES complex. This further evidence that the alcohol binding area is hydrophobic in character[23,29] is supported by the higher (relative to **7** and **10**) K_m observed for **15**.[30] Under the assay conditions the tropane residue of this substrate is partially protonated and is thus quite hydrophilic in character. The specificity constant

(23) P. W. Inward and W. P. Jencks, *J. Biol. Chem.*, **240**, 1986 (1965).

(24) By analogy with structurally similar steroid esters studied by L. Ruzicka, M. Furter and M. W. Goldberg, *Helv. Chim. Acta*, **21**, 468 (1938).

(25) The usual[26] α-chymotrypsin steady-state kinetics terminology has been used as outlined below.

$$E + S \underset{}{\overset{K_s}{\rightleftharpoons}} ES \xrightarrow[\text{acylation}]{k_2} ES' \xrightarrow[\text{deacylation}]{k_3} E + P$$

For such situations $k_{cat} = k_2k_3/k_2 + k_3$ and $K_m = k_3/K_s/k_2 + k_3$.

(26) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971, p 494.

(27) M. L. Bender, F. J. Kézdy, and C. R. Gunter, *J. Amer. Chem. Soc.*, **86**, 3714 (1964).

(28) While the lower [relative to $C_6H_5(CH_2)_2COOCH_3$] k_2 values of **7** and **10** are partly responsible for the lower K_m's observed, it is unlikely that the k_2 changes are large enough to account completely for the >tenfold K_m reductions observed for these compounds. Thus, while the K_m values of Table II are not equal to K_s, they are considered to reflect the strength of binding in the ES complex. However, the fact that the substrates evaluated are racemates must be borne in mind, since the limited data available[29] indicate that significant stereospecificity is possible for interactions of enantiomeric alcohol moieties with the active site.

(29) N. S. Isaacs and C. Niemann, *Biochim. Biophys. Acta*, **44**, 196 (1960); B. Halpern, J. Ricks, and J. W. Westley, *Aust. J. Chem.*, **20**, 389 (1967). Additional data on this aspect have been obtained: J. B. Jones, Y. Y. Lin, and D. N. Palmer, *Can. J. Chem.* in press.

(30) The tropane diester **15** was soluble enough in aqueous solutions to enable the kinetic constants to be obtained without the addition of the acetonitrile. Lower k_{cat} and higher K_m constants would be anticipated[31] for **15** if measurements had been made under the 20% acetonitrile conditions required for the more hydrophobic substrates of Table II.

(31) T. H. Applewhite, R. B. Martin, and C. Niemann, *J. Amer. Chem. Soc.*, **80**, 1457 (1958).

k_{cat}/K_m is considered the most reliable indicator of substrate activity[32] and the values recorded in Table II for **7**, **10**, and **15** correlate well with their rates of hydrolysis under preparative conditions. However, for the most hydrophobic of the substrates included in Table I, solubility factors become a very important consideration and predictions regarding preparative viability based on specificity constant data of very hydrophobic compounds must be applied with caution.

The current and previous[1-5] results demonstrate clearly that the use of α-chymotrypsin to achieve selective ester hydrolysis represents a useful addition to the methods of protecting group chemistry. Furthermore, the often encountered problems of epimerization, racemization, isomerization, rearrangement, etc., should be minimal since the hydrolyses are effected under mild, neutral conditions. In view of the hydrophobic nature and broad structural tolerance of the alcohol moiety binding site of the enzyme, the method should be applicable to most classes of organic compounds, provided that a satisfactory balance of hydrophobic and hydrophilic properties is maintained.

Experimental Section[33]

1β-Hydroxy-8aβ-methyl-1,2,3,4,4aα,5,8,8a-octahydronaphthalen-6(7*H*)-one (2).—Reduction of 8aβ-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (1) with sodium borohydride as described by Boyce and Whitehurst[34] gave the corresponding 1β alcohol, mp 49–53° (lit.[34] mp 50–55°), which on subsequent treatment with lithium in liquid ammonia according to the method of Birch, *et al.*,[8] yielded the 1β-hydroxy-6-ketone **2**, mp 67–68° (lit.[8] mp 68–70°), nmr δ 1.07 (3, s, C-8a Me) and 3.33 ppm (1, m, C-1α H).

1β-Acetoxy-6β-dihydrocinnamoyloxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (5) and 1β-Acetoxy-6α-dihydrocinnamoyloxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (6).—The 1β-hydroxy-6-ketone **2** was acetylated with acetic anhydride in pyridine[8] to give the corresponding 1β-acetoxy-6-ketone: mp 49–51° (lit.[8] mp 49–50°); nmr δ 1.13 (3, s, C-8a Me), 2.07 (3, s, $COCH_3$), and 4.57 ppm (1, m, C-1α H). The preceding keto acetate (3 g, 13.4 mmol) was reduced with sodium borohydride (300 mg, 7.9 mmol) in absolute ethanol (100 ml). Following the usual[34] work-up and chromatography on alumina (grade II) with ethyl acetate–benzene elution, 2 g of a mixture containing the 6β and 6α epimers **3** and **4** in the ratio 9:1 was obtained. Further purification by distillation, bp 170° (0.025 Torr), and exhaustive chromatography gave small samples of the 1β-acetoxy-6β-hydroxy-8aβ-methyl-*trans*-decalin **3**, nmr δ 0.92 (3, s, C-8a Me), 2.02 (3, s, $COCH_3$), 3.57 (1, m, C-6α H), and 4.53 ppm (1, m, C-1α H), and the 1β-acetoxy-6α-hydroxy-8aβ-methyl-*trans*-decalin **4**, nmr δ 4.06 ppm (1, m, C-6β H).

The mixture of 6α- and 6β-hydroxy epimers **3** and **4** (1.3 g, 5.7 mmol) in pyridine (1 ml) and dry ether (30 ml) was heated under reflux with dihydrocinnamoyl chloride (1.04 g, 6.2 mmol) for 3 hr. The reaction mixture was then diluted with ether (50 ml) and washed with dilute hydrochloric acid, then with saturated aqueous sodium bicarbonate, and the ether solution was dried ($MgSO_4$). Evaporation of the ether followed by chromatography on Florisil (ethyl acetate–benzene elution) gave the 6α-dihydrocinnamate **6** (50 mg): nmr δ 0.87 (3, s, C-8a Me), 1.93 (3 s, $COCH_3$), 2.77 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.49 (1, m, C-1α H), 4.97 (1, m, 6β-H) and 7.20 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 73.84; H, 8.53.

Continued elution with the same solvent yielded the 6β-dihydrocinnamate **5** (820 mg): bp 205° (bath, 0.025 Torr); nmr δ 0.90 (3, s, C-8a Me), 1.95 (3, s, $COCH_3$), 2.76 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.51 (2, m, C-1α and C-6α H), and 7.17 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 73.61; H, 8.46.

1β-Dihydrocinnamoyloxy-6β-hydroxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (7).—Dihydrocinnamoyl chloride (1.9 g, 11.3 mmol) and the 1β-hydroxy-6-ketone **2** (2 g, 11 mmol) were refluxed for 3 hr in dry ether (30 ml) and pyridine (2 ml). After dilution with ether, the reaction mixture was washed with dilute hydrochloric acid, then with aqueous sodium bicarbonate, and the dried ($MgSO_4$) ether solution was evaporated. The residual oil (2.3 g) was recrystallized from ether–hexane to give the 1β-dihydrocinnamoyloxy-8aβ-methyl-1,2,3,4,4aα,5,8,8a-octahydronaphthalen-6(7*H*)-one: mp 53–53°; nmr δ 1.06 (3, s, C-8a Me), 2.83 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.57 (1, m, C-1α H), and 7.26 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.39; H, 8.83. Found: C, 76.61; H, 8.40.

The above 1β-dihydrocinnamoyloxy-6-ketone (2.2 g, 7 mmol) was reduced with sodium borohydride (132 mg, 3.5 mmol) in dry ethanol (50 ml) in the usual[34] manner. The oil (2.1 g) obtained contained the 6β- and 6α-hydroxy epimers in the ratio of ~4:1. After careful chromatography of this mixture on alumina (cyclohexane–ethyl acetate elution), the 6β-hydroxy-1β-dihydrocinnamate **7** (1 g), bp 200° (0.05 Torr), was isolated: nmr δ 0.91 (3, s, C-8a Me), 2.78 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 3.58 (1, m, C-6α H), 4.51 (1, m, C-1α H), and 7.23 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.91. Found: C, 75.84; H, 8.89.

6β-Acetoxy-1β-dihydrocinnamoyloxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (8).—The 6β-hydroxy-1β-dihydrocinnamate **7** (500 mg, 1.6 mmol) was acetylated with acetic anhydride (2 g) in pyridine (3 ml). After work-up, the reaction product was chromatographed on Florisil (benzene–ethyl acetate elution) and then further purified by tlc. The diester **8** was obtained as an oil (200 mg): nmr δ 0.87 (3, s, C-8a Me), 1.93 (3, s, $COCH_3$), 2.72 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.50 (2, m, C-1α and C-6α H), and 7.17 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 73.72; H, 8.48.

6β-Dihydrocinnamoyloxy-1β-hydroxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (10).—To a solution of the 1β-hydroxy-6-ketone **2** (2.2 g, 12.1 mmol) in dry ether (40 ml) was added dihydropyran (3.05 g, 36.3 mmol) and phosphoryl chloride (0.2 g). The mixture was stirred at 20° for 10 min and methanolic potassium hydroxide was added until the mixture remained basic. Following dilution with ether (100 ml), the solution was washed with water, dried ($MgSO_4$), and evaporated. The oil obtained was recrystallized from petroleum ether (bp 40–60°) to give 8aβ-methyl-1β-tetrahydropyranyloxy-1,2,3,4,4aα,5,8,8a-octahydronaphthalen-6(7*H*)-one (3 g): mp 66–71°; nmr δ 1.04 (3, s, C-8a Me) and 4.63 ppm (2, m, C-1α H and THP-CH).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.83. Found: C, 72.17; H, 9.84.

The above tetrahydropyranyloxy ketone (2.9 g, 11 mmol) was reduced with sodium borohydride (126 mg, 3.1 mmol) in dry ethanol (50 ml) as before.[34] The product obtained (2.9 g) was mainly the 6β epimer of **9**, nmr δ 0.96 (3, m, C-8a Me) and 4.56 ppm (2, m, C-1α H and THP-CH).

The 6ξ-hydroxy-1β-tetrahydropyranyloxy mixture **9** (2.8 g, 10.4 mmol) in dry ether (50 ml) and pyridine (0.5 ml) was treated with dihydrocinnamoyl chloride (1.75 g, 10.4 mmol) as described previously. After chromatography of the crude product on Florisil using benzene–ether elution, 6β-dihydrocinnamoyloxy-8aβ-methyl-1β-tetrahydropyranyloxy-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (2.9 g, containing ~5% of the 6α epimer) was obtained: nmr δ 0.87 (3, s, C-8a Me), 2.73 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.60 (3, m, C-1α, C-6α H, THP-CH), and 7.17 ppm (5, s, C_6H_5).

The above material (2.8 g, 7 mmol) in ethanol (20 ml) and 2 *N* HCl (4 ml) was heated at 50° for 3 hr. The solvent was then

(32) F. E. Brot and M. L. Bender, *J. Amer. Chem. Soc.*, **91**, 7187 (1969).

(33) Melting points were determined on a Fisher-Johns block and are uncorrected. The purity of all compounds was checked by glc and tlc analyses. Glc data were obtained using an F & M 400 chromatograph equipped with 1%, 2% QF-1 and 1% PDEAS columns. Tlc analyses and separations were performed on silica gel G; all solvents were redistilled before use. Ir spectra (measured in $CHCl_3$ solutions) were all as expected for the assigned structures and are not recorded. Nmr data were obtained in CCl_4 or $CDCl_3$ (unless indicated otherwise) using TMS as internal standard. Starting materials were generally purchased from Aldrich and were used as obtained unless impurities were detected by glc or tlc. α-Chymotrypsin (three times crystallized) was purchased from the Worthington Biochemical Corp. Solvent removals were effected by rotary evaporation under reduced pressure at room temperature.

(34) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

removed and the residue was dissolved in ether (50 ml). The ether solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to give an oil (2 g) which was then chromatographed on alumina. Careful elution with ethyl acetate–cyclohexane yielded the 1β-hydroxy-6β-dihydrocinnamate **10** (1.3 g): bp 205° (bath) (0.04 Torr); nmr δ 0.85 (3, s, C-8a Me), 2.71 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 3.42 (1, m, C-1α H), 4.62 (1, m, C-6α H), and 7.20 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.91. Found: C, 75.93; H, 8.75.

3α,6β-Dihydroxytropane (12).—6β-Hydroxytropinone (**11**, 1 g, 6.4 mmol, prepared according to the procedure of Nedenskov and Clauson-Kaas[11]) and Raney nickel W-4 (2 g) in ethanol (20 ml) were kept at 21° under hydrogen (50 psi) for 14 hr. The filtered solution was then evaporated and the product was recrystallized from ethyl acetate to give the 3α,6β-diol **12** (800 mg): mp 183–184° (lit.[12] mp 179–180°); nmr (acetone-d_6) δ 2.46 (3, s, NCH_3), 3.97 (1, t, J = 5 Hz, C-3β H), and 4.73 and 4.81 ppm (1, d of d, J = 4 Hz, C-6α H).

3α,6β-Bis(dihydrocinnamoyloxy)tropane (13).—The above diol **12** (600 mg, 3.8 mmol) and freshly distilled dihydrocinnamoyl chloride were heated for 6 hr at 100°. The cooled reaction mixture was then neutralized with aqueous sodium carbonate and extracted with ethyl acetate (3 × 50 ml). The dried ($MgSO_4$) extract was evaporated and the solid obtained was recrystallized from ethyl acetate–ethanol to give **13** as its hydrochloride salt (800 mg): mp 166–168°; nmr (acetone-d_6 + D_2O) δ 2.5–3.0 (8, m, $C_6H_5CH_2CH_2CO$), 3.03 (3, s, NCH_3), 5.17 (1, t, J = 5 Hz, C-3β H), 5.56 and 5.64 (1, d of d, J = 4 Hz, C-6α H), and 7.4 ppm (10, s, C_6H_5).

Anal. Calcd for $C_{26}H_{32}NO_4Cl$: C, 68.18; H, 7.04. Found: C, 68.14; H, 6.86.

3α-Dihydrocinnamoyloxy-6β-hydroxytropane (14).—The diester **13** (650 mg, 1.42 mmol), acetone (30 ml), and 0.1 N aqueous sodium hydroxide (100 ml) were stirred at 30° for 6 hr. The mixture was then neutralized with 1 N aqueous hydrochloric acid, concentrated, and saturated with sodium carbonate. Extraction with ethyl acetate (3 × 50 ml) yielded a solid (310 mg) which on recrystallization from ether–hexane gave 3α-dihydrocinnamoyloxy-6β-hydroxytropane (**14**, 250 mg): mp 94°; nmr δ 2.50 (3, s, NCH_3), 2.78 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 4.33 and 4.41 (1, d of d, J = 4 Hz, C-6α H), 5.0 (1, t, J = 5 Hz, C-3β H), and 7.30 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.72; H, 8.12.

6β-Acetoxy-3α-dihydrocinnamoyloxytropane (15). A. From 14.—The 3α-dihydrocinnamate-6β-ol **14** (150 mg, 0.52 mmol) in acetyl chloride (2 ml) was warmed at 35° for 3 hr. The mixture was then evaporated to dryness and recrystallized from ethyl acetate–ethanol or acetone–ethanol to give the hydrochloride salt of **15** (110 mg): mp 155–156°; nmr δ 2.10 (3, s, $COCH_3$), 2.82 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 3.00 (3, s, $^+NCH_3$), 5.16 (1, "t," C-3β H), 5.44 and 5.53 ppm (1, d of d, J = 4 Hz, C-6α H), and 7.30 ppm (5, s, C_6H_5).

Anal. Calcd for $C_{19}H_{26}O_4NCl$: C, 62.02; H, 7.13. Found: C, 62.09; H, 7.36.

The above hydrochloride (1 g) in water (3 ml) saturated with K_2CO_3 was continuously extracted with ether for 15 hr. Evaporation of the dried ($MgSO_4$) ether solution yielded 6β-acetoxy-3α-dihydrocinnamoyloxytropane (**15**, 0.9 g): nmr δ 2.02 (3, s, $COCH_3$), 2.46 (3, s, NCH_3), 2.87 (4, A_2B_2 m, $C_6H_5CH_2CH_2CO$), 3.17 (2, broad, C-1 and C-5 H), 5.01 (1, t, J = 5 Hz, C-3β H), 5.32 and 5.40 (1, d of d, J = 4 Hz, C-6α H), and 7.23 ppm (5, s, C_6H_5).

B. From 17.—A solution of 6β-acetoxy-3α-hydroxytropane (**17**, 3 g, 15 mmol) and dihydrocinnamoyl chloride (3 g, 18 mmol) in dry ether (30 ml) was stirred at 21° for 15 hr. The precipitated hydrochloride salt of **15** formed was filtered off and recrystallized from acetone–ethanol. The sample, mp 155–156°, obtained, which was identical in all respects with the previously characterized material, was converted into the free base **15** by the procedure outlined in A above.

6β-Acetoxytropinone (16).—A solution of 6β-hydroxytropinone[11] (**11**, 1.6 g, 10.3 mmol) in acetic anhydride (10 ml) was stirred at 20° for 14 hr. Water (10 ml) was then added and the mixture was evaporated to dryness. The residue was dissolved in water (3 ml) containing K_2CO_3 (1 g) and the solution was extracted continuously with ether for 15 hr. Evaporation of the dried ($MgSO_4$) ether extract gave 6β-acetoxytropinone (**16**, 2 g): bp 110° (0.03 Torr); nmr δ 2.05 (3, s, $COCH_3$), 2.65 (3, s, NCH_3), 3.57 (2, broad, C-1 and C-5 H), and 4.97 ppm (1, t, J = 5 Hz, C-6α H).

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.88; H, 7.68. Found: C, 61.12; H, 7.72.

6β-Acetoxy-3α-hydroxytropane (17).—6β-Acetoxytropinone (**16**, 3 g, 15 mmol) in absolute ethanol (30 ml) was hydrogenated (50 psi) for 14 hr in the presence of W-4 Raney nickel (5 g). The catalyst was then removed and the solvent was evaporated to give 6β-acetoxy-3α-hydroxytropane (**17**, 2.9 g): bp 122° (0.3 Torr); nmr δ 2.03 (3, s, $COCH_3$), 2.47 (3, s, NCH_3), 2.86 (1, s, OH), 4.05 (1, t, J = 5 Hz, C-3β H), and 5.64 and 5.56 ppm (1, d of d, J = 4 Hz, C-6α H).

Anal. Calcd for $C_{10}H_{17}O_3N$: C, 60.26; H, 8.61. Found: C, 60.28; H, 8.67.

Hydroxide-Ion Hydrolysis of 1β-Acetoxy-6β-dihydrocinnamoyloxy-8aβ-methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (5).—To the diester **5** (16.7 mg, 0.047 mmol) in methanol (2 ml) was added 0.1 N aqueous sodium hydroxide (0.47 ml, 0.047 mmol) and the solution was stirred at 20° for 6 hr under nitrogen. The mixture was then diluted with water (10 ml) and thoroughly extracted with ethyl acetate. The product contained the starting diester **5** (1.6 mg), the 1β-acetate **3** (5.7 mg), and the 1β,6β-diol **18** (3 mg). Each compound was identified by comparison with authentic samples.

Selective Hydroxide-Ion Hydrolysis of the C-6β-Ester Functions of 13 and 15. A. Of 6β-Acetoxy-3α-dihydrocinnamoyloxytropane (15).—The acetate dihydrocinnamate **15** (100 mg, 0.27 mmol) in acetone (5 ml) and 0.1 N aqueous sodium hydroxide (20 ml) was stirred at 30° for 6 hr. After it was neutralized with 1 N hydrochloric acid, the mixture was concentrated, saturated with sodium carbonate, and extracted with ethyl acetate (2 × 25 ml). Evaporation of the dried ($MgSO_4$) ethyl acetate solution followed by recrystallization from ether–hexane gave the 6β-hydroxydihydrocinnamate **14** (60 mg), mp 94°, identical in all respects with the sample prepared previously.

B. **Of 3α,6β-Bis(dihydrocinnamoyloxy)tropane (13).**—This was carried out as described in the reaction sequence **13** → **14**.

α-Chymotrypsin-Catalyzed Hydrolyses. Preparative Scale Experiments.—The general procedure followed was as detailed previously.[5] The diester substrates were suspended in 0.1 M aqueous potassium chloride at 25° in a magnetically stirred Radiometer pH-Stat reaction vessel of up to 100-ml capacity fitted with a rubber stopper through which a combination electrode, needle of the sodium hydroxide filled syringe, and nitrogen line were introduced. The pH-Stat was set to maintain a pH of 7.8 automatically.[20] The desired hydrolyses were initiated by adding sufficient amounts of a stock solution of α-chymotrypsin in 0.1 M aqueous potassium chloride to give a concentration in the reaction mixture of 1 mg/ml. After the addition of ~1 equiv of base, the rate of hydrolysis slowed markedly for the better substrates. The reaction mixtures were often homogeneous by this time and were then extracted with a suitable organic solvent and the products were isolated and purified. Except in the case of the kojic acid esters,[21] no hydrolysis was detectable at pH 7.8 in the absence of the enzyme. For the more hydrophobic compounds, small amounts (2–5%) of acetonitrile sometimes increased the rate of hydrolysis. For reactions requiring >10 hr for completion, autolysis of the enzyme began to become significant and a correction for the additional base uptake involved was made. In general, however, the enzyme activity remained relatively constant during the course of selective dihydrocinnamate cleavage for the better substrates.

Kinetic Studies.—All studies were performed at 25° in 0.1 M aqueous potassium chloride solutions at pH 7.8. The relative rates of hydrolyses of the substrates under the heterogeneous preparative-scale conditions were determined from the initial velocities of reaction mixtures 0.7 mM in substrate and 3.8 × 10^{-6} M in α-chymotrypsin. The base used was 0.01 N aqueous sodium hydroxide. For the decalin esters, for which the addition of organic cosolvents was beneficial in some cases, 5% acetonitrile was added.

The kinetic constants for the 6β-hydroxy-1β-dihydrocinnamate **7**, the 1β-hydroxy-6β-dihydrocinnamate **10**, and the tropane-6β-acetate-3α-dihydrocinnamate **15** were determined by the usual pH-Stat procedure, Enzyme concentrations were determined by the spectrophotometric method of Cunningham.[35] For **7** and **10**, homogeneous solutions were obtained on addition of 20% acetonitrile as cosolvent. Concentrations in the 0.17–0.9 mM range

(35) L. W. Cunningham, *J. Biol. Chem.*, **207**, 443 (1954).

were studied using an enzyme concentration of 3.7×10^{-6} M. For comparison purposes, the k_{OH} values for both compounds were also determined in the same solvent composition using pH 11 solutions. The data for methyl dihydrocinnamate in 20% acetonitrile were obtained using a substrate concentration range of 1–7 mM and α-chymotrypsin at 4.15×10^{-7} M. For **15** no cosolvent was required; the enzyme concentration used was 0.8×10^{-6} M with a substrate range of 1–10 mM. The kinetic data were subjected to least-squares regression analysis and the k_{cat} and K_m constants were computed using the reciprocal method of Lineweaver and Burk.[36]

α-Chymotrypsin-Catalyzed Hydrolysis of 5.—The 1β-acetoxy-6β-dihydrocinnamoyloxydecalin **5** (140 mg, 0.39 mmol) was hydrolyzed at 25° using α-chymotrypsin (10 mg) in 0.1 M aqueous potassium chloride (10 ml) containing 2% acetonitrile by the general preparative procedure; 0.5 N aqueous sodium hydroxide was used to maintain the pH at 7.8. After 24 hr, when 0.3 mmol of base had been taken up, the rate slowed dramatically and the reaction mixture was extracted with ether (3 × 50 ml). Glc analysis showed that the extract contained 0.31 mmol of the 1β-acetate product of specific 6β cleavage and 0.08 mmol of the starting diester. Tlc separation of the mixture using ethyl acetate–benzene (1:6) as developing solvent yielded the 1β-acetoxy-6β-hydroxydecalin **3** (46 mg) which was identical with an authentic sample. None of the 6β-dihydrocinnamate **10** was detected. Extraction of the acidified aqueous mother liquors of the reaction with chloroform (3 × 50 ml) give dihydrocinnamic acid (37 mg, 0.25 mmol).

α-Chymotrypsin-Catalyzed Hydrolyses of 6.—The 1β-acetate-6α-dihydrocinnamate **6** (10 mg, 0.27 mmol) in 0.1 M aqueous potassium chloride (5 ml) was treated with α-chymotrypsin (5 mg) as described above. Aqueous sodium hydroxide (0.1 N) was the base used and after 24 hr, when ~2 equiv of alkali had been consumed, the reaction was worked up as before. (The excess base uptake is due to autolysis of the enzyme.) Glc analysis showed hydrolysis to have been 96% selective for the 6α position, and the 1β-acetoxy-6α-hydroxy compound **4** (3 mg), identical with authentic material, was obtained following tlc purification.

α-Chymotrypsin-Catalyzed Hydrolysis of 15.—The hydrochloride salt of 6β-acetoxy-3α-dihydrocinnamoyloxytropane (**15** HCl, 1.55 g, 4.22 mmol) in 0.1 M aqueous potassium chloride (60 ml) was placed in the pH-Stat under the standard conditions. The pH of the reaction solution (~5.5) was adjusted to 7.8 with 1 N aqueous sodium hydroxide (2.3 mmol required), and α-chymotrypsin (60 mg) was then added. The hydrolysis stopped after 4 hr (0.2 mmol of base uptake). The reaction mixture was saturated with potassium chloride and extracted continuously with ether for 24 hr. Evaporation of the dried ($MgSO_4$) ether extract yielded the dihydrocinnamate salt of 6β-acetoxy-3α-hydroxytropane (100 mg). The aqueous solution was then saturated with potassium carbonate and again continuously extracted with ether for 24 hr. Evaporation of the dried ether solution gave 6β-acetoxy-3α-hydroxytropane (**17**, 780 mg, 3.9 mmol), identical in all respects with an authentic sample. A further 62 mg (0.21 mmol) of **17** was obtained by treatment of the dihydrocinnamate salt with aqueous potassium carbonate.

Acknowledgment.—This work was generously supported by the National Research Council of Canada.

Registry No.—**1** 1β-alcohol derivative, 878-47-7; **2**, 41163-95-5; **2** 1β-OAc derivative, 36925-35-6; **2** 1β-ODHC derivative, 41163-97-7; **2** 1β-OTHP derivative, 38538-76-0; **3**, 41163-98-8; **4**, 41163-99-9; **5**, 41164-00-5; **6**, 41164-01-6; **7**, 41164-02-7; **8**, 41164-03-8; **10**, 41164-04-9; **10** 1β-OTHP derivative, 41172-09-2; **11**, 5932-53-6; **12**, 41164-06-1; **13**, 41164-07-2; **13** HCl, 41164-08-3; **14**, 41164-09-4; **15**, 41164-10-7; **15** HCl, 41164-11-8; **16**, 41164-12-9; **17**, 41164-13-0; dihydrocinnamoyl chloride, 645-45-4.

(36) H. Lineweaver and D. Burk, *J. Amer. Chem. Soc.*, **56**, 658 (1934).

The Bimolecular Decarboxylative Self-Condensation of Oxaloacetic Acid to Citroylformic Acid and Its Conversion by Oxidative Decarboxylation to Citric Acid

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Oxaloacetic acid undergoes a bimolecular decarboxylative self-condensation to give 4-carboxy-4-hydroxy-2-ketohexane-1,6-dioic acid (**1**) (citroylformic acid). The reaction goes in high yield at pH 3–7, at 25–30°, and in aqueous media. The acid is converted to citric acid by oxidative decarboxylation and to its lactone by dehydration but is not obtainable from the previously described oxalocitrolactone ester structures.

Although the chemistry of oxaloacetic acid has been studied in considerable detail, there are unexplained observations in some of the reported data. These are reported in studies of the nmr[1] and uv[2] spectra in which anomalous behavior is attributed to unidentified dimeric structures. Since dimerization has been noted for pyruvic acid, and characterized in some detail,[3-7] it seems reasonable to postulate the dimerization[8] of oxaloacetic acid. Furthermore, because such dimeric structures are formed under physiological conditions (aqueous, pH 7) and are, therefore, possibly significant in biological systems, and since the extensive studies of the kinetics and mechanism of the decarboxylation of oxaloacetic acid[9] (based on the rate of evolution of carbon dioxide) should be interpreted for the possibility of rate-determining dimerization preceding decarboxylation,[10] additional information on this dimerization reaction is desirable. We wish to describe the results of a study of the decarboxylative self-condensation of oxaloacetic acid to citroylformic acid (**1**) (CFA) and isolation and characterization of this new acid.

Oxaloacetic acid undergoes a bimolecular aldol-type condensation in aqueous solution at room temperature (25–30°) and pH 3–7 with the loss of carbon dioxide to

(1) W. D. Kumler, E. Kun, and J. N. Shoolery, *J. Org. Chem.*, **27**, 1165 (1962).

(2) C. R. Goucher and E. H. Strikland, *U. S. Army Med. Res. Lab. Rep.*, Dept. No. 571 (1964); *Chem. Abstr.*, **62**, 14489 (1965).

(3) L. Wolff, *Justus Liebigs Ann. Chem.*, **305**, 154 (1899).

(4) A. W. K. Dedong, *Recl. Trav. Chim. Pays-Bas*, **20**, 81 (1901).

(5) E. Waldman, V. Prey, and F. Jellinek, *Monatsh. Chem.*, **85**, 872 (1953).

(6) V. Prey, E. Waldman, and H. Besbalk, *Monatsh. Chem.*, **86**, 408 (1955).

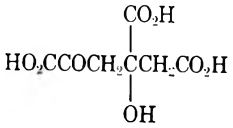
(7) D. L. Leussing and C. K. Stanfield, *J. Amer. Chem. Soc.*, **86**, 2805 (1964).

(8) F. L. Breusch and R. Tulus, *Rev. Fac. Sci. Univ. Istanbul*, **6**, 144 (1941); *Chem. Abstr.*, **37**, 4366 (1943).

(9) E. Gelles, *et al.*, *J. Chem. Soc.*, 4136 (1956); 3673, 3683, 3689 (1958); and references cited therein.

(10) This is especially true since many of the decarboxylation studies are designed to evaluate the effect of metal ions which are known to catalyze aldol dimerization of α-keto acids. See E. H. Abbott and A. E. Martell, *J. Amer. Chem. Soc.*, **91**, 6931 (1969).

give 1, which we have named citroylformic acid (CFA).[11] This is isolated as its water-insoluble calcium salt in



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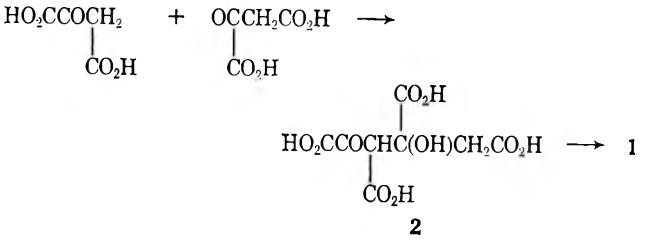
65–96% yields and converted to the free acid in 40% crude yield by treatment with sulfuric acid in dry ether. Recrystallization from ethyl acetate–carbon tetrachloride gave the analytically pure sample in 19% yield, mp 154–156° with gas evolution. Characterization data include elemental analysis, nmr, mass, and uv spectral data, titration, thin layer chromatography (tlc) R_f values (two solvent mixtures), and conversion with hydrogen peroxide or *tert*-butyl hydroperoxide to citric acid (CA). Oxaloacetic acid can be converted directly to citric acid without isolation of the intermediate **1**. Citroylformic acid sequesters calcium ions over the pH range of 2.5–10 as is shown by lowering of the pH in the presence of calcium ions. Evaporation of the decationized reaction mixture gives a solid product from which CFA is obtained as its γ-lactone by recrystallization from acetone–nitromethane. An insoluble polymeric material is also obtained. This lactone, characterized by ultimate analysis and titration, when dissolved in water gives the same tlc R_f values as does CFA.

The mechanism of the reaction is visualized as that of a base-catalyzed aldol-type condensation followed by hydroxyl-initiated decarboxylation of the β-keto acid structure of the initial product, oxalocitric acid (2).



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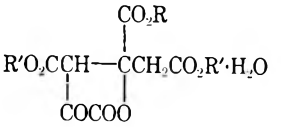
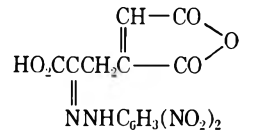
Since there is no indication that these reactions are mechanistically unique, kinetic and mechanistic studies of the decarboxylation of oxaloacetic acid,[9] particularly in the presence of ions which catalyze dimerization,[10] need to be reevaluated to determine whether or not dimerization precedes decarboxylation. There is no evidence for the independent existence of the initial condensation product, oxalocitric acid (2), under the conditions used in our studies.

The structure 1, assigned to the product of the decarboxylative condensation, is consistent with all of the available data. The key points in these data, in addition to all of the confirming analytical data, are the nearly quantitative oxidative decarboxylation to citric acid and the absence of both aldehydic reaction (Schiff's fuchsin aldehyde test) and aldehydic proton in the nmr spectrum. Alternative structures involving the loss of any one of the other three carboxyl groups in the intermediate 2 are inconsistent with these key points. Thus, loss of one of either of two of the other carboxyl groups would give a structure incapable of conversion to citric acid. Loss of the third would give a β-aldehydo acid for which there is no confirming support, *i.e.*, no aldehydic proton, no enol test, no aldehyde test, and comparative stability toward decarboxylation. In the course of our studies we have repeated and confirmed earlier reports[12–15] of the base-catalyzed formation of trimethyl and triethyl oxalocitrolactone esters **3a**. We have observed for the first time that partial hydrolysis of their esters gives the corresponding monoester or its hydrate, which, short of degradation, is resistant to further hydrolysis. We take this to indicate that the unhydrolyzed ester is the most hindered one and assign the formula **3b** in which the molecule of



3a, R, R′ = CH_3 or C_2H_5
b, R = CH_3 or C_2H_5; R′ = H

water is present as a hydrated carboxyl. The neutralization equivalent data and the ease of removal of the molecule of water indicate that the lactone ring has not been opened by addition of the molecule of water. Such hydrates are formed from α-keto acids.[10,16] The dinitrophenylhydrazine (DNPH) derivatives of CFA have been obtained and structures have been assigned on the basis of their analytical data. Mass spectral data confirm the structures **4**–**7**. The ethyl esters are formed from ethanolic DNPH solutions.



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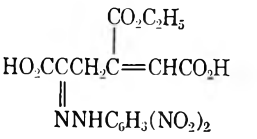

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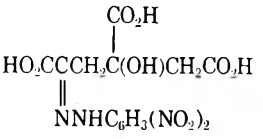

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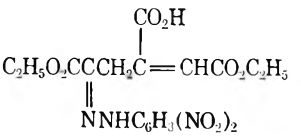

7

Experimental Section

Equipment.—The mass spectra were obtained with a Varian M66 and are accurate to well within ±0.2 amu, except as noted for the precision analysis of the oxalocitrolactone ester. The ultraviolet spectra were determined with a Cary Model 14 and the nmr with a Varian A-60A.

Chromatographic Techniques.—Thin layer chromatograms were on 3 × 3 in. sheets of Eastman chromagram silica gel sheets, no. 6061. They were developed with BFW (1-butanol–90% formic acid–water 8:3:2 by volume; the upper layer which separates on standing is used)[17] and with EAW (ethanol–water–concentrated ammonium hydroxide, 78:9.5:12.5 by volume).[18]

(11) The systematic name for this compound is 4-carboxy-4-hydroxy-2-ketohexane-1,6-dioic (or -adipic) acid. The name citroylformic acid is used here to show the relation to citric acid. Similar names have been used for benzoylformic and acetylformic (pyruvic) acids. The name is admittedly ambiguous in not specifying which of the citric acid carboxyls (1- or 2-) is involved in the citroyl radical. A prefix 1- or 2- may be used if specification on this point is desired.

(12) L. Claisen and H. Hori, *Ber.*, **24**, 120 (1891).
(13) W. Wislicenus and W. Beckh, *Justus Liebigs Ann. Chem.*, **295**, 339 (1897).
(14) A. Michael and H. D. Smith, *Justus Liebigs Ann. Chem.*, **363**, 36 (1908).
(15) W. Dieckmann, *Ber.*, **49**, 2213 (1916).
(16) M. Becker, *Ber. Bunsenges. Phys. Chem.*, **88**, 669 (1964).
(17) J. Lugg and B. Overall, *Aust. J. Sci. Res.*, **1**, 98 (1948).
(18) D. Braun and H. Greenen, *J. Chromatogr.*, **7**, 56 (1962).

R_f values for citric and aconitic acid are 60 ± 3 and 85 ± 5 (BFW) and 20 ± 2 and 34 ± 3 (EAW).

Materials.—The oxaloacetic acid used in these experiments was obtained commercially (Calbiochem Co., no. 5000) or prepared from diethyl oxaloacetate by hydrolysis with concentrated hydrochloric acid.[19] It was stored at 0° and used as a white powder with a neutralization equivalent (neut equiv) of 67–69 (theory 66) and ϵ (265 nm) 7200 for a 0.01% solution in *tert*-butyl alcohol–chloroform (5:95, v/v) acidified with 6 *N* sulfuric acid. Some commercially available materials do not meet these specifications. The preferred procedure for this hydrolysis has not been given in detail before, and, since it has certain advantages over other procedures,[20] it is given below. R_f data from thin layer chromatography were obtained for oxaloacetic acid by conducting the operations rapidly and spraying with ferric chloride solution and by low-temperature techniques, but these are neither highly reliable nor sensitive.

Preparation of Oxaloacetic Acid.—The following procedure is much simpler and gives purer product than preparations described previously. A sample of 20 g of commercial (EK Co., no. P4830) sodium diethyl oxaloacetate was partially dissolved in 200 ml of water at 30° and filtered to remove insoluble material. The solution was acidified with sulfuric acid and extracted with ether to give 12 g (80% recovery) of diethyl oxaloacetate. This ester (5 ml) was added to 10 ml of concentrated hydrochloric acid in an ice bath. The mixture was stirred for 2 hr and the solution was stored in the cold (0°) for 9 days, during which time crystals of oxaloacetic acid separated. The supernatant liquid was decanted and the crystals were dried for 10 hr at 50°. The residue was washed with cold carbon tetrachloride–ethyl acetate (4:1) and again dried to give 35% yield. This material, with ϵ (265 nm) 7200 and neut equiv 67–69, was comparable in purity to the best commercial materials that we have received.

The mass spectral data for the DNPH derivative of oxaloacetic acid, but not that of the free acid itself, is of assistance in detecting small quantities of oxaloacetic acid. The spectrum of oxaloacetic acid showed a prominent peak at 113 amu for the molecular ion less 19 amu but no peak for the molecular ion itself, which is presumably lost in the source heater. The mass spectrum of the DNPH of oxaloacetic acid recrystallized from ethyl alcohol showed peaks at 268 and 222 amu for the dinitrophenylhydrazones of pyruvic acid and acetaldehyde. There was also an intense peak at 368 amu corresponding to the carbethoxydinitrophenylpyrazolone. This peak was also prominent in the spectrum of the dinitrophenylhydrazine derivative obtained from diethyl oxaloacetate itself.

Citroylformic Acid (1).—A solution of 1.5 g of oxaloacetic acid in 10 ml of water was adjusted to a pH of 7.5 with 20% sodium hydroxide and held at 25–30° for 48 hr. To the reaction mixture was added 3 ml of 60% calcium chloride solution and the precipitate was collected and dried to give 1.62 g (95%) of the calcium salt of citroylformic acid. On warming to 60° for 10 min the calcium salt of oxaloacetic acid (0.14 g, dried) precipitated from the filtrate. Two grams of the calcium citroylformate and 0.6 g of anhydrous magnesium sulfate in 30 ml of dry ether were treated with 0.6 ml of concentrated sulfuric acid in 20 ml of dry ether.[21] The addition was dropwise with cooling and stirring. The mixture was filtered and the filtrate was evaporated to give 0.6 g (40%) of a crystalline residue of 1. Recrystallization from ethyl acetate–carbon tetrachloride gave 0.26 g (19%) of pure 1: mp (with gas evolution and decomposition) 154–156° (slow heating), 164–165° (rapid heating); ϵ (240 nm) 7300. The acid turned brown at 145°. The Schiff fuchsin aldehyde test was negative. The analysis was for samples vacuum dried at room temperature.

Anal. Calcd for $C_7H_8O_8$: C, 38.19; H, 3.66; neut equiv, 73.3, 110, 220. Found: C, 38.12; H, 3.47; neut equiv, 73.9, 108.6, 217.2.

The mass spectrum of citroylformic acid ($C_7H_8O_8$, mol wt 220) showed, as the most intense peaks above mass 100, peaks at the following mass values: 112 ($C_5H_4O_3$, theory 112), 139 ($C_6H_3O_4$, theory 139), and 184 ($C_7H_4O_6$, anhydrocitroylformic acid anhydride or lactone, theory 184). These fragments were derivable by thermal or electron impact degradation reactions from citroylformic acid in processes observed with oxaloacetic acid and citric acid in their mass spectra. The molecular ion of citroylformic acid was not observed.

The nmr spectrum in perdeuteriodimethyl sulfoxide showed a singlet at 2.95 ppm [(measured with reference to the residual DMSO-d_5 peak as corrected to TMS) for CH_2], 3.16 ppm (CH_2 adjacent to CO), broad absorption at *ca.* 10 ppm, and no low-field absorption as required for HCO. These data were in accord with the citroylformic acid structure. The sample turned brown at once on dissolution in DMSO, presumably owing to dehydration as is evidenced by a peak at 6.35 ppm whose intensity as integrated indicates that the ratio of unsaturated product to citroylformic acid is 4:1.[22]

On chromatographic analysis by the method of Kesner[23] the acid appeared before malic and after aconitic acids.[24] The ferric chloride enol test with citroylformic acid showed a slight change in color about like that observed with pyruvic acid.

Citric Acid from Citroylformic Acid and Oxaloacetic Acid.—Citroylformic acid was converted to citric acid, with or without isolation as such from the oxaloacetic acid condensation, by oxidative decarboxylation with aqueous acidic potassium permanganate, hydrogen peroxide, or *tert*-butyl hydroperoxide. Similar reagents have been used previously for the decarboxylation of other α-keto acids.[25,26] Details of the reactions with hydrogen peroxide and *tert*-butyl hydroperoxide are given.

A solution of 100 mg of 1 in 1 ml of water and 0.5 ml of 30% hydrogen peroxide was allowed to stand at room temperature for 23 hr. The presence of citric acid was confirmed by tlc: R_f (BFW) 61 (CA), 73 (CFA); R_f (EAW) 21 (CA), 28 (CFA).

A solution of 5 mg of 1 in 0.25 ml of water was heated to 70° for 4 hr with 0.1 ml of *tert*-butyl hydroperoxide. The presence of citric acid was confirmed by tlc: R_f (BFW) 59 (CA), 71 (weak CFA); R_f (EAW) 19 (CA), 28 (CFA).

The bimolecular decarboxylative self-condensation of the oxaloacetic acid product can be converted directly to citric acid without isolation of 1. The procedures with hydrogen peroxide and *tert*-butyl hydroperoxide are given.

A solution of 3 g of oxaloacetic acid in 20 ml of water was adjusted to a pH of 7.5 with 20% sodium hydroxide and allowed to stand at room temperature for 3 days. To this was added 2.5 ml of *tert*-butyl hydroperoxide and the resulting mixture was stirred for 4 hr at 50°. To this solution was added 6 ml of 60% calcium chloride to precipitate 3 g (93%) of calcium citrate hydrate (vacuum dried at room temperature). This calcium salt was suspended in 100 ml of dry ether with 1 g of anhydrous magnesium sulfate and treated with 0.8 ml of concentrated sulfuric acid in 50 ml of dry ether with stirring and cooling. The mixture was stirred for 4 hr and filtered. Evaporation of the filtrate gave 0.2 g (9.3%) of crystalline citric acid hydrate identified by tlc: R_f (BFW) 58, R_f (EAW) 23.

A solution of 10 g of oxaloacetic acid in 40 ml of water was adjusted to pH 7 with 20% sodium hydroxide. After 3 days at room temperature the pH was 8.5. To this solution was added 10 ml of 30% hydrogen peroxide and the mixture was heated to 45–50° for 1 hr. Calcium chloride (60%, 30 ml) was added; the mixture was boiled for 15 min and filtered. The filtrate was washed with water and methanol and dried to give 9.5 g (87%) of hydrated calcium citrate. This was suspended in 350 ml of dry ether with 3 g of anhydrous magnesium sulfate. To this was added a solution of 2.7 ml of concentrated sulfuric acid in 50 ml of dry ether. After stirring for 6 hr the mixture was filtered and the filtrate was evaporated to give 3.1 g (41.6%) of citric acid hydrate identified by tlc: R_f (BFW) 57, R_f (EAW) 21.

Dinitrophenylhydrazone Derivatives of Citroylformic Acid.—A solution of 50 mg of 1 in 1 ml of 95% ethanol was combined with 2 ml of DNPH solution prepared by adding 0.4 g of DNPH to 2 ml of concentrated sulfuric acid and adding 3 ml of water and 10 ml of ethanol. The crystalline precipitate which formed was collected, washed with cold ethanol, and dried under vacuum, mp 119–127° dec. The mass spectrum of this material showed, as the most intense peaks above 190 amu, two peaks at 364–365 amu and above that a set of peaks at 392–394 amu. The 364 peak corresponded to the DNPH of citroylformic acid less two molecules of water and can be formulated as the unsaturated anhy-

(19) W. Wislicenus, *Justus Liebgis Ann. Chem.*, **246**, 306 (1888).

(20) C. Heidelberger, *Biochem. Prep.*, **3**, 58 (1953).

(21) G. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959), and references cited therein.

(22) The authors wish to thank R. Lichter for assistance with these measurements.

(23) L. Kesner and E. Muntwyler, *Anal. Chem.*, **38**, 1164 (1966).

(24) The authors wish to thank L. Kesner for this determination.

(25) L. Claisen, *Ber.*, **12**, 632 (1879).

(26) A. F. Holleman, *Recl. Trav. Chim. Pays-Bas*, **23**, 169 (1904).

dride 4 or possibly as a lactam. The 393 peak corresponded to the anhydride of the monoethyl ester formulated as 5. Elemental analysis gave values in accord with those for an equimolar mixture of the DNPH of CFA 6 and its monoethyl ester.

Anal. Calcd for $(C_{13}H_{12}N_4O_{11}$–$C_{15}H_{16}N_4O_{11})0.5$; C, 40.5; H, 3.4; N, 13.5. Found: C, 40.2; H, 3.8; N, 13.35.

Slow recrystallization from ethanol containing sulfuric acid gave crystals, mp 150–155°, with analysis corresponding to the diethyl ester 7.

Anal. Calcd for $C_{17}H_{18}N_4O_{10}$: C, 46.57; H, 4.11; N, 12.78. Found: C, 46.12; H, 4.09; N, 12.08.

Citroylformic Acid Lactone.—A solution of 20 g of oxaloacetic acid in 60 ml of water was adjusted to pH 3 with 20% sodium hydroxide and allowed to stand for 19–20 hr at 25–30°. Carbon dioxide was evolved during this period. The solution was decationized by passing through an acidified ion exchange resin bed (22 × 500 mm column of Dowex 50W-X8) and evaporated to dryness under a vacuum evaporator at 35°. The final drying was completed in a vacuum desiccator over anhydrous calcium sulfate to give 12–15 g. The dried residue was partially dissolved in a minimum amount (30 ml) of warm, dry acetone. Nitromethane (dry, about 4 volumes) was added to incipient cloudiness. The mixture was filtered and the solution was allowed to stand at room temperature to deposit crystals. Recrystallization gives the pure lactone of citroylformic acid, mp 160–164° dec, turns brown at 150°. Toluene or xylene can be used in place of the nitromethane. The acetone-insoluble residue is apparently polymeric. The lactone is assigned the butyro-γ-lactone structure arbitrarily. The ir data show absorption (in mineral oil) at 1770, 1740, 1700, and 1660 cm^{-1}.

Anal. Calcd for $C_7H_6O_7$: C, 41.6; H, 2.99; neut equiv, 67.3. Found: C, 41.51; H, 2.98; neut equiv, 67.9.

Oxalocitrolactone Monomethyl Ester Hydrates.—The oxalocitrolactone used in this preparation was prepared from dimethyl oxaloacetate and trimethylamine as previously described[13,14] and was obtained analytically pure (neut equiv calcd, 288; found, 285) on recrystallization from water. The molecular weght (mass spectrometer) was found to be 288.048 (theory 288.050) with reference to the $C_6{}^{35}Cl_3{}^{37}Cl_3$ peak at 287.8043 amu. We confirmed the mp 104–106° reported by Dieckmann.[15]

A mixture of 1.0 g of citrolactone trimethyl ester prepared as above and 20 ml of concentrated hydrochloric acid was heated on a steam bath at 50° for 20 min. The residual oil on cooling deposited crystals in 55% yield. The solution remaining was evaporated at room temperature to 10 ml to deposit additional crystals. The yield is 0.3 g, mp 150–154° dec, R_f 24 (EAW).

Anal. Calcd for $C_9H_8O_9 \cdot H_2O$: C, 38.84; H, 3.59; neut equiv, 92.6. Found: C, 38.93; H, 3.53; neut equiv, 91.37. On prolonged drying under vacuum the material lost water.

Anal. Calcd for $C_9H_8O_9$: neut equiv, 86.6. Found: neut equiv, 85.0. The nmr spectrum of the methyl ester in perdeuteriodimethyl sulfoxide showed maxima at about 3.5 (5 H, two carboxylic, one enolic, two water), 3.8 (3 H, one methyl), and 3.3–3.4 ppm (doublet, two methylene H on asymmetric carbon).

The monomethyl ester hydrate was converted to citric acid in low yield by refluxing with lithium hydroxide, R_f (BFW) 63, but is otherwise stable to alkaline hydrolysis short of further degradation.

Oxalocitrolactone Monoethyl Ester Hydrates.—This compound was prepared following the above procedure for the methyl ester, mp 72–75°, R_f (BFW) 65.

Anal. Calcd for $C_{10}H_{10}O_9 \cdot H_2O$: C, 41.1; H, 4.14; neut equiv, 97.3. Found: C, 41.1; H, 4.13; neut equiv, 94.19.

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Registry No.—**1**, 39118-31-5; **3** (R = R′ = H), 41118-38-1; **3a** (R = R′ = CH_3), 41118-39-2; **3b** (R = CH_3; R′ = H), 41118-40-5; **3b** (R = C_2H_5; R′ = H), 41118-41-6; **4**, 41118-42-7; **5**, 41118-43-8; **6**, 41118-44-9; **6** monoethyl ester, 41118-45-0; **7**, 41118-46-1; diethyl oxaloacetate, 108-56-5; oxaloacetic acid, 328-42-7; citric acid, 77-92-9; DNPH, 119-26-6; citroylformic acid γ-lactone, 41118-47-2.

The Beckmann Fragmentation Reaction of Some α-Hydroxy Ketoximes

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The Beckmann fragmentation reaction of 3β,17β-dihydroxy-16-oximino-5-androstene (2) and 2-*exo*-hydroxy-3-oximinobornane (8) was readily achieved with *p*-toluenesulfonyl chloride in pyridine at 0° or by short boiling with 20% (v/v) H_2SO_4. The structures of the primary fragmentation products 3 and 9 were deduced on the basis of spectral and analytical properties of the corresponding 2,4-dinitrophenylhydrazones 4 and 10; in addition, 3 was converted into the known lactone 6. Anti configurations were assumed for the hydroxy oximes 2 and 8 obtained by $NaBH_4$ reduction of 1 and 7, based on studies of the $NaBH_4$ reduction of *syn*- and *anti*-benzil monoximes.

The fragmentation reaction of some α-oxo and α-hydroxy oximes, under the conditions of Beckmann rearrangement was discovered by Werner and Piguet in 1904.[1] The mechanism and synthetic utility of the reaction has recently been discussed[2] and the geometry (syn or anti) of the oximes has been shown to influence the nature of the fission products.[1,3] Thus, the *anti*-benzoin oxime (anti to the α-hydroxyl group), on treatment with benzenesulfonyl chloride and pyridine, gives equimolar amounts of benzaldehyde and benzonitrile, whereas the syn isomer, under the same experimental conditions, forms benzaldehyde and phenyl isocyanide.[1] Generally, the anti isomers of α-hydroxy oximes, when treated with variety of reagents which induce Beckmann rearrangement, yield aldehydes or ketones, and nitriles, whereas the syn isomers occasionally yield isocyanides[1,3] The Beckmann fission of α-hydroxy oximes has not been widely studies but a recent report described the fragmentation reaction of 5-hydroxy-5α-cholestan-4- and -6-one oximes with thionyl chloride at −20°. A nearly quantitative yield of 5-oxo-4,5-*seco*-cholestano-4-nitrile and 5-oxo-5,6-*seco*-cholestano-6-nitrile was obtained. It should be noted that no direct evidence was given for the geometries of the starting oximes; owing to exclusive formation of oxo nitriles the authors assumed them to have anti configurations.[4]

We wish to report the results of our studies which were undertaken in order to explore the possibility of

(1) A. Werner and A. Piguet, *Chem. Ber.*, **37**, 4295 (1904); A. Werner and Th. Detscheff, *ibid.*, **38**, 69 (1905).

(2) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960); P. A. S. Smith in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 483–507; R. T. Conley and S. Ghosh in "Mechanisms of Molecular Migrations," B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971, pp 197–308.

(3) A. H. Blatt, *Chem. Rev.*, **12**, 215 (1933); A. H. Blatt and R. P. Barnes, *J. Amer. Chem. Soc.*, **56**, 1148 (1934).

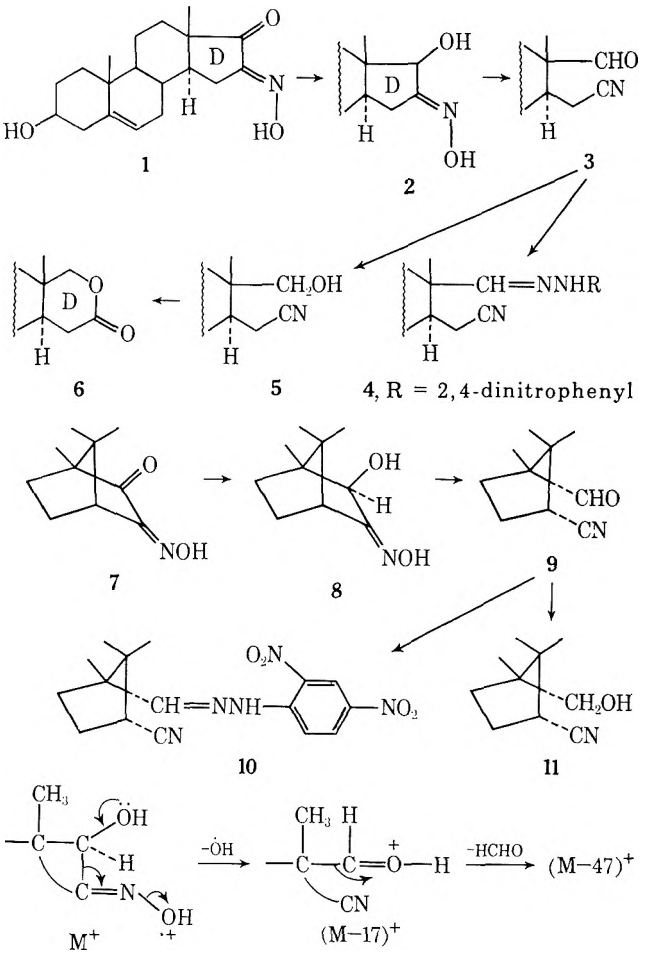
(4) C. W. Shoppee and S. K. Roy, *J. Chem. Soc.*, 3774 (1963).

using the Beckmann fission reaction for the synthesis of ring-D seco steroids (certain ring- D seco steroids in the estrone series are known to be very active hypocholesterolemic agents[5]). For our studies we selected the readily available 3β-hydroxy-5-androsten-17-one which was converted into the corresponding 16-oximino derivative (**1**) according to the procedure of Stodola, Kendall, and McKenzie.[6] The anti configuration of 3β-hydroxy-16-oximino-5-androsten-17-one (with respect to the 17-carbonyl group) was proved by a shift in λ_{max} from 240 to 288 nm upon addition of base to the oximino ketone.[7] We intended to reduce the oximino ketone (**1**) with $NaBH_4$ to the corresponding oximino alcohol (**2**) and then to study the Beckmann cleavage reaction using **2** as a substrate. Except for one example,[8] the selectivity of $NaBH_4$ reductions of the keto function in α-oximino ketones has not been studied. Besides, there exists a possibility for syn–anti isomerization during such a reduction. Therefore, we examined the $NaBH_4$ reduction of the syn and anti isomers of benzil monoximes since all the geometrical isomers of benzil monoximes and benzoin oximes are well known.[9] The $NaBH_4$ reduction was carried out in dilute aqueous NaOH or in methanol at room temperature. It was observed that the reduction of the syn isomer proceeded at a considerably slower rate than that of the anti isomer, but, in both cases, the reduced products were obtained in high yield without any syn–anti isomerization detectable.

Thus, the $NaBH_4$ reduction of *anti*-3β-hydroxy-16-oximino-5-androsten-17-one (**1**) should afford only *anti*-3β,17β-dihydroxy-16-oximino-5-androstene (**2**). The 17β orientation was assumed on the basis of the well-known stereochemical course of the $NaBH_4$ reduction of 17-keto group in steroids.[10] The Beckmann cleavage of **2** using *p*-toluenesulfonyl chloride in pyridine at 0° afforded in almost quantitative yield the unstable cyanoaldehyde (**3**), isolated as the 2,4-dinitrophenylhydrazone (**4**). In addition to analytical and spectroscopic data for the 2,4-dinitrophenylhydrazone (**4**), the structure of the primary fragmentation product **3** was proved by its unambiguous transformation to the known lactone (**6**).[11]

An analogous sequence of reactions was carried out in the camphor series. The *anti*-oximinocamphor (**7**) was prepared according to the procedure of Claisen and Manasse[12] (the geometry of **7** was verified by the method used in the case of **1**[7]). The $NaBH_4$ reduction of **7** according to Chittenden and Cooper[8] yielded **8** (60%) where the exo configuration of the 2-hydroxyl group was assigned on the basis of nmr measurements.[8] Although the authors did not discuss the geometrical isomerism of **8**, it seems that the anti configuration can be assumed on the basis of the $NaBH_4$ reduction of the benzil monoximes.

SCHEME I



The Beckmann fragmentation of **8** proceeded extremely easily. Boiling of **8** with dilute H_2SO_4 for 2 min, in the presence of a slight excess of 2,4-dinitrophenylhydrazine, afforded in quantitative yield the corresponding 2,4-dinitrophenylhydrazone (**10**). The unstable cyanoaldehyde **9** was reduced with $NaBH_4$ to the cyano alcohol **11**[13] which, however, could not be hydrolyzed to the known lactone.

The facile formation of the cyano aldehydes **3** and **9** as the only products indicates that the Beckmann fission of α-hydroxy oximes is a concerted process. It can be seen that the axis of the lone pair on the oxygen, the carbon–carbon bond to be broken and the bond between the nitrogen and the leaving group are all parallel, which is the required condition for concerted fragmentation as was first pointed out by Grob.[14]

Finally, it is interesting to note that the α-hydroxy oximes **2** and **8** undergo the Beckmann fission in the vapor phase under the conditions of mass spectrometry. In **8** the most abundant peak is M − 47, whereas in **2**, owing to the presence of the 3β-hydroxyl group and the 5,6 double bond, the mass spectrum is more complex; the M − 47 peak is still of considerable intensity. In both cases, however, the unusual M − 17 peaks are formed as a consequence of the fragmentation process.

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(12) L. Claisen and O. Manasse, *Justus Liebigs Ann. Chem.*, **274**, 73 (1893).

(13) The structures **2–11** were deduced on the basis of spectroscopic evidence and the satisfactory elemental analyses.

(14) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, pp 712–718 and references cited therein.

Experimental Section

The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded in KBr pellets with a Perkin-Elmer infrared spectrophotometer, Model 257, and nmr spectra with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Chemical shifts (σ) are expressed in parts per million. Mass spectra were recorded with a Varian CH-5 spectrometer.

Sodium Borohydride Reduction of *anti*-Benzil Monoxime.—To an aqueous NaOH solution (20 ml of H_2O; 0.5 g of NaOH, 12.5 mmol) of *anti*-benzil monoxime[9] (0.5 g, 2.2 mmol) sodium borohydride (0.1 g, 2.6 mmol) was added, and the reaction mixture was kept 12 hr at room temperature. After the solution was acidified with 2 *N* sulfuric acid to pH 5, white crystals of the *anti*-benzoin oxime were collected, washed with water, and dried *in vacuo*. Recrystallization from benzene gave a pure sample (0.43 g; 85% yield; mp 152°) which was identical (ir, nmr and mixture melting point) with independently synthesized *anti*-benzoin oxime.[9]

Sodium Borohydride Reduction of *syn*-Benzil Monoxime.—An aqueous solution (20 ml of H_2O) containing NaOH (0.5 g, 12.5 mmol), $NaBH_4$ (0.1 g, 2.6 mmol), and *syn*-benzil monoxime[9] (0.5 g, 2.2 mmol) was kept for 72 hr at room temperature (the reduction was followed by tlc using 4:1 benzene–ethyl acetate as eluent). The reaction mixture was then acidified to pH 5 with 2 *N* H_2SO_4 and extracted with ether. In order to obtain the *syn*-benzoin oxime in a crystalline form, the method described by Werner[1] was used. The ether solution of noncrystalline *syn*-benzoin oxime was kept in a loosely covered beaker for several days at room temperature. The separated crystals were collected, washed with 1:1 ether–hexane, and dried at 50° *in vacuo* (0.42 g; 83% yield; mp 99°). An authentic sample of *syn*-benzoin oxime, synthesized by Werner's method,[1] was identical (ir, nmr and mixture melting point) with the sample prepared by $NaBH_4$ reduction of *syn*-benzil monoxime.

3β,17β-Dihydroxy-16-oximino-5-androstene (2).—An aqueous methanolic solution (15 ml of H_2O and 45 ml of MeOH) containing 3β-hydroxy-16-oximino-5-androsten-17-one (**1**)[6,7] (1.0 g, 3.15 mmol), KOH (0.5 g, 8.9 mmol), and $NaBH_4$ (1.0 g, 26 mmol) was kept for 12 hr at room temperature (at the end of this time a portion of the reduction product separated out). Sulfuric acid (2 *N*) was added to pH 5 and the reaction mixture was kept for several hours at room temperature in order to complete crystallization. The crude **2** was collected and washed thoroughly with 50% aqueous methanol. Recrystallization from methanol (120 ml) afforded analytically pure **2**: 0.75 g; 75% yield; mp 255–257° dec; $[\alpha]^{27}D$ −80° (*c* 1.0 in Py); ir 3600–3050, 1635, 1080, 1050, and 950 cm^{-1}; nmr (Py-d_5): 0.97 (18 methyl), 1.02 (19 methyl), 3.80 (3 α proton, m), 4.43 (17 α proton, s), and 5.40 (C-6 olefinic proton, m); mass spectrum 319 (19, M^+), 301 (38), 286 (34), 283 (28), 272 (52), 268 (43), 231 (33), and 105 (100).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.56; H, 8.88; N, 4.29.

3β-Hydroxy-16,17-*seco*-17-oxo-5-androsteno-16-nitrile 2′,4′-Dinitrophenylhydrazone (4).—To a cold (0°) pyridine solution (20 ml) of 3β,17β-dihydroxy-16-oximino-5-androstene (**2**) (1.0 g, 3.1 mmol) a pyridine solution (5 ml) of *p*-toluenesulfonyl chloride (0.665 g, 3.5 mmol) was added dropwise over a period of 5–10 min. The reaction mixture was kept at 0° for 12 hr and then poured into an excess of cold 2 *N* HCl. The crude 16,17-*seco*-cyanoaldehyde **3** was extracted with $CHCl_3$. After drying and evaporating the chloroform extract, **3** remained in a form of foam: 0.89 g; *ca.* 95%; ir 3600, 3430, 2250, 1720, 1075, 1050, and 1025 cm^{-1}. The crude **3** was dissolved in ethanol (50 ml) and mixed at once with a solution of 2,4-dinitrophenylhydrazine (0.60 g, 3.5 mmol) in 20% H_2SO_4 (25 ml). The fine yellow precipitate of the 2,4-dinitrophenylhydrazone (**4**) separated almost immediately upon mixing; this was filtered off, washed with water until neutral, and dried at 110° *in vacuo* (1.35 g; *ca.* 90% yield, calcd on basis of **2**; mp 218–220°). The crude **4** was recrystallized twice from benzene, giving an analytically pure sample: 1.20 g; 80% yield, mp 228–230°; $[\alpha]^{27}D$ +26° (*c* 1.0 in $CHCl_3$); ir 3600–3150, 3300, 3100, 2245, 1620, 1580, 1340, 1310, 1135, 1055, 840, 830, and 740 cm^{-1}; nmr (in Py-d_5) 1.00 (19 methyl), 1.33 (18 methyl), 3.80 (3α proton, m), 5.40 (C-6 olefinic proton, m), 7.83 (C-17 aldehydic proton, s), 8.07 (C-6′ proton, d, $J_{5',6'}$ = 10 Hz), 8.42 (C-5′ proton, d, $J_{5',6'}$ = 10 Hz), and 9.01 (C-3′ proton, s); mass spectrum 481 (5, M^+).

Anal. Calcd for $C_{25}H_{31}N_5O_5$: C, 62.35; H, 6.49; N, 14.55. Found: C, 62.44; H, 6.60; N, 14.46.

3β,17β-Dihydroxy-16,17-*seco*-5-androsteno-16-nitrile (5).—The crude 3β-hydroxy-16,17-*seco*-16-oxo-5-androsteno-16-nitrile (**3**) (0.9 g) obtained as described in the preceding preparation was dissolved in methanol (30 ml). $NaBH_4$ (1.0 g) was added portionwise to this solution at room temperature, and after 30 min, the reaction mixture was poured into cold 2 *N* HCl. The precipitate was filtered off, washed with water, and dried *in vacuo* at 100° (0.83 g; 87% yield based on **2**; mp 160°). Recrystallization from benzene or methylene chloride–hexane afforded pure **5**: mp 188°; $[\alpha]^{27}D$ −70° (*c* 1.0 in $CHCl_3$); ir 3600–3300, 2250, and 1050 cm^{-1}; nmr (Py-d_5) 1.02 (18 methyl), 1.05 (19 methyl), 3.5 and 3.7 (C-17 protons, AB system, J_{AB} = 10 Hz), 3.6 (3α proton, m), 5.4 (C-6 olefinic proton, m); mass spectrum 303 (13, M^+), 285 (19), 270 (21), 245 (27), 159 (19), 145 (26), 105 (45), 91 (60) and 31 (100).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.09; H, 9.52; N, 4.57.

Lactone of 3β,17β-Dihydroxy-16,17-*seco*-androsten-16-oic Acid (6).—A methanolic solution (10 ml) containing 3β,17β-dihydroxy-16,17-*seco*-5-androsteno-16-nitrile (**5**) (100 mg, 0.33 mmol) and KOH (200 mg, 3.5 mmol) was refluxed for 2 hr, and, after cooling, the solution was acidified with 2 *N* HCl. The crude lactone (**6**) was filtered, washed with water, and dried at 50° *in vacuo* (92 mg; 92% yield; mp 203°). Recrystallization from benzene or methylene chloride–hexane afforded pure **6** (mp 207°, $[\alpha]^{27}D$ +92.6°; this is in an excellent agreement with the reported data[11]).

2-Oxo-3-cyano-2,3-*seco*-bornane 2′,4′-Dinitrophenylhydrazone (10).—*anti*-3-Oximinocamphor (**7**)[12,15] (1.0 g, 6 mmol) and $NaBH_4$ (1.0 g, 26 mmol) were dissolved in water (100 ml) and the solution was kept for 6 hr at room temperature. During this time formation and crystallization of 2-*exo*-hydroxy-3-oximinobornane (**8**)[8,16] was completed. The crude **8** was recrystallized from petroleum ether (bp 70–100°, 70 ml) affording a pure sample (0.605 g; 60% yield; mp 156° in accordance with reported data[8]).

anti-2-*exo*-Hydroxy-3-oximinobornane (**8**) (1.83 g, 10 mmol) was heated for 2 min at 80–100° with dilute sulfuric acid (20 ml; 4:1 v/v H_2O–H_2SO_4); an oily fragmentation product (**9**) separated from the hot solution. Upon cooling in an ice bath a semicrystalline solid (1.60 g; *ca.* 95% yield; ir 2800, 2700, 2220, and 1715 cm^{-1}) was recovered. The crude **9** was dissolved in methanol (50 ml) and mixed with a solution of 2,4-dinitrophenylhydrazine (2.18 g; 11 mmol) in 20% H_2SO_4 (25 ml). The yellow precipitate was filtered, washed with water, and dried at 50° *in vacuo* (3.40 g; 98% yield; mp 182–185°).[17] Recrystallization from methylene chloride–hexane afforded the analytical sample: mp 194–196°; 88% yield; $[\alpha]^{27}D$ +35° (*c* 1.0, $CHCl_3$); ir 3280, 3260, 3110, 2240, 1615, 1585, 1510, 1330, 1140, 1070, 835, 830, and 740 cm^{-1}; nmr ($CDCl_3$) 1.13 (2 methyl groups), 1.16 (1 methyl group), *ca.* 3.0 (CHCN, m), 11.10 (NH, broad), 9.01 (C-3′ proton, d, $J_{3',5'}$ = 2.4 Hz), 8.36, C-5′ proton, two doublets, $J_{3',5'}$ = 2.4 Hz, $J_{5',6'}$ = 10 Hz), 7.95 (C-6′ proton, d, $J_{5',6'}$ = 10 Hz), and 7.6 (C-2 aldehydic proton, s).

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55; N, 20.28. Found: C, 55.66; H, 5.55; N, 20.29.

2-Hydroxy-3-cyano-2,3-*seco*-bornane (11).—The crude **9** (1.60 g), obtained as described above, and $NaBH_4$ (1.0 g) were dissolved in methanol (50 ml). After standing for 2 hr at room temperature, the reaction mixture was acidified with 2 *N* HCl, diluted with water (200 ml), and extracted with ether. After drying and evaporating the ether extract, the residue was recrystallized several times from hexane: mp 140°; 1.25 g; 80% yield; $[\alpha]^{20}D$ +84° (*c* 1.0, $CHCl_3$); ir 3600–3300, 2240, 1460, 1380, 1050, and 1030 cm^{-1}; nmr ($CDCl_3$) 0.97 (1 methyl group),

(15) The mixture of *syn*- and *anti*-3-oximinocamphor prepared according to Claisen and Manasse[12] was converted almost completely into only anti isomer by boiling the mixture for several hours with water.

(16) This presents a considerable simplification over the procedure of Chittinden, *et al.*[8] Mass spectrum of **8**: 183 (4.4, M^+), 166 (29), 136 (100), 122 (40), 109 (94), and 95 (98).

(17) 2,4-Dinitrophenylhydrazone **10** can be prepared in a simpler way: boiling of **8** with dilute H_2SO_4 in the presence of a slight molar excess of 2,4-dinitrophenylhydrazine. An almost quantitative yield of compound **10** was obtained.

1.07 (2 methyl groups), *ca.* 3.0 (CHCN, m), 3.60 (CH_2OH, broad s).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.70; H, 10.15; N, 8.44.

Registry No.—**1**, 40962-87-6; **2**, 40962-88-7; **3**, 40962-89-8; **4**, 40962-90-1; **5**, 40962-91-2; **6**, 40962-92-3; **7**, 13854-87-0; **8**, 32231-98-4; **9**, 40962-95-6; **10**, 40962-96-7; **11**, 40962-97-8.

Synthetic Reactions of Propynyllithium and Propynylsodium

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An investigation of the reactions in aprotic solvents of propynyllithium and propynylsodium is reported. Optimum conditions for the formation of 1-(1-propynyl)cyclohexanol, 91% yield, and 2-butynoic acid, 87% yield, are given. A number of other reagents reacted with these two propynyl alkali metal compounds in good to high yield. The coupling of these compounds with alkyl halides was studied in a number of solvents.

Considerable literature exists describing the optimum conditions for the reaction of alkali metal acetylides ($HC{\equiv}CM$) with organic compounds in aprotic solvents, but there are few such references delineating preferred reaction conditions for propynyl alkali ($CH_3C{\equiv}CM$), and higher alkynyl alkali metal ($RC{\equiv}CM$) compounds in aprotic solvents. The optimum reaction conditions for lithium or sodium acetylide with organic compounds should not necessarily correspond to the higher alkynyl alkali metal compounds because of the greater basicity of the substituted acetylenic anions and potential solubility differences. This paper reports a study of the optimization of reaction conditions for propynyllithium and propynylsodium with cyclohexanone and carbon dioxide in aprotic solvents. A number of other organic compounds also reacted with these two compounds. An optimization study of the reaction of *n*-butyllithium with ketones has recently been published in which the higher reactivity observed of the alkyl anion contrasts with the greatly reduced reactivity of the alkynyl anion in this study.[1]

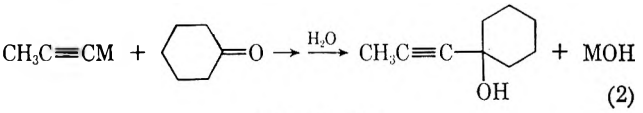
Propynyllithium and propynylsodium may be prepared from the corresponding metal and propyne in liquid ammonia or other solvents, by the reaction of an organometallic and propyne, and by the reaction of lithium or sodium hydride with dimethyl sulfoxide (DMSO) with subsequent addition of propyne.[2] These references also include examples of specific reactions of propynyl alkali compounds. Propynyllithium and propynylsodium are nonpyrophoric, white to off-white powders rapidly decomposed by air and moisture, and are insoluble in hydrocarbon solvents, diethyl ether, 1,2-dimethoxyethane and tetrahydrofuran (THF).[3,4] These two compounds are soluble in DMSO, but the metalation of the DMSO is a competing reaction (eq 1).[2c,5] In fact, this equilibrium appears to be

$$CH_3C{\equiv}CM + CH_3SOCH_3 \longrightarrow CH_3SOCH_2M + CH_3C{\equiv}CH \quad (1)$$

general and favors the dimsyl anion for all alkynes higher than acetylene itself. *N*,*N*-Dimethylacetamide was slowly attacked by propynyllithium when it was used as the reaction solvent. Therefore, this study focused on the use of the nonreactive solvents, THF, diethyl ether, and hydrocarbons.

Results and Discussion

Optimization of Reaction Conditions for Cyclohexanone.—A commonly used reaction of acetylenic alkali metal compounds is the reaction with ketones to form tertiary alcohols.[6] Cyclohexanone which is sensitive to enolization side reactions was selected as a model ketone to determine the optimum conditions and important factors for the reaction of propynyllithium and propynylsodium with ketones (eq 2).



(2)

M = Li, Na

The results of this study are summarized in Table I. Solvent and temperature were found to be the most critical factors in obtaining a good yield of the tertiary alkynyl alcohol from cyclohexanone. An explanation for the higher yields obtained in THF than in diethyl ether or benzene may be a greater "incipient" solubility of the propynyllithium and/or the lithium salt of the product. The presence of ethylenediamine (EDA) increased the yields greatly in diethyl ether and slightly in THF, probably owing to the increased solubility of the propynyllithium–EDA complex. [The $(CH_3C{\equiv}CLi)_2$–EDA complex has been isolated.][7] The effect of the EDA is almost catalytic considering the first 0.1 mol gives the greatest increase in yield and there is no benefit above 0.5 mol. The dramatic effect of temperature may also be due to a slightly increased "incipient" solubility of the propynyllithium or the salt of the reaction product. Competing side reactions become a problem over 40–45° so that this is the optimum temperature range for cyclohexanone. The addition of lithium bromide to suppress the amount of enolization and increase the solubility of the propynyl-

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(3) G. M. Whitesides and W. J. Ehman, *J. Amer. Chem. Soc.*, **91**, 3800 (1969).

(4) Solubility in THF with 1 mol of LiBr present is 0.05 *M*.

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(7) O. F. Beumel, Jr., unpublished work.

TABLE I

REACTION OF PROPYNYLLITHIUM[a] AND PROPYNYLSODIUM[b] WITH CYCLOHEXANONE[c]

Run[d]	Propynyl M	Solvent	Additive	Reactn temp, °C	Addn time, hr	Yield,[e] %
1	Li	Et_2O		35	0.25	12[f]
2	Li	Et_2O	0.5 equiv EDA	35	1.5	71
3	Li	THF		40	0.25	84
4	Li	THF		25	1.5	74
5	Li	THF	0.1 equiv EDA	25	1.5	83
6	Li	THF	0.5 equiv EDA	25	1.5	86
7	Li	THF	1.0 equiv EDA	25	1.5	73
8	Li	THF	0.5 equiv RDA	40	1.5	83[e]
9	Li	THF	0.5 equiv EDA	40	1.5	81[g]
10	Li	THF		0	1.5	6
11	Li	THF		40	1.5	87[g,h]
12	Li	THF		40	1.5	87[g,i]
13	Li	THF	LiBr satd	40	1.5	89[g]
14	Li	THF		40	1.5	91[g,j]
15	Li	THF		50	1.5	82[g]
16	Li	THF		64	1.5	76
17	Li	Benzene		40	1.5	3
18	Li	DMSO		30	1.25	26
19	Li	DMSO	Propyne satd	30	1.25	51
20	Na	Et_2O		20	1.5	2
21	Na	THF	1.0 equiv EDA	40	1.5	8
22	Na	THF		40	1.25	23
23	Na	DMSO	Propyne satd	30	1.25	68

[a–c] Registry numbers are, respectively, 4529-04-8, 10486-71-2, and 108-94-1. [d] All runs made at 0.8–1.0 *M* and reacted 1 hr after addition of 5% excess propynyl compound. [e] Yield by isolation; ethylenediamine (EDA). [f] Reacted 3 hr. [g] 15% excess propynyllithium used. [h] Run at 0.47 *M*. [i] Run at 1.35 *M*. [j] 90% yield after sublimation.

lithium had little effect in the case of cyclohexanone. Slow addition gave only a slight increase in yield. The 91% yield in run 14 represents the maximum yield obtained under any conditions with cyclohexanone.

Solutions of propynyllithium and propynylsodium in DMSO reacted rapidly, but gave only moderate yields, even when run under a propyne atmosphere owing to the equilibrium in eq 1.

Propynylsodium in general did not give good yields with cyclohexanone, but it and its reaction products are generally less soluble than the corresponding lithium compounds in aprotic organic solvents. The higher yield found with DMSO under propyne supports the explanation that a lack of solubility, with increased enolization, accounts for the lower yields of propynylsodium with cyclohexanone in other solvents.

Reactions of Propynyllithium with Other Ketones and Reagents.—The optimum conditions for reaction of propynyllithium with cyclohexanone were used initially with other ketones (THF, and 40–45° for addition and reaction temperature). The results for a number of reactions of propynyllithium are listed in Table II. If the yield was relatively poor, then several other conditions were examined. For more reactive reagents than ketones, such as propionyl chloride, carbon dioxide, and ethyl chloroformate, lower temperatures gave better results with propynyllithium. Less reactive compounds required higher temperatures for reasonable yields such as ethyl sulfate, paraformaldehyde, and ethylene oxide. The yields were generally lower the more rapidly the ketone underwent enolization, and sodium or lithium bromide was added to suppress this. Reactions with esters using 2 equiv of propynyllithium to form the tertiary alcohols gave low yields of unidentified oils.

Reaction of propynyllithium in DMSO with benzophenone at 30° gave a 93% yield of the dimsyl anion–benzophenone adduct providing further evidence of the existance of the dimsyl–alkynyl anion equilibria.[5]

$$MCH_2SOCH_3 + (C_6H_5)_2C{=}O \longrightarrow \xrightarrow{H_2O} (C_6H_5)_2\overset{OH}{\overset{|}{C}}CH_2SOCH_3 \qquad (3)$$

The reaction of carbon dioxide and propynyllithium was extensively studied. The two sets of conditions listed in Table II represent the best result out of a large number of runs, and a typical lower yield result.

Reactions of Propynylsodium.—Propynylsodium gave either low yields or no isolable product with enolizable ketones, although other reactions did proceed in good yield. The optimum conditions for propynyllithium were not effective for propynylsodium, for example, run 22 in Table I. The reactions of propynylsodium investigated are listed in Table III. The reactions of propionyl chloride and of ethyl chloroformate gave higher yields with propynylsodium than with propynyllithium. The insolubility of the propynylsodium during the reaction, especially considering that toluene was the solvent in one case, minimized side reactions with the reactive soluble product, which is produced directly in these two cases. The explanation for the high yield of tetrolic acid from carbon dioxide and propynylsodium may be that the relative molar volumes of the propynylsodium and sodium tetrolate are about the same permitting the solid–gas reaction to proceed. There may be a greater difference in the lithium case causing a tapering off in the rate of reaction. This reaction was extensively studied under a wide variety of conditions with propynylsodium and the two runs in Table II represent the optimum and a near optimum condition.

Reaction of Organic Halides.—Another frequently used reaction of alkynyl alkali metal compounds is the coupling reaction with an organic halide. A number of attempts to force the coupling reaction (4) to take place with propynyllithium and propynylsodium in THF and other solvents with several reactive halides all essentially failed, with the starting halide isolated unchanged. This reaction apparently cannot proceed unless there is significant solubility of the alkynyl alkali metal compound in the reaction solvent.

$$R'X + RC{\equiv}CM \longrightarrow RC{\equiv}CR' + MX \qquad (4)$$

In spite of the presence of equilibrium 1 in DMSO, this solvent was tried for the coupling reaction. Only when the solvent was pure DMSO and saturated with propyne were significant yields of the coupled alkyne obtained. These results are listed in Table II. Even an alkyl chloride gave a reasonable yield, but as expected the yield was higher with the corresponding iodide.

Experimental Section

Materials.—Ketones, organic halides, acyl chlorides, and other organic reagents were reagent grade or the best grade available and were obtained from Aldrich Chemical and Eastman Organic Chemicals. EDA was Dow anhydrous commercial grade. DMSO was obtained from Crown Zellerbach. All liquid reagents were distilled before using. Propynyllithium, propynylsodium, and anhydrous LiBr were Foote Mineral Co. products. The hydrocarbon solvents and Et_2O were dried over Na wire before use. THF was purified by drying over KOH

TABLE II

REACTIONS OF PROPYNYLLITHIUM

Run	Reagent	Registry no.	Addn time, hr	Reactn temp, °C	Reactn time, hr	Product	Registry no.	% yield[a]
1	Acetone	67-64-1	0.3	40	1.0	2-Methyl-3-butyn-2-ol	115-19-5	50
2	Acetophenone	98-86-2	0.7	40	1.5	2-Phenyl-3-pentyn-2-ol	6712-32-9	23
3	Acetophenone[b]		1.5	40	1.5	2-Phenyl-3-pentyn-2-ol		58
4	Benzaldehyde	100-52-7	1.0	40	1.0	1-Phenyl-2-butyn-1-ol	32398-66-6	66
5	Benzophenone	119-61-9	0.5	40	1.0	1,1-Diphenyl-2-butyn-1-ol	836-87-3	91
6	Carbon dioxide	124-38-9	0.5[c]	64	0.5	2-Butynoic acid (tetrolic acid)	590-93-2	78
7	Carbon dioxide[d]		1.5	20		2-Butynoic acid (tetrolic acid)		27
8	Chlorotriphenyltin	639-58-7	1.5	50	0.5	Triphenyl(1-propynyl)tin	1231-17-0	84
9	Cyclopentanone	120-92-3	0.7	64	0.3	1-(1-Propynyl)cyclopentanol	2809-80-5	50
10	Cyclopentanone		0.7	40	0.3	1-(1-Propynyl)cyclopentanol		30
11	Cyclopentanone		0.7	55	0.3	1-(1-Propynyl)cyclopentanol	41174-76-9	43
12	Diisopropyl ketone	565-80-0	0.7	40	0.3	3-Isopropyl-2-methyl-4-hexyn-3-ol		68
13	Diisopropyl ketone		0.7	65	0.3	3-Isopropyl-2-methyl-4-hexyn-3-ol		57
14	Ethyl chloroformate[e]	541-41-3	0.7	35	1.0	Ethyl 2-butynoate	4341-76-8	6
15	Ethyl chloroformate[e]		0.7	30	1.0	Ethyl 2-butynoate		5
16	Ethyl chloroformate[e]		0.3	64	0.5	Ethyl 2-butynoate		Trace
17	Ethyl chloroformate[b]		0.3	30	0.5	Ethyl 2-butynoate		68
18	Ethyl chloroformate[b]		0.3	10	0.5	Ethyl 2-butynoate		71
19	Ethylene oxide[f]	75-21-8	0.5	55	2.0	3-Pentyn-1-ol	10229-10-4	43
20	Ethylene oxide[d]		0.3	55	1.0	3-Pentyn-1-ol		0
21	Ethylene oxide[g]		0.3	50	1.0	3-Pentyn-1-ol		10
22	Ethylene oxide[h]		2.0	60		3-Pentyn-1-ol		30
23	Fluorenone	486-25-9	0.5	40	1.0	9-(1-Propynyl)fluoren-9-ol	16557-07-6	85
24	Methyl ethyl ketone	78-93-3	0.5	40	1.5	3-Methyl-4-hexyn-3-ol	6320-68-9	53
25	Paraformaldehyde[b]	30525-89-4	0.3	60	1.0	2-Butyn-1-ol	764-01-2	55
26	Paraformaldehyde		0.3	60	18.0	2-Butyn-1-ol		0
27	Paraformaldehyde[h]		0.3	60	1.0	2-Butyn-1-ol		53
28	Paraformaldehyde[i]		0.3	60	3.0	2-Butyn-1-ol		0
29	Propionyl chloride[b]	79-03-8	0.3	25	0.8	4-Hexyn-3-one	10575-41-4	54
30	Ethyl sulfate	64-67-5	0.3	64	2.5	2-Pentyne	627-21-4	46
31	1-Chlorobutane[i]	109-69-3	0.5	35	2.0	2-Heptyne	1119-65-9	36
32	1-Chlorobutane[j]		0.5	35	2.0	2-Heptyne		35[l]
33	1-Chlorobutane[k]		1.0	40	2.0	2-Heptyne		13
34	1-Iodobutane[j]	542-69-8	0.5	20	1.5	2-Heptyne		48

[a] Yields are calculated on isolated product; reactions were run at 0.6–1.0 *M* concentrated with 10% excess propynyllithium in THF; addition temperature was the same as the reaction temperature unless otherwise stated. [b] Solution was saturated with NaBr. [c] CO_2 was added at 0° initially. The slurry was then permitted to warm slowly over 1 hr to 64° and held for 0.5 hr under CO_2. [d] 0.5 equiv of EDA present. [e] Solvent: Et_2O. [f] Contained 1.0 equiv of LiBr. [g] Contained 1.2 mol of DMSO; propyne saturated. [h] 0.5 equiv of LiBr present. [i] 0.1 equiv of EDA present. [j] Solvent: DMSO; propyne saturated. [k] Solvent: 50:50 DMSO:THF; propyne saturated. [l] Propynylsodium was used.

TABLE III

REACTIONS OF PROPYNYLSODIUM

Run	Reagent	Solvent	Addn time, hr	Reactn temp, °C	Reactn time, hr	Product	% yield[a]
1	Benzophenone	THF	1.1	66	1.3	1,1-Diphenyl-2-butyn-1-ol	64
2	Ethyl chloroformate[b]	THF	0.8	35	18	Ethyl 2-butynoate	77
3	Ethyl chloroformate	Toluene	1.0	75	0.5	Ethyl 2-butynoate	51
4	Ethyl chloroformate	Toluene	0.05	90	2.5	Ethyl 2-butynoate	50
5	Propionyl chloride	Toluene	0.05	30	2.5	Ethyl (1-propynyl) ketone	64
6	Carbon dioxide	Xylene	1.0[c]	65	0.5	2-Butynoic acid (tetrolic acid)	87
7	Carbon dioxide	Xylene	1.5	60		2-Butynoic acid (tetrolic acid)	78
8	Ethyl sulfate	THF	0.15	64	3.0	2-Pentyne	46
9	Ethyl sulfate	Et_2O	0.15	35	3.0	2-Pentyne	0
10	Stannic chloride	THF	0.5	25	18	Tetra(1-propynyl)tin	53[d]

[a] Reactions were run at 0.6–2.0 *M* with yields based on isolation. [b] Contained 0.1 equiv of NaBr. [c] Addition of CO_2 was at 0–5° for 1 hr; then temperature was raised to 65°. [d] Decomposes slowly in air.

overnight, then over $CaCl_2$ overnight, and finally distilled from $LiAlH_4$ under argon. All elemental analyses were performed by Microanalysis, Inc., of Wilmington, Del.

General.—All reaction setups were flushed with argon for 1 hr before use. Glc analyses were performed on a Varian Aerograph 90P3 using a 6 ft × 0.25 in. SE-30 on Chromosorb W column. Ir spectra were run on a Perkin-Elmer Infracord. The same reaction setup and procedure was used for all runs unless otherwise noted.

Gases were added using a gas addition tube fitted to the flask. Liquid reagents were added neat. Paraformaldehyde, fluorenone, and benzophenone were added as saturated solutions in THF. Satisfactory elemental (±0.3% for C and H) were obtained for all compounds. Ir spectra were consistent with all products

obtained. The physical constants of the known compounds prepared were in agreement with literature values. Table IV lists the physical properties obtained for the products together with the corresponding literature values.

TABLE IV
PHYSICAL PROPERTIES OF PRODUCTS

Product	Bp, (mm), or mp, °C	Corresponding lit. value
1-(1-Propynyl)cyclohexanol	49.5	49.5[a]
2-Methyl-3-butyn-2-ol	104–106 (760)	104 (760)[b]
2-Phenyl-3-pentyn-2-ol	39 (0.3)	
	41–42	42–43[c]
1-Phenyl-2-butyn-1-ol	91–92 (0.3)	88 (0.2)[d]
1,1-Diphenyl-2-butyn-1-ol	153–154 (0.5)	165 (1.5)[e]
	48.5–49.5	
2-Butynoic acid	75	76[d]
1-(1-Propynyl)cyclopentanol	53 (1.0)	99 (30)[f]
3-Isopropyl-2-methyl-4-hexyn-3-ol	46 (0.4)	99 (45)[g]
Ethyl 2-butynoate	160 (760)	160 (760)[b]
3-Pentyn-1-ol	158–159 (760)	152–153 (760)[h]
9-(1-propynyl)fluoren-9-ol	103–104	107–108[c]
3-Methyl-4-hexyn-3-ol	59 (15)	53.5 (20)[i]
2-Butyn-1-ol	140–141 (760)	143 (760)[b]
4-Hexyn-3-one	46 (12)	35–39 (10)[j]
2-Pentyne	52–56 (760)	56 (760)[b]
2-Heptyne	110–113 (760)	112 (760)[b]
1,1-Diphenyl-2-methylsulfinylethanol	129–135[k]	148[l]
Triphenyl(1-propynyl)tin	111 dec	74–75[m]
Tetra(1-propynyl)tin	159–160	150[m]

[a] R. Mantione, *C. R. Acad. Sci., Paris, Ser. C24*, 1668 (1967). [b] Handbook of Chemistry and Physics, 53rd ed, CRC Publishing Co., Cleveland, 1972. [c] C. Schopf and J. H. Strauss, *Monatsh. Chem.*, **98** (4), 1274 (1967). [d] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951). [e] S. G. Kuznetsov and L. V. Fedorova, *Zh. Obshch. Khim.*, **32**, 3775 (1962); *Chem. Abstr.*, **58**, 11179c (1963). [f] B. R. Fleck and J. E. Kmiecik, *J. Org. Chem.*, **22**, 90 (1957). [g] I. A. Favorskaya and Yu. P. Artsybasheva, *Zh. Obshch. Khim.*, **30**, 789; *Chem. Abstr.*, **55**, 350*i* (1960). [h] M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 1788 (1957). [i] K. Suga, S. Watanabe, and T. Suzuki, *Can. J. Chem.*, **46**, 3041 (1968). [j] E. S. Turbanova, Yu. I. Porfir'eva, and A. A. Petrov, *Zh. Org. Khim.*, **2** (5), 772 (1966); *Chem. Abstr.*, **65**, 10480c (1966). [k] Not recrystallized. [l] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **85**, 3054 (1963). [m] M. L. Quan and P. Cadiot, *Bull. Soc. Chim. Fr.*, **1**, 35 (1965).

The propynylsodium and propynyllithium were bottled in 6-oz bottles with Polyseal caps. These compounds were added to the flasks under argon by weighing the bottle, then transfering the bottle into a closed plastic bag purged with argon and with the cap removed. The closed plastic bag was carefully fitted over one neck of a three-neck flask being purged with argon and the desired amount of propynyl alkali compound carefully poured from the bottle into the flask while grasping it through the bag film. The flask was quickly stoppered, the cap of the bottle put back on, and the bottle weighed. The amount of propynyl alkali compound used was the difference in weight.

Reaction of Cyclohexanone with Propynyllithium (Propynylsodium).—A 500-ml flask, equipped with pressure-equalizing dropping funnel, stirrer, condenser, and thermometer and sealed from the atmosphere by an oil bubbler, was charged with 160 ml of THF and 16 g of propynyllithium (0.35 mol). The slurry was heated to 40° and 33 ml of cyclohexanone (0.32 mol) was added over 1.5 hr. The slurry was stirred an additional hour and then hydrolyzed with excess water. The aqueous solution was extracted with Et_2O three times; the extracts were combined and dried over anhydrous Na_2SO_4. The product oil, after solvent removal using a rotary film evaporator, weighed 42.9 g (93% purity by glc or 91% yield). This oil was sublimed to give 39.5 g of 1-(1-propynyl)cyclohexanol, 90% yield, mp 47°, resublimation mp 49.5°.

Carbonation of Propynyllithium.—A slurry of 20.8 g of propynyllithium (0.45 mol) in 300 ml of THF in a 500-ml flask was stirred and cooled to 0° under argon. At this point, CO_2 was bubbled into the slurry while maintaining 0° with cooling. The rate of addition was observed using an oil bubbler with the system. The solution was no longer exothermic after 0.25 hr. After 0.5-hr total time, the slurry was warmed gradually to 64° over 1.0 hr under CO_2. After 0.5 hr at reflux, the slurry was cooled under CO_2 and then hydrolyzed with an excess of water. The aqueous layer was extracted twice with Et_2O. The aqueous layer was then acidified with aqueous HCl to pH 2 and the organic layer formed separated from the solution. The acidified aqueous layer was then extracted four times with Et_2O. These Et_2O extracts and the organic layer were combined. (Tetrolic acid appears to form a stable monohydrate.) The oil left after removal of the Et_2O with a rotary film evaporator was extracted three times with boiling cyclohexane in the presence of excess anhydrous Na_2SO_4. The hot cyclohexane extracts were decanted. The solvent from the combined cyclohexane extracts was removed on a rotary film evaporator and the solid tetrolic acid obtained weighed 29.8 g or 78% yield, mp 70–72°. (This product was almost quantitatively sublimed, mp 74.5–75.0°.)

Carbonation of Propylsodium.—The same experimental setup as described before was used. CO_2 was added to a slurry of 27.0 g of propynylsodium in 300 ml of xylene at 0–5° for 1.0 hr (exotherm lasts for 0.3 hr). The slurry was warmed to 65° gradually over 1.0 hr and maintained at 65° for 0.5 hr. The slurry was cooled and hydrolyzed at 20° with excess water. The yield was 31.8 g or 87% of tetrolic acid using the previously described work-up procedure.

Reaction of 1-Chlorobutane with Propynyllithium.—The same laboratory setup was used as described for the reaction with cyclohexanone. The solution of 17.1 g of propynyllithium (0.37 mol) in 300 ml of DMSO was saturated with propyne at 33°. A propyne atmosphere was maintained while 34.4 g of 1-chlorobutane (0.37 mol) was added over 0.5 hr at 36–40°. The reaction was exothermic. The solution was permitted to cool to room temperature, while stirring over an additional 2-hr period, and then hydrolyzed with a large excess of water. The aqueous DMSO layer was extracted two times with Et_2O. The combined Et_2O extracts were dried over anhydrous Na_2SO_4. A yield of 72.9 g of 2-heptyne, 36%, was obtained on fractional distillation, bp 110–113° (760 mm).

Radical Anions Related to Naphtho[1′,8′]bicyclo[3.2.0]hepta-2,6-diene

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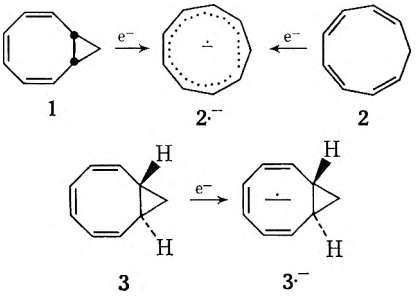
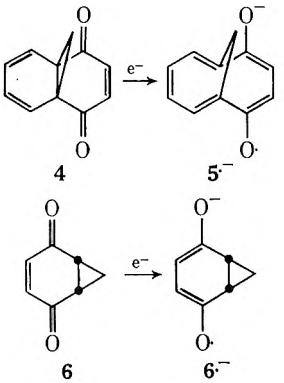
The title radical anion is unstable, and its esr spectrum is replaced by that of the ring-opened dihydro compound (2-pleiadene radical anion) at −80°. Possible reasons for this result are discussed. The esr splitting constant for the methylene hydrogens of 2-pleiadene and related compounds are surprisingly high, and this is attributed to π spin density in the vinyl group arising from weak overlap of the vinyl group with the naphthalene π system.

Electrocyclic bond cleavage reactions of the type $\sigma + n\pi \rightarrow (n + 1)\pi$ were the first to which orbital symmetry concepts were applied, and have received a great deal of study.[1] There has been a limited amount of work on such cleavage reactions in radical anionic systems. The stereochemistry of ring opening in radical anionic systems has received some attention. If the symmetry of the highest occupied MO is the determining factor, one would expect the opposite preferred stereochemistry as for the reaction of the neutral molecule. Winstein and coworkers[2] showed that *cis*-bicyclo[6.1.0]nonatriene (**1**) reduced to give the opened radical anion ($2\cdot^-$), the same species as is formed by reduction of cyclononatetraene (**2**),[3] whereas only the closed anion ($3\cdot^-$) was observed upon reduction of *trans*-bicyclo[6.1.0]nonatriene (**3**).[4]



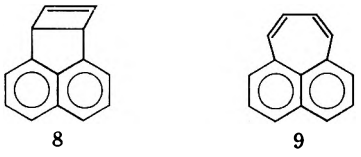
This result is consistent with the reversal of the Woodward–Hoffmann-predicted stereochemistry for neutral species being operative for radical anions. With the reversal, $1\cdot^-$ should open in an allowed reaction to *all-cis*-cyclononatetraene, as observed, but $3\cdot^-$ would be required to open to *trans,cis,cis,cis*-cyclononatetraene, which is very strained and has poor overlap.[4] The generality of such concepts seems rather limited, however. Russell and coworkers[5] showed that, although the radical anion produced from **4** has the opened structure $5\cdot^-$, the closed radical anion is observed upon reduction of **6**.

The cyclobutene–butadiene interconversion, the parent case of electrocyclic reactions, was studied in radical anions using substituted compounds such as benzo- and naphthocyclobutene. It has been established that the radical anions observed from these substrates at low temperatures have the closed structures,[6] although the ring-opening reaction is "allowed"



using the reversed prediction for the radical anion, and substantial ring strain would be relieved.

We report here our esr studies of the reduction of 2-naphtho[1′,8′]bicyclo[3,2.0]hepta-2,6-diene (**8**) and related compounds. Ring opening of **8** is, of course, a forbidden reaction, since it is required to be disrotatory. Heating **8** for 30 sec at 250° results in only partial ring opening to pleiadiene (**9**).[7] We expected



that the radical anion of **8** would open to that of **9** much more rapidly than the neutral species, and that $9\cdot^-$ would be stable under the reaction conditions.

Results

The splitting constants for pleiadiene radical anion have been reported separately.[8a] We found that the esr spectrum of $9\cdot^-$, generated from **9** and sodium–potassium alloy in THF, persists for hours at room temperature, and that several minutes of heating on a steam bath are required to destroy the spectrum. It could also be generated electrolytically in DMSO, although under these conditions further reduction took place at high applied potentials.

In contrast, $8\cdot^-$ proved to be an extremely labile species. We had to work at low temperatures to even observe it, but were ultimately successful using a 1:2 mixture of dimethoxyethane and 2-methyltetrahydrofuran with sodium–potassium alloy as the reductant,

(1) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(2) R. Rieke, M. Ogliaruso, R. McClung, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 4729 (1966).

(3) T. J. Katz and C. Talcott, *J. Amer. Chem. Soc.*, **88**, 4732 (1966).

(4) G. Moshuk, G. Petrowski, and S. Winstein, *J. Amer. Chem. Soc.*, **90**, 2179 (1968).

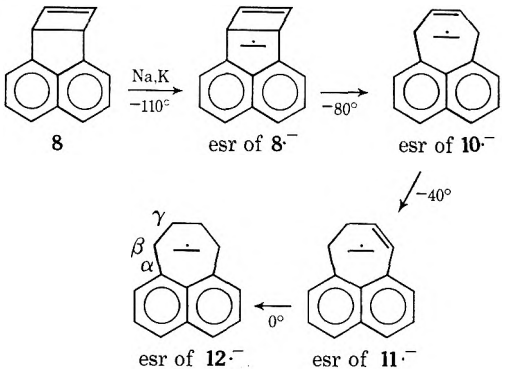
(5) G. A. Russell, T. Ku, and J. Lokensgard, *J. Amer. Chem. Soc.*, **92**, 3833 (1970).

(6) (a) R. D. Rieke, S. E. Bales, P. M. Hudnall, and C. F. Meares, *J. Amer. Chem. Soc.*, **92**, 1418 (1970); (b) R. D. Rieke, C. F. Meares, and L. I. Rieke, *Tetrahedron Lett.*, 5275 (1968); (c) R. D. Rieke, W. Rich, and T. Ridgway, *ibid.*, 4361 (1969).

(7) J. Meinwald, G. Samuelson, and M. Ikeda, *J. Amer. Chem. Soc.*, **92**, 7604 (1970).

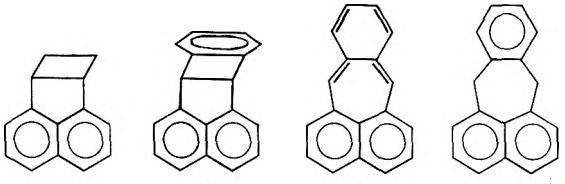
(8) (a) S. F. Nelsen and J. P. Gillespie, *J. Amer. Chem. Soc.*, **95**, 1874 (1973); (b) *ibid.*, **95**, 2940 (1973).

and developing the radical anion in an ethanol slush (*ca.* −110°). The procession of radical anions observed upon careful warming of such a tube is outlined below. When the temperature of the tube was raised from −90° to −80°, the esr spectrum of **8**·⁻ faded rapidly, and was replaced by that of the symmetrical dihydro radical anion, **10**·⁻, as was verified by carrying out the reduction starting with **10**. Upon further warming, the spectrum of **10**·⁻ faded and was replaced by that of the unsymmetrical dihydropleiadiene, **11**·⁻, also verified by starting with the authentic



neutral compound. Finally, near 0°, the esr spectrum of the tetrahydro compound appeared and eventually was the only radical anion observable. Exactly analogous behavior was shown by 3′,6′-di-*tert*-butyl-**8** (**8a**) and led to observation of **8a**·⁻, **10a**·⁻, **11a**·⁻, and **12a**·⁻.

The great lability of **8**·⁻ is in substantial contrast to that of the hydrogenated derivative **13**·⁻, which gave an esr spectrum which was stable at −40° for hours. We did not observe radical anions other than **13**·⁻ from these sample tubes.



In contrast to the instability of **8**·⁻, the esr spectrum of the benzo derivative **14**·⁻, generated in THF using sodium–potassium alloy, did not disappear rapidly even at room temperature. Brief warming of the sample tube resulted in a poorly resolved spectrum consisting of nine overlapping multiplets. The total width of this spectrum was only 17.5 G, which is by far the narrowest spectrum observed in any of this work.[8a,b] Since Hückel calculations[9] indicate that the spectrum of **15**·⁻ should be 20 G wide (Q = 24), we assign the spectrum to **15**·⁻. Unfortunately, **15** is not stable enough to handle at ordinary temperatures[10] and we did not verify our assignment by independent reduction of **15**. Room-temperature electrolytic reduction of **14** in DMSO gave **16**·⁻,[11] the benzo analog of **10**.

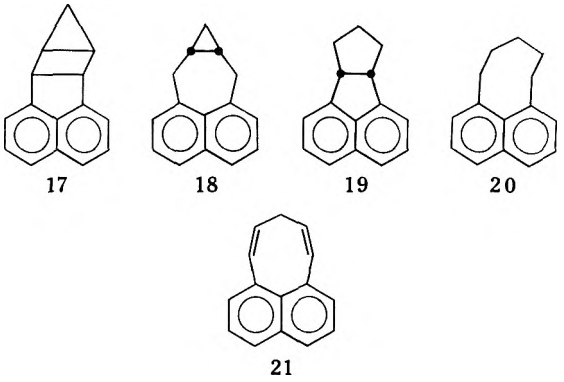
(9) A. Streitwieser and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, New York, N. Y., 1965, p 713.

(10) (a) J. Kolc and J. Michl, *J. Amer. Chem. Soc.*, **92**, 4147 (1970); (b) J. Michl, *ibid.*, **93**, 523 (1971).

(11) R. D. Allendoerfer, P. E. Gallagher, and P. T. Lansbury, *J. Amer. Chem. Soc.*, **94**, 7702 (1972).

We also investigated the reduction of the housane derivative **17**, in which the double bond of **8** is replaced by a cyclopropane ring. The radial anion of **17** was easily observed, but proved to be somewhat labile, and upon standing at room temperature the esr spectrum of **17**·⁻ was replaced by that of an unknown radical anion. The structure of this radical anion has eluded all of our efforts at guessing, although the spectrum was relatively easily analyzed, and the splitting constants 5.92 (2 H), 4.20 (2 H), 2.54 (2 H), 0.66 (1 H), 0.49 (2 H), 0.20 (2 H), and 0.09 (2 H) simulate the observed spectrum well. The only thing we can say about the structure is that it may have the naphthalene ring partially reduced, since splittings assignable to meta hydrogens are absent.

Upon standing at room temperature for 1 day, the spectrum of the "unknown" species faded, and was replaced with that of **18**·⁻ (verified by reduction of the authentic neutral compound[8b]), as the ultimate reduction product. We did not observe the esr spectra of either **19**·⁻ or **20**·⁻ [8b] during the reduction of **1**. There is no evidence from these results that the radical anion of **17** opens to **21** (which we know reduces to **20**·⁻ under the reduction conditions used), which is the thermal product from **17**.[8b]



The splittings of the radical anions observed in this work are summarized in Table I. We were unable to completely analyze the spectrum of the unsymmetrical reduction product, **11**·⁻, because of the large number of splittings. A partial analysis (using the outer lines, which are far more resolved than the center portion of the spectra) gave splittings of 0.27 (1 H), 0.79 (1 H), 1.08 (1 H), 3.07 (1 H), 2.37 (2 H), and 4.97 (2 H), leaving splittings caused by four hydrogens, summing to 15.92 G, unaccounted for.

Discussion

Splitting Constants.—The only unexpected splittings reported in Table I are the large β splittings observed for the unsaturated compounds **8**·⁻ and **10**·⁻. Introduction of the double bond in going from **13**·⁻ to **8**·⁻ results in a 53% increase of a_β, which certainly cannot be accounted for by a change in θ in the β coupling equation,[12] $a_\beta = (B_0 + B_2 \cos^2\theta)\rho_\alpha^\pi$, since the geometry for **13**·⁻ and **8**·⁻ must be very similar. A substantial increase in ρ_α^π for **8**·⁻ is ruled out by the other ring splittings, which actually sum to indicate slightly more spin density in **8**·⁻ than in **13**·⁻. Increases of similar

(12) See ref 8b for a discussion of the application of this equation. We designate the alkylated ring carbon as C_α, an attached sp^2 hybridized carbon as C_β, and so on (see **12**·⁻).

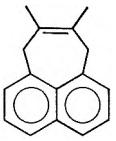
TABLE I

ESR SPLITTING CONSTANTS (G)[a]

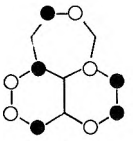
Radical anion of	Temp, °C	Line width,[b] mG	a_p	a_m	a_o	a_β	Other
19	−45	110	4.18	2.48	1.11	6.60	0.28 (4 H)
13	−40	115	4.24	2.42	1.17	5.80	0.57, 0.14
17	−90	70	4.22	2.37	1.20	6.23	0.25 (2 H), 0.24 (1 H), 0.17 (1 H)
8	−100	95	4.39	1.94	1.48	8.87	0.12
8a	−100	220	4.04		1.52	9.05	Unobsd
8b	−70	90	4.25	2.10	1.71	7.97	0.32 (6 H)
10	−80	110	4.70	1.89	1.66	10.84, 0.50	0.24
10a	−75	150	4.47		1.91	11.28, 0.53	Unobsd
10b	10	110	4.61	2.02	1.50	9.57, 0.28	0.28 (6 H)
14	−100	160	4.33	2.14	1.42	7.70	Unobsd

[a] In THF or THF–MeTHF mixtures, generated with Na–K alloy. [b] Peak-to-peak line width used in simulation of the spectra.

8b



10b



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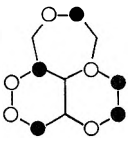
23a

23b



24

magnitude in a_β were also observed for *sym*-pleiadenes compared to pleiadanes; the largest β splitting of **10**$\cdot^-$ is 50% larger than that of **12**$\cdot^-$.[8b] Although **10**$\cdot^-$ and **12**$\cdot^-$ probably have somewhat different θ values, application of the β coupling equation leads to unreasonably large ρ_α^π values for **10**$\cdot^-$. We also determined the spectra of **8b**$\cdot^-$ and **10b**$\cdot^-$, which have the vinyl hydrogens of **8** and **10** replaced by methyl groups. As Kosman and Stock have discussed,[13] such a replacement will result in a methyl splitting which is slightly larger than the hydrogen splitting of the unsubstituted compound if the hydrogen splitting had been caused by π spin density in the vinyl group, whereas a much smaller methyl splitting would result if a long-range spin polarization mechanism had been responsible for the hydrogen splitting. Since we observed methyl splittings for **8b**$\cdot^-$ and **10**$\cdot^-$ this is evidence for a modest π spin density in the vinyl groups of these compounds. Even a modest π spin density at a second center next to a CH group can cause large changes in the observed splittings, however, as was first pointed out by Whiffen.[14] When a C–H bond can hyperconjugate with two π centers (designated here as α and α'), the splitting depends upon the amount of spin at each π center, as given by the relation in eq 1. The coefficients c_α^π must be summed before squaring [$\rho_\alpha^\pi = (c_\alpha^\pi)^2$]. To see the enhanced a_β values we do,

$$a(\mathrm{H}) = Q(C_\alpha^\pi + c_{\alpha'}^\pi)^2 \qquad (1)$$

the signs of the coefficients must be the same at both carbons attached to c_β, as is shown diagramatically in **22**, which represents positive coefficients with dark circles and negative ones with open circles. It should be noted that the pattern of coefficients which would result from spin introduction into the vinyl group by homohyperconjugation (as indicated in **23a** and **23b**) is that shown in **24**, and would result in low a_β values. The pattern of coefficient signs shown in **22** does result when a vinyl group is allowed to overlap with the 1,8 positions of a naphthalene ring, and, if the overlap is 0.1β, McLachlan calculations give a vinyl spin density of 0.011, quite close to the ρ of 0.010 estimated from the observed splitting of 0.24 G for **10**$\cdot^-$ using $Q_\alpha = 24$. Assuming that ρ_α^π for **10**$\cdot^-$ has the same value as it does for the saturated compound **12**$\cdot^-$, about 0.13,[8b] the apparent spin density necessary for calculation of a_β of **10**$\cdot^-$ would be $[(0.13^{1/2} + (0.010)^{1/2}]^2 = 0.22$, considerably larger than ρ_α^π. The low spin density shown to be present at the vinyl group does adequately account for the large increase in a_β observed.

Ring Opening of 8$\cdot^-$ **and 14**$\cdot^-$.—The prediction that cyclobutene cleavage of **8**$\cdot^-$ should be more facile than that of **8** seems to be borne out experimentally. Since $t_{1/2}$ for opening of **8** is greater than 30 sec at 250°[7] and $t_{1/2}$ for decomposition of **8**$\cdot^-$ is less than 2 min at −80°, the difference in activation energies is at least 9 kcal/mol (assuming the same $\Delta S^\ddagger$). In calculating the above difference, we have assumed that the reaction leading to the destruction of the esr signal for **8**$\cdot^-$ is ring opening, which would give **9**$\cdot^-$. We believe that this contention is made reasonable by the fact that many peri-disubstituted naphthalene anions are stable for hours even at considerably higher temperatures,[8b] including **13**$\cdot^-$. The instability of **8**$\cdot^-$ is unusual, and seems uniquely associated with the presence of the cyclobutene ring. We do not, however, observe **9**$\cdot^-$, in spite of the fact that it is quite stable, even at room temperature in DMSO. A cause for this striking anomaly is suggested by the cyclic voltammetry spectrum of **9**. In addition to the reversible one-electron **9** $\rightleftharpoons$ **9**$\cdot^-$ couple at $E_{1/2} = -1.85$ V (in DMSO, *vs.* sce),[8a] there is a totally irreversible wave at $E_p = -2.64$ (V 200 mV/sec scan rate, no corresponding reoxidation wave observed up to 300 V/sec scan rate). This second wave must correspond to reduction of **9**$\cdot^-$ to the dianion, which is far more basic, and immediately protonates and is further reduced, removing the electroactive species. Since reduction of **8** requires a potential somewhat more negative than the −2.6 V of naphthalene, **9**$\cdot^-$ is only formed from **8**$\cdot^-$ under

(13) D. Kosman and L. M. Stock, *J. Amer. Chem. Soc.*, **91**, 2011 (1969).
(14) D. H. Whiffen, *Mol. Phys.*, **6**, 223 (1963).

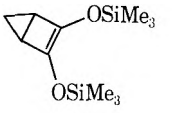
conditions where a reducing agent capable of forming the very basic dianion 9^{2-} is present. We suggest that this dianion protonates, giving $10\cdot^-$ rapidly, and never allowing 9^- to build up. We only observed $11\cdot^-$ after the solutions containing $10\cdot^-$ had stood at −40° for many minutes. This rearrangement is most reasonably formulated as a base-catalyzed tautomerization of neutral **10** to **11**, followed by electron transfer. Since **11** has a lower reduction potential than **10** ($E_{1/2}$ for **11** is −2.25 V *vs.* sce in DMSO), if substantial amounts of **11** were formed initially, the esr spectrum of $11\cdot^-$ should have been observed. The protonation reaction leading ultimately to $10\cdot^-$ at −80° in THF appears to be considerably more selective than that observed at room temperature in acetate-buffered methanol, where we observed a 77:20:2.8:<0.5 mixture of 10:11:9:12 upon 8% sodium amalgam reduction of **9**, although we have no proof that the latter product ratios are kinetic ones.

A qualitative correlation diagram for the ring opening of $8\cdot^-$ to $9\cdot^-$ shows that, as in the simple case of cyclobutene → butadiene (disrotatory), the symmetric doubly occupied MO of cyclobutene (or **8**) correlates with the first antibonding excited level of butadiene (or **9**), while the antisymmetric lowest antibonding level of cyclobutene (singly occupied in $8\cdot^-$) correlates with the highest bonding level of butadiene.[1] Starting with $8\cdot^-$, an electronically excited state of $9\cdot^-$ would result if the correlation diagram is followed. The unusual, two-quantum excitation (which only takes place in a glass) necessary for photochemical ring opening of neutral **8** to **9**, which is also suggested by the correlation diagram discussed above, has received experimental verification,[7,10] and might bolster one's belief that there is something quite unusual about the opening of **8** to **9**, and that the simple correlation diagram has practical validity. Our experiments only demonstrate that $8\cdot^-$ cleaves the 1,5 bond remarkably easily compared to neutral **8**, and do not address the question of the electronic state of the product. Since forcing in antibonding electron raises the energy of the starting material, a lower activation energy for cleavage does not seem qualitatively unreasonable. It should be pointed out that we cannot rule out an irreversible cleavage of 8^{2-}, instead of $8\cdot^-$, although we do not favor this explanation, since the large separation in the two reduction waves of naphthalene requires that only tiny amounts of the dianion would be present.

The benzo analog $14\cdot^-$ was considerably more thermally stable than $8\cdot^-$, which is reasonable since part of the resonance energy of benzene is lost upon benzocyclobutene ring opening. Here we were able to observe the esr spectrum of the opened form, $15\cdot^-$, in THF. Presumably the extended conjugation makes the dianion rather less basic than that of **9**. We did not observe $15\cdot^-$ in the more acidic solvent, DMSO, in which protonation of the dianion apparently does occur.

Replacing the 6,7 double bond of **8** by a cyclopropyl group (giving **17**) results in substantially less reactivity for the radical anion. Hydrogenation products are not observed until room temperature is reached, and then the ultimate naphthalene-containing reduction product was $18\cdot^-$, in which the 1,5 σ bond has been cleaved, but not the 6,7 bond. The 6,7 cyclopropyl "bent bond" was not observed to be the equivalent of a 6,7 π bond in these reactions. The unknown radical observed between the spectra of $17\cdot^-$ and $18\cdot^-$ appeared from its splittings not to contain a naphthalene ring, and, if this was the case, further reduction and proton abstraction would lead to a polyalkylbenzene derivative, which would not be expected to give an esr spectrum under our conditions as long as any naphthalene-containing products (like **18**) were present.

Other cases in which substituted cyclobutene anion → butadiene anion conversions were observed to take place only with formation of the dihydro product include the reduction of **25**[15] and **26**.[16] In the latter



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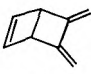

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case the unhydrogenated product, *o*-xylylene anion, is apparently stable enough for detection by esr,[6a] if generated from the dibromide. In both cases, it seems likely that reduction of the cyclobutene occurs at potentials beyond the second reduction wave of the butadiene; so observation of dihydro product seems entirely reasonable.

Experimental Section

Reduction of Pleiadiene (9). A. By Reduction with 8% Sodium Amalgam.[17]—To a solution of 520 mg (2.92 mmol) of **16** in 180 ml of 95% ethanol was added 180 ml of 10% sodium acetate. Over a period of 3 hr, chunks of 8% sodium amalgam (from 16.8 g of Na and 21 g of Hg) and 4.38 g (7.3 mmol) of acetic acid were added alternately to the bright red solution. After 4 hr, the color had faded almost completely. The solution was decanted from the mercury, and ether was added. The aqueous layer which separated was extracted (2 × 100 ml) with ether and the combined organic extracts were dried, after which filtration and rotovaporation left about 520 mg of a pale reddish residue. Analysis by vpc revealed the following product ratio, compound (%): 2-pleiadene (**10**) (77), 1-pleiadene (**11**) (20), pleiadiene (**9**) (2.8), pleiadane (**12**) (0.5). Preparative tlc (PF_{254}, 12.5% $AgNO_3$, benzene) gave 380 mg (73%) of 2-pleiadene (R_f 4–5.2): mp 99–100°; nmr (HA-100, $CDCl_3$) δ 8.86 (m, 1 H), 6.22 (m, 2 H), 7.06–7.80 (m, 6 H); ir (CCl_4) 3.26, 3.36, 3.46, 3.50, 6.21, 6.29, 6.35, 7.19, 7.26 μ; uv (95% EtOH) λ_{max} (log ε) 225 (4.73), 269 (sh) (3.60), 277 (3.79), 287 (3.89), 298 (3.76), 306 (3.43), 316 (2.97), 321 (2.97); exact mass 180.0932 (calcd for $C_{14}H_{12}$, 180.0939).

The other major band (R_f 0.58) contained 100 mg of 1-pleiadene contaminated with a trace of pleiadiene. Purification by preparative vpc gave pure 1-pleiadene: mp 47–47.5° (lit.[18] mp 43–45°); nmr ($CDCl_3$) δ 3.4–3.8 (m, 2 H), 3.05–3.40 (m, 2 H), 5.95–7.85 (m, 2 H), 7.1–8.0 (m, 6 H); ir (CCl_4) 3.27, 3.30, 3.41, 3.42, 3.51, 6.30, 6.36, 6.65, 6.98, 7.21, 7.39, 7.91 μ; uv (95% EtOH) λ_{max} (log ε) 231 (sh) (4.57), 235 (4.59), 246 (4.14), 255 (4.00), 297 (3.97), 309 (4.11), 324 (3.97).

B. By a Diimide Reduction.—To a suspension of dipotassium azodicarboxylate (3.93 mmol, 763 mg) in a solution of 70 mg of pleiadiene in 50 ml of pyridine was added intermittently, over a period of 3 days, 240 mg (8 mmol) of acetic acid in 10 ml of pyridine. Rotovaporation of the pyridine left a residue which was suspended in ether and extracted successively with 1 *M* HCl (3 × 50 ml), saturated Na_2CO_3 (3 × 50 ml), and finally with water.

(15) G. A. Russell, J. J. McDonnell, R. R. White, R. S. Givens, and R. G. Keske, *J. Amer. Chem. Soc.*, **93**, 1452 (1971).

(16) F. R. Farr and N. L. Bauld, *J. Amer. Chem. Soc.*, **92**, 6695 (1970).

(17) Analogous to a Bayer reduction: A. Bayer, *Justus Liebigs Ann. Chem.*, **269**, 189 (1882).

(18) P. D. Gardner and W. J. Horton, *J. Amer. Chem. Soc.*, **74**, 657 (1952).

The dried extracts were rotovaporated to yield 65 mg of a residue, which was shown by vpc to be a mixture of 1-pleiadene (41%), pleiadane (21%), and pleiadiene (38%). Preparative vpc gave a sample of 1-pleiadene, mp 47–47.5°.

6,9-Di-*tert*-butyl-1-pleiadene (11a) was prepared as in the unsubstituted case. Treatment of **9a** with diimide for 5 days gave the following mixture (vpc): 6,9-di-*tert*-butylpleiadane (10%), 6,9-di-*tert*-butyl-1-pleiadene (43%), and 6,9-di-*tert*-butylpleiadiene (47%). Preparative tlc (silica gel, PF_{254} 12.5% $AgNO_3$, benzene, 2×, R_f 0.4) gave 28 mg of product, which was sublimed: mp 99–100.5°; nmr ($CDCl_3$) δ 13.8 (s, 18 H), 2.55 (m, 2 H), 3.20 (m, 2 H), 5.90–6.82 (m, 2 H), 7.2 (d, J = 2 Hz, 1 H), 7.33 (d, J = 2 Hz, 1 H), 7.58 (d, J = 2 Hz, 2 H); ir ($CHCl_3$) 3.48, 6.22, 6.30, 6.81, 7.39, 11.41 μ; uv λ_{max} (log ε) 238 (4.65), 256 (4.26), 299 (sh) (3.91), 3.08 (4.00), 321 (sh) (3.89); exact mass 292.2207 (calcd for $C_{22}H_{28}$, 292.2191).

The compounds **10a** and **10b** were never prepared, although esr spectra, observed upon allowing reducing mixtures of **8a** and **8b** to warm, were recorded. The esr spectra were recorded on a Varian E.15 spectrometer, and sample preparation was as previously described.[8a,b]

6b,10b-Dihydrobenzo[3,4]cyclobut[1,2-*a*]acenaphthylene (14).—A refluxing methylene chloride solution (30 ml) of 1.25 g of acenaphthylene was treated with 1.25 g of solid benzenediazonium 2-carboxylate[19] in small portions over a period of 4 hr. The black solution was concentrated, and preparative tlc (silica gel PF_{254}, 12.5% $AgNO_3$, benzene, R_f 0.5) gave 100 mg (5%) of **14**, mp 129–130° (lit.[10a] mp 133–134°).

Acknowledgment.—We thank the National Science Foundation, the Sloan Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial financial support of this work, and the National Science Foundation's major instrument program for funds used in purchase of the nmr, esr, and mass spectral equipment used.

Registry No.—**8**·⁻, 40782-39-6; **8a**·⁻, 40782-69-2; **8b**·⁻, 40782-70-5; **9**, 208-20-8; **9a**, 40949-40-4; **10**, 40949-41-5; **10**·⁻, 40949-42-6; **10a**·⁻ 40949-43-7; **10b**·⁻, 40949-44-8; **11**, 40949-45-9; **11a**, 40949-46-0; **13**·⁻, 40949-47-1; **14**·⁻, 40949-48-2; **17**·⁻, 40949-49-3; **18**·⁻, 40949-50-6.

(19) M. Stiles, R. G. Miller, and U. Burkhart, *J. Amer. Chem. Soc.*, **85**, 1792 (1963).

Palladium(II) Chloride Catalyzed Decomposition of Vinyl Acetate in Dry Acetic Acid[1]

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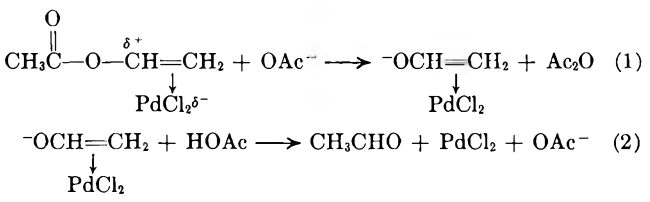
The decomposition of vinyl acetate to give acetaldehyde and acetic anhydride was found to have two regions of kinetic behavior. In one, which occurs at low chloride, high Pd(II), and high vinyl acetate concentrations, the reaction rate had little dependence on these variables and addition of acetic anhydride depressed the rate only slightly. In the second region, which occurs at high chloride, low Pd(II), and low vinyl acetate concentrations, the kinetic behavior becomes conventional and follows the rate expression $-d[C_2H_3OAc]/dt = k[Li_2Pd_2Cl_6]\cdot[C_2H_3OAc]/[LiCl]$. In this range the reaction is strongly inhibited by acetic anhydride. The mechanism which best fits all the data involves the slow formation of water and acetic anhydride in a reaction not involving Pd(II) catalysis. The water then reacts with vinyl acetate in a Pd(II)-catalyzed reaction to give acetaldehyde and acetic acid. The two regions of kinetic behavior arise from the fact that either water formation or the reaction of water with vinyl acetate can be the rate-limiting step.

The palladium(II)-catalyzed decomposition of vinyl acetate, first reported in 1959,[3] has been the subject of at least two mechanistic studies.[4,5] Noting that both palladium(II) chloride and sodium acetate were required for the decomposition, Clement and Selwitz proposed a mechanism involving attack of acetate on a Pd(II)–olefin complex (eq 1 and 2).



(1) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969; *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14** (2), B15 (1969).

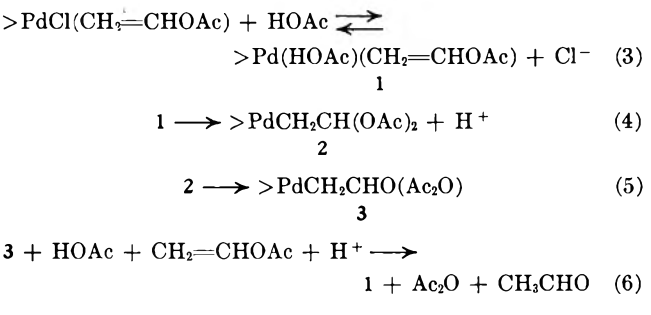
(2) Address correspondence to author at the Department of Chemistry, University of Guelph, Guelph, Ontario, N1G 2W1, Canada.

(3) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Ruttinger, and H. Kojer, *Angew. Chem.*, **71**, 176 (1959).

(4) W. H. Clement and C. M. Selwitz, *Tetrahedron Lett.*, 1081 (1962).

(5) R. G. Schultz and P. R. Rony, *J. Catal.*, **16**, 133 (1970).

Schultz and Rony,[5] on the other hand, found that sodium acetate was not required for the decomposition and, in fact, was a mild inhibitor. Furthermore, they found the reaction to be zero order in vinyl acetate and inhibited by LiCl. They also found that addition of Ac_2O had no effect on the rate. They explained these observations by first proposing that the predominant species in solution is either $Cl_2PdCl(CH_2{=}CHOAc)^-$ or the dimeric species $Cl_2PdCl_2PdCl(CH_2{=}CHOAc)^-$, which was found to be the active species in vinyl ester exchange.[6] Further steps in the sequence are given by eq 3–6.



There is one serious objection to this reaction scheme. Vinyl ester exchange, which almost certainly proceeds by way of an intermediate such as **2**, exhibits quite different kinetics from decomposition. Exchange is first order in both vinyl acetate and acetate ion. This

(6) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3853 (1971).

difference in kinetic behavior would not be expected if 2 is a common intermediate for both reactions. A further problem is that Schultz and Rony[5] did not measure the order in Pd(II). A first-order dependence would have been expected on the basis of the mechanism represented by eq 3–6.

This paper will describe the author's own studies of the decomposition reaction which indicate that the reaction is considerably more complex than suggested by previous workers.

Results

All runs were carried out at 25° in dry acetic acid using palladium(II) chloride as catalyst in the presence of either NaCl or LiCl. In acetic acid saturated with NaCl (0.013 *M*), the Pd(II) is known to exist almost exclusively as the dimeric species $Na_2Pd_2Cl_6$.[7] When the chloride is introduced in the form of LiCl, the following two equilibria must be considered, where K_1 has a value of 0.1 M^{-1} and K_D a value of 2.6 M^{-1}

$$Li_2Pd_2Cl_6 + 2LiCl \overset{K_1}{\rightleftharpoons} 2Li_2PdCl_4 \quad (7)$$

$$2LiCl \overset{K_D}{\rightleftharpoons} Li_2Cl_2 \quad (8)$$

at 25°. The concentrations of all species can be calculated from a knowledge of total palladium(II), $[Pd(II)]_t$, and total chloride, $[Cl]_t$, concentrations.

Kinetic Dependence on Vinyl Acetate Concentration.—In any given run it was difficult to determine the kinetic order in vinyl acetate since the runs could not be carried out for much over one half-life because of precipitation of solids. Therefore, the order in vinyl acetate was studied by varying the initial vinyl acetate concentration.

The order in vinyl actate was found to be neither zero order nor first order, but rather somewhere between the two. If plotted as first-order reactions, reasonably good plots were obtained which usually varied with initial vinyl acetate concentration. On the other hand, the zero-order rate constants also varied with initial vinyl acetate concentration. Only at higher chloride and lower vinyl acetate concentrations did the reaction appear to be first order in vinyl acetate. Some representative data are given in Table I. The rate data in this paper will be reported in terms of psuedo-first-order rate constants obtained from the first-order plots of the data, since they offer a reasonable measure of rate.

Effect of Lithium Acetate Concentration.—Above a concentration of about 0.1 *M*, the rate was independent of [LiOAc]. A plot of k_{obsd} *vs.* [LiOAc] under one set of reaction conditions is shown in Figure 1. Except where indicated otherwise all runs in this paper were carried out at [LiOAc] = 0.1 *M*.

Dependence of Rate on Palladium(II) Concentration.—The order in palladium(II) was also not simple. At low chloride the dependence was less than one-half order. Table II shows some results in solutions saturated with NaCl to maintain a low but constant [NaCl] (0.013 *M*). The palladium(II) concentration varies by a factor of 32 while the rate varies by a factor of only 3. Even a half-order dependence would have predicted a change by a factor of 5.6.

(7) P. M. Henry and O. Marks, *Inorg. Chem.*, **10**, 373 (1971).

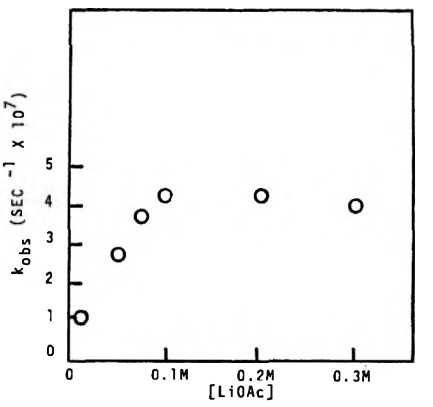


Figure 1.—Plot of k_{obsd} *vs.* [LiOAc]: $[Pd(II)]_t$, 0.02 *M*; $[Cl]_t$, 0.27 *M*; initial [vinyl acetate], 0.2 *M*.

TABLE I
REACTION ORDER IN VINYL ACETATE UNDER SEVERAL REACTION CONDITIONS[a]

$[Pd(II)]_t$	$[Cl]_t$	Initial [vinyl acetate]	First-order plot, k_{obsd}, $sec^{-1} \times 10^6$	Zero-order plot, M/hr $\times 10^4$
0.02644	0.0994[b]	0.19	1.08	1.8
0.02644	0.0994[b]	0.48	0.43	5.6
0.0224	0.0852[c]	0.10	0.8	1.9
0.0224	0.0852	0.825	0.46	14
0.02540	0.2908[d]	0.082	0.80	1.05
0.02540	0.2908[d]	0.18	0.71	2.1
0.02540	0.2908[d]	0.47	0.31	3.5
0.02540	0.2908[d]	0.98	0.16	5.2

[a] [LiOAc] = 0.1 *M*; [Ac_2O] = 0.3 *M*. [b] Chloride added as NaCl; free NaCl was 0.013 *M* (saturated solution). [c] Chloride added as LiCl; free LiCl was 0.017 *M*. [d] Chloride added as LiCl; free LiCl was *ca.* 0.15 *M*.

TABLE II
DEPENDENCE OF RATE ON $Na_2Pd_2Cl_6$ CONCENTRATION IN SOLUTIONS SATURATED WITH NaCl[a]

$[Na_2Pd_2Cl_6]$, $M \times 10^2$	k_{obsd}, $sec^{-1} \times 10^6$
2.68	1.51
1.34	1.17
0.67	0.96
0.335	0.77
0.0167	0.64
0.0835	0.48

[a] [NaCl] = 0.013 *M*; [LiOAc] = 0.1 *M*; [Ac_2O] = 0.3 *M*; initial [vinyl acetate] = 0.2 *M*.

However, at higher chloride concentrations the dependence becomes much more pronounced. A plot of k_{obsd} *vs.* $[Pd(II)]_t$ at [LiCl] = *ca.* 0.2 *M* is shown in Figure 2. At lower $[Pd(II)]_t$ there is a first-order dependence on $[Pd(II)]_t$. If $[Li_2Pd_2Cl_6]$ is used in place of $[Pd(II)]_t$, the plot is somewhat more curved at higher values of $[Li_2Pd_2Cl_6]$, but a linear dependence is still observed at low values.

Effect of [LiCl] on Rate.—A plot of k_{obsd} *vs.* 1/[LiCl] is shown in Figure 3.[8] At high [LiCl] the reaction displays a first-order inhibition by LiCl while, at lower [LiCl], the reaction becomes independent of lithium chloride concentration. A plot of $k_{obsd}/[Li_2Pd_2Cl_6]$ *vs.* 1/[LiCl], which would correct for removal of dimer

(8) Schultz and Rony plotted $1/k_{obsd}$ *vs.* [LiCl] and obtained a straight line with a positive intercept. The data used for Figure 3 would have given a similar plot. However, we feel the type of plot shown in Figure 3 is more indicative of mechanism.

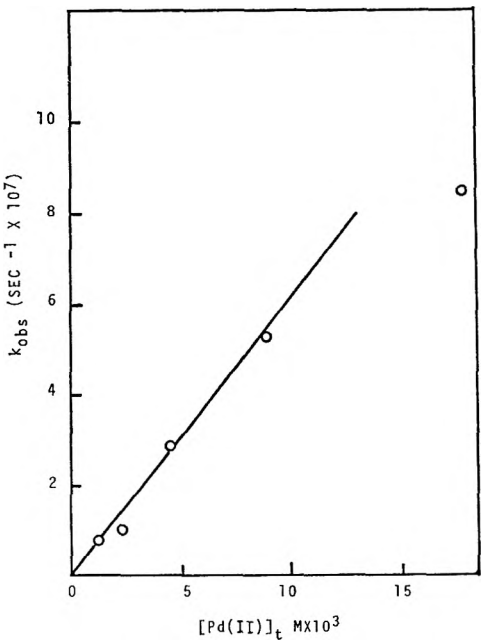


Figure 2.—Plot of k_{obsd} *vs.* [Pd(II)]$_t$ in the LiCl system: [LiCl], 0.2 ± 0.02 *M*; [LiOAc], 0.1 *M*; initial [vinyl acetate], 0.2 *M*.

because of the equilibrium shown in eq 7, is very similar to the plot shown in Figure 3.[9]

Effect of Acetic Anhydride Concentration.—Most of the runs in this study were made at acetic anhydride concentrations of 0.3 *M*. However in several runs the concentration was varied to determine the effect on rate (see Table III). At the low chloride concentrations of the $Na_2Pd_2Cl_6$ system, increasing the Ac_2O concentration by a factor of 10 decreased the rate by a factor of about 2. On the other hand, at higher chloride concentration the addition of AcO_2 strongly depressed the rate. For runs at 0.3 and 0.6 *M* [Ac_2O] the rate was proportional to 1/[Ac_2O].

TABLE III

EFFECT OF ACETIC ANHYDRIDE ON RATE AT TWO DIFFERENT REACTION CONDITIONS[a]

[Pd(II)]$_t$, *M*	[Cl]$_t$, *M*	[Ac_2O], *M*	k_{obsd}, sec^{-1} × 10^6
0.05288	0.186[b]	0.1	1.15
0.05288	0.186[b]	1.0	0.51
0.02540	0.2908[c]	0.3	0.71
0.02540	0.2908[c]	0.6	0.34
0.02540	0.2908[c]	2.0	Very slow[d]

[a] [LiOAc] = 1.0 *M*; initial [vinyl acetate] = 0.2 *M*. [b] Chloride added as NaCl; free NaCl was 0.013 *M* (saturated solution). [c] Chloride added on LiCl; free LiCl was *ca.* 0.15 *M*. [d] No change in vinyl acetate concentration in 600 hr.

Effect of Enol Acetate Structure on Rate.—As the rates of decomposition were already too slow for convenient measurement and substituents on the vinylic carbon would be expected to decrease the rates even further, no quantitative study of the effect of enol ester structure was undertaken. Qualitative observations, however, indicated that substituents on the double bond depressed rates of decomposition much less than rates of vinyl ester exchange. Thus 1-cyclopenten-1-yl acetate, which does not undergo exchange, decomposes at an appreciable rate. Isopropenyl propionate exchanges with acetic acid at low [LiOAc] (~0.01 *M*) about 200 times slower than vinyl propionate.[11] However, its rate of decomposition under these conditions is about equal to its rate of exchange, while vinyl propionate under these conditions still exchanges much faster than it decomposes.

(9) A plot of k_{obsd}/[$Li_2Pd_2Cl_6$] *vs.* 1/[LiCl] is, of course, based on the assumption that the dimer is the reactive species. This assumption is very reasonable since the dimer has been found to be the reactive species in most Pd(II)-catalyzed reactions in acetic acid containing lithium chloride.[10]

(10) P. M. Henry, *Accounts Chem. Res.*, **6**, 16 (1973).

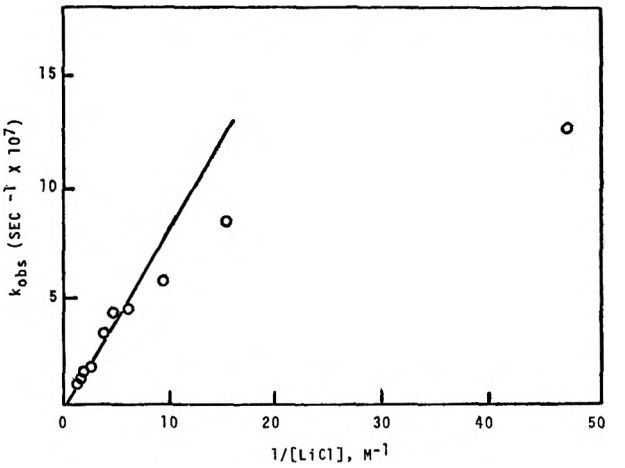


Figure 3.—Plot of k_{obsd} *vs.* 1/[LiCl]: [Pd(II)]$_t$, 0.02 *M*; [LiOAc], 0.02 *M*; initial [vinyl acetate], 0.2 *M*.

Discussion

The results clearly indicate two kinetic domains. One is that, at low [vinyl acetate], low [Pd(II)]$_t$, and high [Cl]$_t$, the reactions follow conventional kinetics. In this range the kinetic expression appears to have the form given by eq 9. The dimeric species is used

$$\text{rate} = [Li_2Pd_2Cl_6][\text{vinyl acetate}][4]/[LiCl] \quad (9)$$

in the rate expression because the rate shows no correlation with Li_2PdCl_4, the only other Pd(II) species present in these reaction mixtures. **4** in the reaction sequence represents some unknown species which must react with vinyl acetate to give the products.

The other domain consists of ill-defined kinetics in which the dependencies on [vinyl acetate], [Pd(II)]$_t$, and [LiCl] rapidly fade as the first two increase and the last decreases. This overall behavior suggests the following reaction sequence

$$\text{reaction mixture} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 4 + \text{other products } (Ac_2O?) \quad (10)$$

$$CH_2{=}CHOAc + 4 \xrightarrow[k_2]{\text{Pd(II)}} CH_3CHO + \text{other products } (Ac_2O?) \quad (11)$$

Under conditions such as low [chloride], high [Pd(II)]$_t$, and high [vinyl acetate], the second reaction becomes the faster of the two, and k_1 becomes rate determining. Alternatively, under conditions of high [chloride], low [Pd(II)]$_t$, and low [vinyl acetate], the rate of the second reaction becomes slower than the first and thus rate determining. The concentration of **4** must, under these conditions, build up to a steady-state concentration.

Several results suggest that water is the reactive species, **4**. First is the inhibition of rate by acetic anhydride. At high [chloride] this inhibition is very

(11) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 7316 (1972).

marked, while at low [chloride] it is not so pronounced. This is exactly what is expected according to the reaction scheme represented by eq 10 and 11. Consider the reaction sequence given by eq 12 and 13.

$$2\mathrm{HOAc} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{H_2O} + \mathrm{Ac_2O} \qquad (12)$$

$$\mathrm{CH_2{=}CHOAc} + \mathrm{H_2O} \xrightarrow[\mathrm{Pd(II)}]{k_2} \mathrm{CH_3CHO} + \mathrm{HOAc} \qquad (13)$$

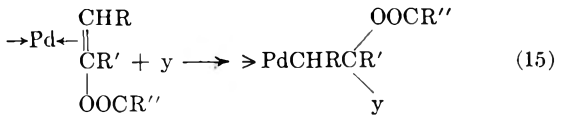
When k_1 is rate determining, the addition of Ac_2O would be expected to have little effect on the rate of the overall reaction. In fact at low [chloride] when k_1 is rate determining, a change in [Ac_2O] by a factor of 10 decreases the rate by a factor of only 2. However, at high [chloride] when eq 12 must reach equilibrium and eq 13 becomes rate determining, addition of Ac_2O strongly inhibits the rate. The failure to observe Ac_2O inhibition in a previous study[5] can also be explained on the basis of this scheme. These studies of the effect of [Ac_2O] were at very low chloride concentrations where k_1 was almost certainly rate determining. Under these conditions inhibition by Ac_2O would not be expected to be observed.

The next reason to believe that water is the reactive species is the rate expression in the Pd(II)-catalyzed region (eq 9). A recent study[12] by the author of the Pd(II)-catalyzed saponification of vinyl acetates in wet acetic acid indicated that the following rate expression was operative where the exponent n is about 1.4.

$$\text{rate} = k_{\mathrm{H}}[\mathrm{Li_2Pd_2Cl_6}][\mathrm{C_2H_3OAc}][\mathrm{H_2O}]^n/[\mathrm{LiCl}] \qquad (14)$$

This rate expression is of the same form as eq 9 if 4 is H_2O. From a knowledge of the value of k_H at higher [H_2O] and the rate of decomposition in this study, an estimate of the equilibrium water concentration when eq 13 is the rate-determining reaction at 0.3 M [Ac_2O] indicates that this concentration is in the range of 0.01–0.05 M [H_2O]. Of course, there is considerable uncertainty in the extrapolation from the range of water concentrations in the hydration study (0.5–5.0 M [H_2O]) to the conditions of the present study.

The final piece of evidence in favor of water being the reactive species is provided by the qualitative observations on the effect of enol acetate structure on rate. The hydration of enol acetates also does not have a strong retardation of rate by substitution on vinylic carbons while in other exchange reactions, such as vinylic ester exchange, substitution does strongly retard rate. The rate-determining step for both reactions is the oxypalladation reaction (y = OAc^-, H_2O) shown in eq 15. The reason for the different



(15)

substituent effects is believed to be the lower steric requirements of H_2O as compared to acetate.

The formation of water in acetic acid in the presence of acetic anhydride would not be expected on the basis of previous experience and the possibility of its formation in the systems used in the present studies should be examined. The hydrolysis of Ac_2O in wet acetic acid has been studied by several workers,[13-16] but the author is aware of only one study of the reverse reaction and equilibirum. This study[17] was carried out in the gas phase at over 400° so is of little use for present purposes. The reaction of Ac_2O with water is slow in the absence of catalysts but is accelerated considerably by addition of protonic acids such as $HClO_4$. The reaction of Ac_2O with equimolar quantities of water catalyzed by small amounts of $HClO_4$ (0.001 M) is rapid and complete and is used to prepare essentially anhydrous acetic acid with water contents of less than 0.01%.[18]

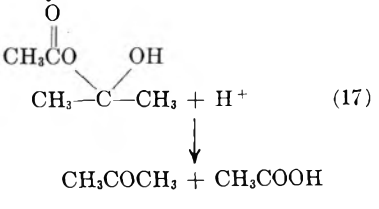
Two questions must be answered. (1) Are the water contents required to explain the rate data in this study too large to be reasonable? (2) Is it reasonable that these amount of water are formed under the reaction conditions *via* eq 12 when in pure acetic acid the equilibria is well to the left? In answer to the first question a water content of 0.01% for "essentially anhydrous" is equivalent to 0.006 M which is slightly less than the range of 0.01 to 0.05 M obtained by the extrapolation of rate data from wet acetic acid. Thus the water contents required are only a little above that found in what is usually considered to be dry acetic acid.

In regard to the second question, although the equilibrium represented by eq 12 is far to the left in pure acetic acid, it might be expected to be shifted to the right by protons or metal salts because of solvation of the water. These reaction energies, of course, are significant. In water the hydration energy of the proton is 263 kcal while that of Li^+ is 125 kcal and that of Na^+ is 100 kcal.[19] The author knows of no studies on the effect of metal salts on this equilibrium. It has been reported that 0.5 M $HClO_4$ solutions with initial water contents of 0.005% will gradualy increase in water content to several hundredths of 1% over a period of a month or more.[18] This could be due to water pickup from the glassware but could also result from eq 12. A reaction which could proceed by a mechanism analogous to eq 12 and 13 is the acid-catalyzed decomposition of isopropenyl acetate to give acetone and Ac_2O.[20] Water could be

$$\mathrm{CH_2{=}C(CH_3)OCOH_3} + \mathrm{H^+} \longrightarrow \mathrm{CH_3COCH_3} + \mathrm{Ac_2O} \qquad (16)$$

formed by eq 12 and then used to hydrate the ester in an acid-catalyzed addition.

$$\mathrm{H_3O^+} + \mathrm{CH_2{=}C(CH_3)OCOCH_3} \longrightarrow$$



(17)

(12) P. M. Henry, *J. Org. Chem.*, **38**, 2766 (1973).

(13) A. Benrath, *Z. Phys. Chem. (Leipzig)*, **67**, 501 (1909).

(14) K. J. P. Orton and M. Jones, *J. Chem. Soc.*, **101**, 1708 (1912).

(15) L. H. Greathouse, H. J. Janssen, and C. H. Haydel, *Anal. Chem.*, **28**, 357 (1956).

(16) C. J. Malm, L. J. Tanghe, and J. T. Schmitt, *Ind. Eng. Chem.*, **53**, 363 (1961).

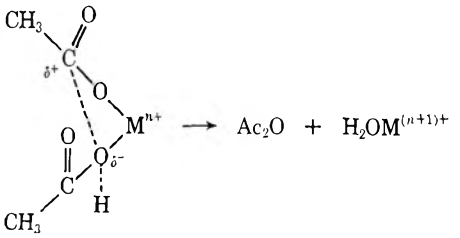
(17) W. Mühlhäusser and M. Trautz, *Z. Phys. Chem. Bodenstein-Festband*, 319 (1931); *Chem. Abstr.*, **25**, 5337[1] (1931).

(18) H. J. Keily and D. N. Hume, *Anal. Chem.*, **36**, 543 (1964).

(19) L. Brewer, L. A. Bromley, P. W. Gilles, and N. L. Lofgren, "Chemistry and Metallurgy of Miscellaneous Materials," L. L. Quill, Ed., McGraw-Hill, New York, N. Y., 1950, p 165 ff.

(20) E. A. Jeffrey and D. P. N. Satchell, *Chem. Ind. (London)*, 1444 (1960).

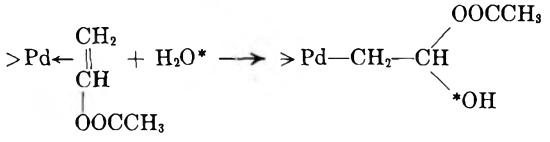
The present work does not give much evidence as to possible catalysis of the formation of water. The kinetics require the order in Pd(II) be less than one. A possible route involves reaction on a positive metal ion center. The thermal decomposition of $Cu(OAc)_2$ has been reported to give acetic anhydride.[21]



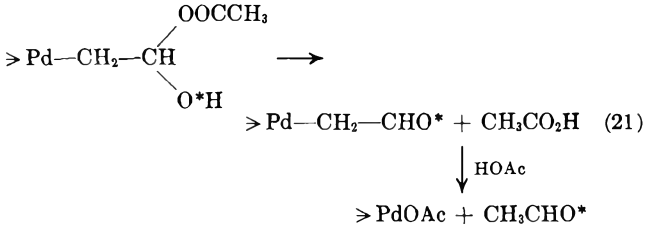
$$\longrightarrow Ac_2O + H_2OM^{(n+1)+} \quad (18)$$

One test of this mechanism would be to run the reaction using an ^{18}O label. As shown below, the ^{18}O label in the acetic acid should end up in the acetaldehyde.

$$2CH_3CO_2{}^*H \longrightarrow (CH_3CO^*)_2O^* + H_2O^* \quad (19)$$



(20)



(21)

$$\downarrow HOAc$$

$$>PdOAc + CH_3CHO^*$$

Other mechanisms such as those given by eq 1 and 2 and 3–6 would predict different distributions. This experiment was tried several times, but two experimental difficulties prevented the obtaining of useful results. First, the exchange of vinyl acetate with labeled solvent[6] (eq 22) is much faster than decomposition, and second, the exchange of acetaldehyde product with the solvent is also fast (eq 23). Perhaps a system could be found which would permit this experiment to give definitive results.

$$CH_2{=}CHO_2CCH_3 + CH_3CO_2{}^*H \longrightarrow CH_2{=}CHO_2{}^*CCH_3 + CH_3CO_2H \quad (22)$$

$$CH_3CO_2{}^*H + CH_3CHO \longrightarrow CH_3COO^*H + CH_3CHO^* \quad (23)$$

Finally, the dependence on [LiOAc] (Figure 1) cannot be explained on the basis of present results nor can the disagreement with earlier workers[5] who found NaOAc was a mild inhibitor at low [NaOAc]. However, the reaction condition for the two sets of runs were quite different. In the present work the concentration of [LiCl] was about 0.15 *M* while in the previous work there was no added chloride. Thus not too much significance can be attached to these differences.

Experimental Section

Materials.—Sources of most chemicals and preparation of stock solutions have been described previously.[6,7]

Kinetic Runs.—Vpc analysis was used for all runs. A 6-ft Carbowax 20M column programmed from 80 to 200° at 7.5°/min with a helium flow rate of 60 ml/min was used for all runs. *m*-Xylene was used as internal standard. Runs were made on 1-, 2-, and 10-ml scales in tubes sealed with serum caps or pop bottle tops. In a given run, all the ingredients except vinyl acetate were added and the reaction mixture was heated on a steam bath for an hour. The run was cooled to room temperature, put in a 25° bath, and the run started by addition of vinyl acetate. In some runs the heating period was eliminated without an effect on the rates.

The reproducibility of the data was poorer than, for instance, the vinyl ester exchange. Rates of decomposition were reproducible to only about 20%.

Runs were usually only followed for 600 hr as after that period solids began to precipitate.

Acknowledgment.—The author gratefully acknowledges helpful discussions with Dr. H. G. Tennent and Professors H. Taube, H. Goering, and the late S. Winstein and the assistance of Mr. F. J. Kriss who did most of the laboratory work.

Registry No.—Palladium(II) chloride, 7647-10-1; vinyl acetate, 108-05-4; acetic anhydride, 108-24-7.

(21) T. Chang and P. Kao, *J. Chem. Eng. (China)*, **4**, 160 (1937); *Chem. Abstr.*, **31**, 6614[1] (1937).

Reductive Dehalogenation of Aryl Chlorides by Alkali Metals and Sodium Naphthalenide. Evidence for Radical Intermediates

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On treatment with sodium or sodium naphthalenide (NaNp), aryl halides undergo reductive dehalogenation. When the aryl halide is *N*-(*o*-chlorobenzal)aniline (1), a molecule of the ether solvent is observed to add to the imine group during the reductive dehalogenation. This reaction is used here as a probe to determine the mechanism whereby the hydrogen atom is abstracted from the solvent. With isopropyl methyl ether as the solvent, attack occurs preferentially on the α H of the isopropyl group. This reaction is most plausibly explained by the aryl radical (generated by the loss of chloride ion from the radical anion of 1) abstracting the proton before it is reduced to an aryl anion. This same behavior is observed when NaNp is used as the dehalogenating agent.

In our earlier examination[1] of the reductive dehalogenation of *N*-(*o*-chlorobenzal)aniline (**1**) by alkali metals, the capture of solvent-derived reactive intermediates was observed (eq 6). The mechanism for the reaction can be formulated as eq 1, 2, 3, and 6 or 1, 4, 5, and 6, the chief distinction being whether or not the aryl radical formed in the initial reduction of **1** (ArCl, eq 1) abstracts a hydrogen from the solvent (HS) faster than it is reduced to an aryl anion. In the case of

$$\mathrm{ArCl} \xrightarrow{e} \mathrm{Ar}\cdot + \mathrm{Cl}^- \quad (1)$$

$$\mathrm{Ar}\cdot + \mathrm{HS} \longrightarrow \mathrm{ArH} + \mathrm{S}\cdot \quad (2)$$

$$\mathrm{S}\cdot \xrightarrow{e} \mathrm{S}^- \quad (3)$$

$$\mathrm{Ar}\cdot \xrightarrow{e} \mathrm{Ar}^- \quad (4)$$

$$\mathrm{Ar}^- + \mathrm{HS} \longrightarrow \mathrm{ArH} + \mathrm{S}^- \quad (5)$$

$$\mathrm{ArCl(or\ ArH)} + \mathrm{S}^- \longrightarrow \mathrm{SArCl}^-\ \mathrm{(or\ SArH}^-) \quad (6)$$

alkyl radicals generated by strong reducing agents, extremely rapid reductions have been detected,[2] but opposing views have been expressed for aryl radicals.[3]

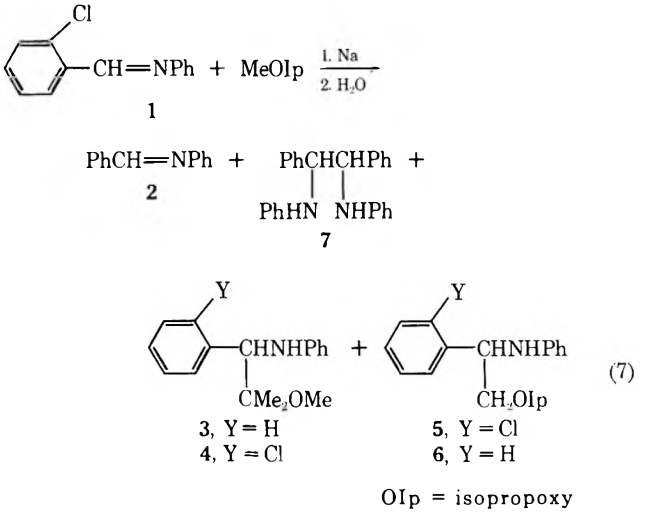
In our initial efforts[1] to use this reaction as a chemical probe and assess the reactive capabilities of the aryl radicals, the competitive behavior of a solvent mixture was examined. However, interpretation was complicated by the basicity differences of the components which can perturb the solvent ratio in the vicinity of the reaction site. The present study avoids this problem by using isopropyl methyl ether (IME) as the solvent. IME was selected since the two alkyl groups contained reactive α hydrogens as far apart on the reactivity scale as possible (primary *vs.* tertiary) and the products formed would not be diastereomeric mixtures as was the case in the earlier study.[1]

The reaction between **1** and sodium proceeded rapidly in IME at room temperature and was essentially complete in 4 hr. Examination of the reaction product by gas chromatography (vpc) disclosed four peaks. The second peak proved to be **1** and the first its dechlorinated analog *N*-benzalaniline (**2**). The remaining two were isolated by preparative vpc. Analytical and spectral data established that the third peak was *N*,1-diphenyl-2-methoxy-2-methylpropylamine (**3**). The fourth peak was a mixture of two compounds and complete resolution could not be achieved by vpc. Column chromatography provided the major component which was identified as 1-(*o*-chlorophenyl)-2-methoxy-2-methyl-*N*-phenylpropylamine (**4**).

The second component of this mixture was the isomeric compound 1-(*o*-chlorophenyl)-2-isopropoxy-*N*-phenylethylamine (**5**). This identification was based on a comparison of the spectral properties of **4** with those of the mixture of **4** and **5**.

The mass spectrum of the mixture showed small but characteristic peaks at $M^+ - OCH_3$ and $M^+ - OIp$ while that of **4** showed only the former. The nmr spectrum of the mixture also supported the presence of **5**. The existence of **6** was indicated by an $M^+ - OIp$ peak in the mass spectrum[4] of the vpc peak corresponding to **3** but supportive evidence (nmr or vpc resolution) could not be obtained because of the small quantities involved.

The dimeric diamines **7** were also detected in the reaction product by their characteristic benzylic proton absorption in the nmr spectrum. Thus the overall reaction was quite analogous to that observed with diethyl ether and tetrahydrofuran, *i.e.*, eq 7. The



(7)

possibility of reductive dechlorination proceeding in the reaction products (*e.g.* **4** → **3**) can be ruled out by the fact that the product composition remained unchanged once the reaction was complete (see Table I, Experimental section). This is not surprising since

(1) J. G. Smith and I. Ho, *J. Org. Chem.*, **37**, 4260 (1972).

(2) (a) J. F. Garst, *Accounts Chem. Res.*, **4**, 400 (1971), and references therein; (b) W. Adam and J. Arce, *J. Org. Chem.*, **37**, 507 (1972); (c) S. Bank and J. F. Bank, *Tetrahedron Lett.*, 4581 (1971); (d) W. C. Danen, T. J. Tipton, and D. G. Saunders, *J. Amer. Chem. Soc.*, **93**, 5186 (1971).

(3) (a) G. D. Sargent, *Tetrahedron Lett.*, 3279 (1971); (b) T. C. Cheng, L. Headley, and A. F. Halasa, *J. Amer. Chem. Soc.*, **93**, 1502 (1971).

(4) Determined on a MS-30 vpc–mass spectrometer by J. M. Miller, Department of Chemistry, Brock University, St. Catharines, Ontario.

the products of the reaction are amine anions and further electron transfers from the reducing agent are discouraged.

Discussion

These product analyses establish that the preferred point of attack on IME is the α H of the isopropyl group. The question is whether this reflects attack by an aryl radical or anion. As a general rule, proton abstraction by a radical occurs with a relative reactivity sequence of tertiary > secondary > primary. This sequence holds true for a wide variety of substrates and radicals.[5] In contrast, the sequence is reversed, *i.e.*, primary > secondary > tertiary, if the attacking species is an anion.[6,7]

Thus it appears that the products observed can be attributed to a radical attack upon the solvent (*i.e.*, reaction 2) although a minor contribution involving anionic attack *via* reactions 4 and 5 cannot be excluded. Indeed, the relative reactivity per hydrogen of primary *vs.* tertiary protons in IME is approximately[8] 1:6, a value similar to that observed[5] for hydrogen abstraction by a variety of radicals.

The possibility that the primary α's of the solvent are actually removed more rapidly than the tertiary but, because of a slower rate of addition of the primary solvent-derived intermediate to the imine, the tertiary solvent-derived intermediate predominates in the product can be countered by the following. Whatever the nature of the solvent-derived intermediates, the amount initially formed equals the moles of organic chlorine lost in the reduction. This amount can be calculated from the product analysis;[9] the difference between this value and the amount of the solvent-derived intermediates[10] appearing in the products represents those intermediates which are not captured but decompose. *Assuming all such intermediates* are formed by attack at the primary α H's of IME, then attack occurs equally at the methyl and isopropyl groups of the solvent. The relative reactivity (per H) is reduced from the observed tertiary:primary = 6:1 to 3:1. Thus, even on this assumption, the results favor an interpretation based upon radical attack on the solvent.

Supporting evidence for deprotonation of the solvent by aryl radicals was obtained with a trapping reagent. The dechlorination of **1** was effected by sodium in a mixed tetrahydrofuran–cumene solvent. Bicumyl was detected in small amounts among the reaction products. Suitable control experiments demonstrated that the bicumyl arose as a consequence of the dechlorination of **1**.

(5) This has been comprehensively reviewed by G. A. Russell in "Free Radicals," J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, Chapter 7, pp 275–331.

(6) See the discussion by D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1.

(7) Particularly pertinent references involving the reaction of butyllithium with a variety of ethers are (a) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972); (b) J. C. Carnahan, Jr., and W. D. Closson, *ibid.*, **37**, 4469 (1972); (c) R. A. Ellison, R. Griffin, and F. N. Kotsonis, *J. Organomet. Chem.*, **36**, 209 (1972).

(8) This assumes that the capture of the solvent-derived fragments by a *single* substrate best approximates the concentration of the reactive intermediates. Thus the ratio of **4** and **5** representing capture by **1** was used in this estimation.

(9) The product analyses of Table I must be converted to equivalents of monomeric units; *i.e.*, the moles of dimer must be doubled.

(10) 65–75% of the intermediates appear in the products.

The behavior described here contrasts with the conclusion of Garst[2a] and of Sargent[3a] who, on the basis of excellent supportive evidence, deduced that the radicals formed on dehalogenation are largely reduced to anions prior to any other reaction. However, it is possible that, *under the reaction conditions employed here*, the intermediate radical anion formed from **1** and sodium might not collapse to chloride ion and aryl radical until it had diffused to a region remote from the sodium. Protonation of the radical would then occur prior to further reduction.

By using sodium naphthalenide as the reducing agent, the physical limitations just described can be eliminated. Since NaNp would not form in IME at room, temperature this was done[11] at −78° using a 2:1, 3:1 and 4:1 ratio of naphthalene to **1**. The composition of products from the first reaction corresponded closely to those obtained in the incomplete (2 hr) reaction with sodium. In the case of the last reaction, both the nmr spectrum and the vpc analysis showed an increase in the amount of **3** relative to **4** and **5** but the ratio of the last two compounds did not change significantly from that observed in the reactions with sodium.

However, in none of these reactions was excess NaNp present. This is indicated by the position of the equilibrium between NaNp and the hydrocarbon, by the presence of **1** and the lack of any dimeric diamines **7** in the reaction products. At this moment, it must be concluded that, in the absence of excess NaNp, the reductive dehalogenation of **1** proceeds by the same radical mechanism with both NaNp and sodium. It is further suggested that NaNp and **1** react to produce the radical anion of **1** which is then the effective reducing agent in the reaction under study. It may well be that this reducing agent is not sufficiently reactive to convert the initial formed aryl radical to its corresponding anion.

Throughout the discussion, it has been assumed that the solvent-derived intermediate adding to the imine is an anion. However, bearing in mind the reducing powers of this system, it is possible that the solvent-derived radical may itself add to the unsaturated substrate. We plan to devote further consideration to this problem.

Experimental Section[12]

All operations with the alkali metal compounds were performed under nitrogen which had been scrubbed by a refluxing solution of benzophenone ketyl in xylene. The solvent, isopropyl methyl ether, was prepared in 73% yield by alkylating[13] sodium isopropoxide with dimethyl sulfate. The fraction boiling 31–32° was further purified by distillation from $LiAlH_4$ immediately before use. Cumene was dried by refluxing over sodium and distilled from sodium immediately before use.

General Procedure.—The procedure described[1] earlier was followed. A normal preparative experiment involved 2.16 g

(11) The equilibrium uptake of sodium in IME was 0.33 g-atom/mol of naphthalene.

(12) Melting points are uncorrected and were determined with a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer and the chemical shifts are reported in δ units. Analytical and preparative vapor phase chromatography (vpc) were performed on a Varian-Aerograph 1520 instrument. Mass spectra were determined on an AEI MS-30 mass spectrometer. Silica gel (70–325 mesh ASTM) from E. Merck AG was used for column chromatography and Eastman chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analyses were determined by M-H-W Laboratories, Garden City, Mich.

(13) An adaptation of the procedure reported by J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 21 (1960).

(0.01 mol) of *N*-(*o*-chlorobenzal)aniline (1), 50 ± 5 ml of IME, and 0.5 g (0.02 g-atom) of sodium shaken for the chosen time interval. The red-brown solution was drained from the excess metal, cooled to −60°, and quenched by injecting 2 ml of methanol.

The IME was recovered by distillation, the residue was treated with water, and the organic products were isolated by an ether extraction. Evaporation of the ether extracts followed by a 24-hr pumping provided solvent-free product which could be analyzed by nmr (see Table I). Analytical separations by vpc were accomplished using flame ionization detectors, a 5 ft by $^1/_8$ in. column packed with 10% Carbowax 20M on 100–120 mesh Chromosorb W at 195° and a He flow rate of 30–40 ml/min. Spiking with authentic samples was used to characterize the elution peaks.

TABLE I

ANALYSIS OF THE REACTION PRODUCTS

	Using sodium, reaction time, hr					Using NaNp, mole ratio[b]		
Compd	2[a]	4	6	8	24	2	3	4
1	32	tr[c]				36	23	13
2	20	tr[c]				23	20	39
3	3	13	13	13	16	7	29	35
4	27	35	35	34	29	26	20	9
5	10	17	16	17	16	8	8	4
7 (meso)	2	18	18	19	18			
7 (racemic)	2	17	18	17	20			

[a] About 4% of the chlorine-containing dimers analogous to 7 were observed. [b] Mole ratio of naphthalene to 1; vpc analyses. [c] <1%.

The products from a 24-hr run were separated by preparative vpc using a 10 ft by $^3/_8$ in. column packed with 10% Carbowax 20M on 60–80 mesh Chromosorb W operated at 185° with a He flow rate of 60 ml/min.

The first peak which eluted was identified as *N*-benzalaniline by comparison of its ir and nmr spectra with those of a reference sample. The second peak, 1, was too small to collect in the 24-hr reactions.

The third peak which eluted was recrystallized from methanol to give **3** as a white solid: mp 96–98°; ir (KBr) 3370, 3060, 2990, 1600, 1500, 1320, 1060, 740, 700, and 690 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (s, 3) and 1.27 (s, 3) (CH_3CCH_3), 3.20 (s, 3, OCH_3), 4.20 (s, 1, benzylic H), 4.90 (br s, 1, NH, exchanging with D_2O), 6.4–7.5 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 255 (1, M^+), 224 (1, $M^+ - MeO$), 183 (15), 182 (100, $M^+ - C_4H_9O$), 104 (8), 77 (18), 73 (22).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.95; H, 8.29; N, 5.49. Found: C, 80.22; H, 8.02; N, 5.53.

The fourth peak which eluted was a partially resolved mixture of two compounds. Chromatography on 60 g of silica gel with benzene as eluent provided the major component and recrystallization from methanol gave **4**: mp 87–90°; ir (KBr) 3370, 3060, 2990, 2930, 1600, 1510, 1320, 1050, 730, 700, and 680 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (s, 3), 1.40 (s, 3) (CH_3CCH_3), 3.27 (s, 3, OCH_3), 4.93 (br s, 2, NH and benzylic H, NH exchanging with D_2O), 6.4–7.7 (m, 9, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 291 (0.6, M^+), 289 (1.5, M^+), 260 (0.6, $M^+ - OCH_3$), 258 (1.7, $M^+ - OCH_3$), 218 (33, $M^+ - C_4H_9O$), 217 (14), 216 (100, $M^+ - C_4H_9O$), 77 (28), 73 (82).

Anal. Calcd for $C_{17}H_{20}NClO$: C, 70.46; H, 6.96; N, 4.83; Cl, 12.24. Found: C, 70.51; H, 7.14; N, 4.78; Cl, 12.46.

The mixture of **4** and **5** as originally isolated by preparative vpc had an nmr spectrum resembling **4** with an additional absorption at 1.20 [half of double d, $OCH(CH_3)_2$] and 3.3–4.0 [m, $CH_2OCH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 291 (0.5, M^+), 289 (1.2, M^+), 260 (0.5, $M^+ - OCH_3$), 258 (1.2, $M^+ - OCH_3$), 232 (0.4, $M^+ - OIp$), 230 (1.1, $M^+ - OIp$), 218 (35), $M^+ - C_4H_9O$), 217 (15), 216 (100, $M^+ - C_4H_9O$), 180 (20), 179 (10), 77 (58), 73 (61), 51 (19).

Reaction in Tetrahydrofuran–Cumene Mixed Solvents.—The procedure was the same as that described. The solvent composition was determined by weighing the reaction vessel after each of the components was distilled in. In a typical experiment, 45 g of tetrahydrofuran (THF) and 31 g of cumene were used with a 24-hr reaction time. The quenched reaction mixture was distilled to remove the solvent and the residue analyzed by vpc as described earlier. Bicumyl[14] (1% of the total reaction mixture) eluted earlier than any of the other components and was identified by spiking with an authentic sample. A confirmatory identification was made using a 5 ft by $^1/_8$ in. column packed with 10% UCW-98 on 100–120 mesh Chromosorb W with the same operating conditions.

Control experiments were performed with sodium metal and THF–cumene, both with and without *N*-benzalaniline (2). No bicumyl was detected, showing that neither sodium metal alone nor the reductive dimerization of 2 was responsible for the bicumyl observed when 1 was present.

Reductive Dehalogenations with Sodium Naphthalenide.—The sodium naphthalenide was prepared by stirring a mixture of excess sodium, naphthalene (0.01, 0.015, or 0.02 mol), and IME (~40 ml) in a flask equipped with a side arm and stopcock at −78° for 8 hr. The dark green solution was drained from the excess metal through the side arm into a second N_2-filled flask precooled to −78°. The Schiff base 1 (0.005 mol) dissolved in 1–2 ml of IME was injected through a septum into the stirred solution. Rapid decolorization to a light yellow color occurred. The solution was stirred for 8 hr at −78°, then warmed to room temperature, and diluted with water, and the products were isolated by an ether extraction. Analyses were conducted as described except that the vpc column length was increased to 10 ft so as to estimate the ratio of **4** and **5**. This was necessary since the large amount of naphthalene made the nmr analysis unreliable except in the case of the 2/1 reaction. Here the nmr analysis showed **1** (36%), **2** (29%), **3** (5%), **4** (22%), and **5** (8%). None of the nmr spectra showed the presence of **7**.

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Registry No.—**1**, 5877-49-6; **3**, 41203-41-2; **4**, 41203-42-3; **5**, 41203-43-4; sodium naphthalenide, 25398-08-7.

(14) Reference sample prepared according to C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).

Solvolysis of Optically Active 1-Phenylethyl Chloride. Polarimetric Rates, Deuterium Isotope Effects, Product Configurations, and Mechanisms[1]

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For 1-phenylethyl chloride, the rate of change of optical activity is found to exceed the solvolysis rate by factors of 1.72, 1.16, and 1.07, respectively, in solvents 97% 2,2,2-trifluoroethanol–3% water (97 T), 80 vol. % ethanol–water (80 E), and 60 vol. % ethanol–water (60 E). α- and β-deuterium effects on the rates of change of optical activity are observed to be similar to those on the rates of solvolysis. The products in all three solvents show appreciable optical activity, indicating that nucleophilic attack on the carbonium ion fragment occurs before the leaving group has completely diffused away. The importance of internal ion-pair recombination is indicated by the initial formation of 1-phenylethyl chloride in sixfold excess over 1-phenylethyl trifluoroethyl ether in the reaction of undissociated HCl with styrene in pure trifluoroethanol (100 T). These results can be nicely accommodated by the solvolysis scheme involving two ion-pair intermediates. Applying this scheme to the present results one concludes that in these solvolyses the tight ion pair is the key intermediate; in 97 T–100 T for every 100 tight ion pairs produced 80 return, 13 solvolyze (*via* the solvent separated ion pair), and 7 invert their configuration; in 60 E, of 100 formed, 70 return, 28 solvolyze, and 1.4 invert. α- and β-deuterium effects on the rates of acid-catalyzed racemization of 1-phenylethanol in trifluoroethanol–water mixtures indicate that the rate-determining step is the ionization of the C–O bond of the conjugate acid.

In earlier publications from these laboratories,[2-5] the effects of α- and β-deuterium substitution on the rates of solvolysis of a series of substituted 1-phenylethyl chlorides and bromides were interpreted to indicate that unsubstituted 1-phenylethyl chloride (and bromide) and their more reactive ring-substituted derivatives solvolyze in aqueous ethanol and aqueous trifluoroethanol solvents *via* a transition state in which there is no partial covalent bond between the reacting carbon and either leaving or incoming group. This is consistent with the rate-determining step in each case being the diffusion apart of an ion pair or the conversion of one type of ion pair to another, but is inconsistent with it being either the formation of an ion pair from the covalent reactant, or nucleophilic attack on the covalent reactant, ion pair, or free carbonium ion.

In these latter reactions, the rate-determining step leads either directly to or directly from a state having at least one of the reactant groups covalently attached to carbon; therefore these transition states must have partial covalent attachment between carbon and incoming or leaving groups, a situation inconsistent with the isotope effect evidence.

If conversion of one ion pair to another is the rate-determining step, then the first ion pair must undergo dominant recombination to covalent reactant (ion pair return).[6] Traditionally, racemization of reactant has been associated with ion-pair return even though return can occur predominantly without racemization.[7] We were, therefore, encouraged to look for racemization of optically active 1-phenylethyl chloride concurrent with solvolysis. The most straightforward way of doing this appeared to be to determine whether or not the rate of change of optical activity of a solvolyzing solution exceeded the solvolysis rate measured by the conductance method. The recent availability of more sensitive commercial polarimeters based on the Faraday magnetooptic effect made it more likely that small rate differences could be conclusively observed and also made the measurement of α- and β-deuterium effects on polarimetric rates appear practical. After this work was undertaken, De La Mare, Hall, and Mauger[9] reported a polarimetric kinetic study of the solvolysis of 1-phenylethyl chloride and related phenomena in aqueous dioxane. The results of the two investigations are similar in some important aspects but the different solvent systems are known to be sufficiently different in behavior[10] for the results to be complementary rather than redundant.

Experimental Section

A. Materials.—All solvents were carefully purified for conductance work by standard methods reported earlier.[2,3] Mixed solvents were prepared by weighing the components, although EtOH–H_2O mixtures are reported in accord with tradition in volume per cent.

1-Phenylethyl alcohol and its β-d_3 analog were prepared from the corresponding ketones by lithium aluminum hydride reduction. The β-d_3 ketone was prepared from the hydrogen compound by exchange in dioxane–D_2O, triethylamine solutions. The α-d alcohol was prepared from acetophenone by reduction with lithium aluminum deuteride. Chlorides for conductance work were prepared from the alcohols by treatment with the hydrogen chloride. Full experimental details have been reported previously.[2,3]

The 1-phenylethyl alcohols were resolved *via* the brucine salts of their hydrogen phthalate esters by the method of Downer and Kenyon.[11] The optically active alcohols were obtained by first treating with dilute hydrochloric acid and ether to decompose the brucine salt and then by refluxing the ether layer with 4 *N* NaOH for several hours to hydrolyze the ester. In typical

(1) Taken in part from the thesis submitted by P. C. Vogel in September of 1967 to the Graduate School of Indiana University in partial fulfillment of the requirements for the Ph.D. Degree.

(2) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, **90**, 418 (1968).

(3) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, **91**, 4838 (1969).

(4) V. J. Shiner, Jr., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *J. Amer. Chem. Soc.*, **90**, 7171 (1968).

(5) V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, p 105 ff.

(6) S. Winstein, B. Appel, R. Baker, and A. Diaz, Special Publication No. 19, The Chemical Society, London, 1965, p 109.

(7) H. L. Goering and H. Hopf, *J. Amer. Chem. Soc.*, **93**, 1224 (1971). However, it has been argued that racemization could be an entirely different process not associated with solvolysis.[8]

(8) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, p 162.

(9) P. B. D. De La Mare, D. M. Hall, and E. Mauger, *Recl. Trav. Chim. Pays-Bas*, **87**, 1394 (1968).

(10) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 287 (1965).

(11) E. Downer and J. Kenyon, *J. Chem. Soc.*, 115b (1939).

preparations the optically active materials were found to have the following specific rotations.

Alcohol	$[\alpha]_{5461}$(neat), deg
1-Phenylethyl	−46.8
1-Phenylethyl-α-*d*	+30.3
1-Phenylethyl-β-d_3	−41.5

These materials were stored in glass vials in a freezer until used.

Optically active chlorides for the polarimetric work were prepared from the alcohols by the method of Burwell, Shields, and Hart.[12] In typical preparations, chlorides with the following specific rotations were obtained.

Chloride	$[\alpha]_{5461}$(neat), deg
1-Phenylethyl	+123
1-Phenylethyl-α-*d*	−39.4
1-Phenylethyl-β-d_3	+113.4

The nmr spectra of all materials were in accord with the assigned structures and revealed no absorptions due to impurities.

B. Conductance Measurements.—The conductometric method of Murr and Shiner[13] was used. Details of this, the conductance parameters, and the statistical method used to treat the kinetic data have all been reported before.[2,3,13]

C. Polarimetric Measurements.—The polarimetric measurements were made using a Bendix Model 965 automatic balancing polarimeter system. A modified Vidar 500 integrating digital voltmeter was used to convert the output from the Bendix into digital display and to BCD form for automatic recording. The digital voltmeter and a Computer Measurements Corp. time interval meter were connected *via* control electronics to a Tally paper tape punch, so that, at preset time intervals, readings from the time interval meter and the digital voltmeter could be punched onto paper tape, thus allowing completely automatic collection of data. The intervals between readings could be adjusted to any value, down to three readings per second. In routine kinetic runs about 200 readings were taken over a period of about two half-lives. The data were transferred from paper tape to computer cards, by an IBM 47 tape-to-card converter, in a format suitable for direct entry into a least-squares program used to treat the results.[14]

The digital voltmeter was calibrated against standard sucrose solutions and found to give a linear response over the range of operation used in this work. It was adjusted so that the display registers (in millivolts) corresponded directly to rotations (in millidegrees) of a sample in the polarimeter. Rotations of optically active samples were measured to the nearest $^1/_{10}$ of a millidegree, although the uncertainty claimed by the manufacturer is $^3/_{10}$ of a millidegree. Reading errors were thus estimated to be of the order of 0.3–1% of the overall rotation changes which were in the range from 50 to 150 millidegrees.

At the beginning of this work we experienced difficulty in reproducing rate constants, and traced this to inadequate temperature control of the polarimeter cell. We finally used a 5-cm jacketed fused quartz cell supplied by Opticell. This was modified to allow a calibrated thermistor probe to be inserted through the side arm of the cell to record the temperature of the sample in the cell. The cell was cooled by circulating a mixture of ethylene glycol–water from a thermostat through the jacket. The thermostat was adjusted to control the cell temperature to 25.00 ± 0.01°.

The solutions for kinetic runs with the chlorides were prepared by adding enough of the chloride to the solvent in a small flask to produce a concentration of 0.02–0.03 *M* in substrate. After mixing well, the solution was placed in the polarimeter cell and allowed to come to thermal equilibrium before taking readings; usually about 3–5 min were required. At this concentration the initial rotations of the solutions were about 100–150 millidegrees.

The same method was used for reactions of the 1-phenylethyl alcohols and HCl in various TFE solutions. The standard solutions of HCl in TFE were prepared by bubbling dry HCl into the TFE solution and determining the concentration by titration with standardized NaOH solutions. The alcohol was then added to a solution of HCl in TFE and placed in the polarimeter cell.

D. Nmr Rate Measurements.—All spectra were recorded with a Varian HA-100 instrument equipped with an internal lock. Reactions were carried out using approximately 0.5 ml of 0.05 *M* solution in 5-mm nmr tubes. Rates were determined by comparing the recorded peak heights of the methyl proton doublet of 1-phenylethyl chloride, 1-phenylethyl trifluoroethyl ether, or 1-phenylethyl alcohol with that of an added internal standard, acetonitrile, at various intervals over approximately two half-lives. In trifluoroethanol solvent, the center of the methyl doublet (J = 6 Hz) of 1-phenylethyl chloride is 11 Hz upfield from acetonitrile; the center of the methyl doublet of 1-phenylethyl trifluoroethyl ether is 43 Hz upfield from acetonitrile, not resolved from the similar doublet of 1-phenylethyl alcohol. In pure trifluoroethanol the solvolysis (at ~0.05 *M*) proceeds only to the extent of about 30%, reaching apparent equilibrium in about 1000 sec. In the presence of a slight excess of potassium hydroxide, a twofold excess of potassium hydroxide, or a twofold excess of pyridine the appearance of ether product followed the first-order rate law smoothly for more than two half-lives; the first-order rate constants at 29° (the probe temperature) under these conditions were 1.19, 1.17, and 1.12 × 10^{-3} sec^{-1}, respectively. In 97% trifluoroethanol–3% water at the same probe temperature the solvolysis of 1-phenylethyl chloride proceeds to apparent completion *via* a first-order process in the absence of a base (k = 1.26 × 10^{-3} sec^{-1}) or in the presence of 2 equiv of pyridine (k = 1.17 × 10^{-3} sec^{-1}).

The rate of conversion of 1-phenylethanol to the chloride in solution in pure trifluoroethanol with HCl was also determined by nmr. These processes were only roughly first order as expected; for 0.05 *M* alcohol the rough pseudo-first-order rate coefficient was 10 × 10^{-3} sec^{-1} for 0.10 *M* HCl and 5 × 10^{-3} sec^{-1} for 0.033 *M* HCl.

The formation of 1-phenylethyl chloride from 0.106 *M* HCl and 0.05 *M* styrene in trifluoroethanol was observed to follow with reasonable accuracy the first-order rate law, k = 5.2 × 10^{-3} sec^{-1}. During the first 10 min of reaction the ratio of the initial peak height for 1-phenylethyl chloride to that for 1-phenylethyl trifluoroethyl ether was 6.0–6.5. This ratio decreased to 4.5 after 0.5 hr and was again observed at that value after 18 hr. Since the rate constant for solvolysis of 1-phenylethyl chloride in pure TFE was about 1.19 × 10^{-5} sec^{-1}, the initial addition of 0.1 *M* HCl to 0.05 *M* styrene occurs much faster than the reverse solvolysis. From the ratio of peak heights after 18 hr, the equilibrium constant for the conversion of 1-phenylethyl chloride to 1-phenylethyl trifluoroethyl ether plus HCl can be calculated, as can the second-order rate constant for the reaction of the ether with HCl. This showed that the initial formation of 1-phenylethyl chloride was faster than could be accounted for in terms of intermediate formation of the trifluoroethyl ether. Thus, the initial ratio of products observed by nmr must be the ratio characteristic of the addition reaction itself.

E. Product Studies.—The products from the solvolysis of optically active 1-phenylethyl chloride at 25° in 60 and 80% ethanol–water solvents were isolated and separated by the procedure of Okamoto and coworkers.[15] In 60% ethanol–water, 1-phenylethyl alcohol was obtained with 32.6% net inversion and in 80% ethanol it was formed with 34.2% net inversion (the balance in each case being racemic). For reactions in TFE solvents the products were identified by their retention times on vpc analysis. A Varian series 1200 gas chromatograph fitted with a flame ionization detector was used. Good separations were obtained with a 12 ft × $^1/_{16}$ in. column packed with 10% Carbowax 20M on Carbosorb P operating at 130° with nitrogen at 60 psi as the carrier gas. The observed retention times in minutes follow: 2,2,2-trifluoroethanol, 3.6; styrene, 6.0; 1-phenylethyl trifluoroethyl ether, 7.2; 1-phenylethyl chloride, 14.2; 1-phenylethyl alcohol, 39.0. It was found from control experiments that both 1-phenylethyl chloride and alcohol gave rise to a small styrene peak owing to elimination in the gas chromatograph. In 97 T, 0.05 *M* 1-phenylethyl chloride in the presence of 0.08 *M* potassium hydroxide gave 79% trifluoroethyl ether, 21% 1-phenylethanol, and less than 1% styrene. With other bases the yields of ether and alcohol, respectively were as follows:

(12) R. L. Burwell, A. D. Shields, and H. Hart, *J. Amer. Chem. Soc.*, **76**, 908 (1954).

(13) B. L. Murr, Jr., and V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **84**, 4672 (1962).

(14) Details of this least-squares program are available in the thesis of P. C. Vogel.[1]

(15) K. Okamoto, N. Uchida, S. Saito, and H. Shingu, *Bull. Chem. Soc. Jap.*, **39**, 307 (1966).

excess $CaCO_3$, 82 and 18%; excess lutidine, 81 and 19%; 0.2 *M* KOH, 84 and 16%.

Results

The results of solvolysis of 1-phenylethyl chloride and its α-*d* and β-d_3 analogs in different solvents are given in Tables I and II. For the conductance work

TABLE I

REACTION RATE CONSTANT FOR 1-PHENYLETHYL CHLORIDE AT 25°

Solvent[a]	Added reagent	Method[b]	$10^4 k_1$[c]	Optical result[d]
60 E	None	C	1.0865[e]	
60 E	None	P	1.136	28.5% inversion
80 E	None	C	0.10019[e]	
80 E	None	P	0.116	25.1% inversion
97 T	None	C	6.70	
97 T	None	P	11.53	5.7% retention
97 T	0.03 *M* pyridine	P	10.81	5.4% retention
100 T	None	P	12.50	Racemic
100 T	0.03 *M* pyridine	P	12.20	8.0% retention
100 T	0.012 *M* KOH	P	12.43	7.5% retention
100 T	0.014 *M* KOH	P	12.48	7.0% retention
100 T	0.080 *M* KOH	P	13.68	8.1% retention

[a] 60 E refers to 60 vol. % ethanol–40 vol. % water, 97 T refers to 97 wt % 2,2,2-trifluoroethanol–3 wt % water, etc. [b] P, polarimetric; C, conductometric. [c] First-order rate constants; error in polarimetric rate constants is estimated as ±2% and in conductometric rate constants as ±0.1%. [d] Figures refer to the optical rotation at the end of the kinetic run as a percentage of the initial rotation. This does not refer to the change in configuration, although this is known for the ethanol–water solvents. [e] From ref 2.

TABLE II

REACTION RATE CONSTANTS FOR DEUTERATED 1-PHENYLETHYL CHLORIDES AT 25°[a–e]

Solvent[a]	Deuterium	Method[b]	$10^4 k_1$[c]	Optical result[d]
60 E	1-*d*	C	0.944[e]	
60 E	1-*d*	P	0.970	29% inversion
97 T	1-*d*	C	5.79	
97 T	1-*d*	P	9.64	5.5% retention
97 T + Py[f]	1-*d*	P	9.44	5.7% retention
100 T	1-*d*	P	10.52	Inactive
100 T + Py[f]	1-*d*	P	10.41	8.0% retention
60 E	2,2,2-d_3	C	0.8867[e]	
60 E	2,2,2-d_3	P	0.893	26.8% inversion
97 T	2,2,2-d_3	C	5.50	
97 T	2,2,2-d_3	P	9.26	6.0% retention
97 T + Py[f]	2,2,2-d_3	P	8.91	
100 T	2,2,2-d_3	P	10.18	Inactive
100 T + Py[f]	2,2,2-d_3	P	9.54	8.3% retention

[a–e] See footnotes of Table I. [f] Py indicates presence of 0.03 *M* pyridine.

the reproducibility of the rate constant between different runs was usually ±0.1% or better and for the polarimetric runs it was usually ±1–2% but in some cases better than ±1%. All kinetic runs were observed to be accurately first order as indicated from an analysis of the error plots printed out by the computer program and a comparison of observed and calculated initial and infinity readings. For example, in an experiment with 1-phenylethyl-*1-d* chloride solvolyzing in 97% TFE at 25° the initial reading was −0.0589° observed and −0.0589° calculated; the infinity reading was −0.0040° observed and −0.0038° calculated. The calculated readings were parameters which gave the best fit of the data to the first-order rate law according to the least-squares criterion.[14]

The results for the reactions of the 1-phenylethyl alcohols with HCl in 70, 97, and 100% TFE are given in Table III. The reactions in 70 and 97% TFE were accurately first order but in 100% TFE only approximately first order.

TABLE III

RATE CONSTANTS FOR RACEMIZATION OF ACTIVE 1-PHENYLETHYL ALCOHOL (AND ITS α-*d* AND β-d_3 ANALOGS) WITH HCl IN TRIFLUOROETHANOL SOLUTIONS AT 25°

Deuterium	Solvent[a]	[HCl], mol $l.^{-1}$	$10^4 k_p$[b]	k_H/k_D
None	100 T	0.0001	~7[c]	
None	100 T	0.0013	~40[c]	
None	100 T	0.0033	~200[c]	
None	97 T	0.0087	0.264	
None	97 T	0.130	8.70	
None	97 T	0.153	12.27	
None	70 T	2.20	6.23	
1-*d*	97 T	0.153	10.33	1.187
1-*d*	70 T	2.20	5.41	1.152
2,2,2-d_3	97 T	0.153	11.03	1.112
2,2,2-d_3	70 T	2.20	5.70	1.094

[a] 70 T represents 70 wt % trifluoroethanol–water, etc. [b] Errors. [c] Errors are ~20%.

Discussion

As indicated in Table IV, the polarimetrically measured rates exceed the conductometrically measured rates in each of the three solvents used, although the difference is small in the ethanol–water solvents. In 97 T internal racemization becomes almost as fast as solvolysis, suggesting a considerable amount of ion-pair return. The occurrence of ion-pair return in 100 T is also indicated by the initial formation of a sixfold excess of 1-phenylethyl chloride over 1-phenylethyl trifluoroethyl ether in the addition of undissociated HCl to styrene; the most straightforward interpretation of this result is to conclude that the 1-phenylethyl cation–chloride ion pair formed after proton transfer from covalent HCl to styrene combines six times faster than it solvolyzes.

TABLE IV

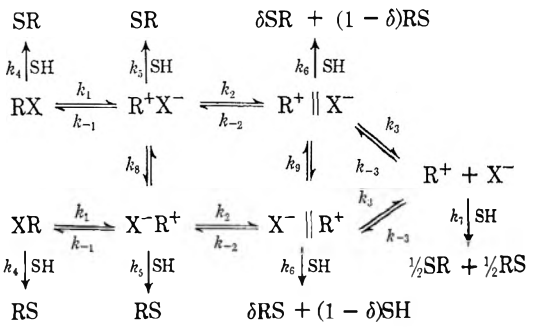
COMPARISON OF RATE CONSTANTS FOR SOLVOLYSIS OF 1-PHENYLETHYL CHLORIDE MEASURED CONDUCTOMETRICALLY (k_c) AND POLARIMETRICALLY (k_α)

Solvent	k_α/k_c[a]
60 E	1.05
80 E	1.16
97 T	1.72

[a] The error in the ratio is estimated to be ±0.02.

We have proposed in earlier publications[16] that the generalized solvolysis scheme below[17] (Scheme I) can

SCHEME I



be used to explain the presently known details of a wide variety of nucleophilic solvolytic substitution reactions. We shall, therefore, discuss the present results, as well as those obtained earlier on these specific reactions, directly in terms of this scheme. In particular, we will attempt to determine for each reaction which step in the scheme represents the rate-determining step and in which step the covalent bond that characterizes the product is formed ("product-forming step"). Particularly important in the present discussion is the designation of racemization as occurring *via* a *reaction* (with rate constant k_8 or k_9) whereby an ion-pair is converted to its enantiomer, rather than as a static property of a particular kind of ion pair.

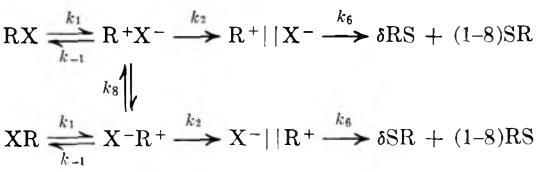
First, the nature of the solvolysis products is only consistent with their being formed predominantly before the free carbonium-ion stage but after the tight ion-pair stage. Nucleophilic attack on the substrate or on the tight ion pair[18,19] is expected to lead to product of completely inverted configuration, while product formed from the free carbonium ion should be completely racemic. It has long been known that the products of solvolysis of optically active 1-phenylethyl chloride show significant amounts of racemization and significant amounts of optical activity generally of inverted configuration. These results, recalculated to more recently determined values for the rotations of the pure enantiomers, are summarized in Table V.

In none of the solvents in which it has been determined is the racemization of reactant rapid enough to account alone for the large extent of racemization of product. It would seem reasonable to infer that, with the possible exception of acetic acid, this would be true of all solvents listed in Table V. Thus the solvolysis itself must lead to significant but unequal yields of each of the two enantiomers.

These results rule out either the substrate, the tight ion pair, or the free carbonium ion as *sole* product forming electrophile. The fact that the extent of racemization of product is not markedly changed by changing solvent from 80% aqueous ethanol to pure water[15] suggests that in these solvents the free carbonium ion is not a precursor to a significant fraction of the product. If the second ion pair were partitioned between nucleophilic attack and dissociation to the free carbonium ion, the extent of this partitioning and the extent of racemization should depend on solvent composition. Thus it appears that most of the product in ethanol–water solvents is derived from nucelophilic attack at the second ion-pair stage. In 100 T (in the presence of base) the overall result is ~8% retention of optical *rotation* in the kinetic reaction mixture. Since the starting material is racemizing almost as fast as it solvolyzes, the substitution on the ion pair intermediate directly formed from optically pure starting material must involve about 15% retention of optical rotation. In 97 T the rotation is *retained* to the extent of ~6%, indicating that the *alcohol* product is probably formed predominantly by inversion as it is in ethanol–water solutions. However, because of the lack of precise data on the extent of inversion of substitution over a range of composition of trifluoroethanol–water mixtures it is not possible to conclude that an insignificant amount of reaction in these solvents goes *via* the free carbonium ion.

Second, we have argued earlier from the fact that the α-*d* isotope effect on the rate is at or near the maximum that the steps with rate constants k_2 or k_3 must be rate determining (see introduction). This and the conclusion that the product is formed predominantly by the step with rate constant k_6 require that the scheme will fit only if the step with rate constant k_2 is the rate-determining step in the solvolysis. This is the conclusion that we had reached earlier[2,3] and can only be strictly true if the racemization of starting material observed in the present work occurs *via* k_8, the interconversion of enantiomeric tight ion pairs; *e.g.*, if racemization involved k_9, some return *via* k_{-2} would also be required and the step with rate constant k_2 could not be rate determining.

Thus, the more detailed scheme reduces for the present reactions to the following, as the simplest explanation of all of the results.[20]



In this simplified scheme the key intermediate is the tight ion pair and several of the reaction variables are simply determined by ratios of the three constants which define its partitioning among return (*via* k_{-1}), solvolysis (*via* k_2), and inversion (*via* k_8). Thus the ratio k_2/k_{-1} determines whether k_1 or k_2 is rate controlling and whether or not the α-*d* isotope effect is at its maximum.[21] k_2/k_{-1} also determines the ratio of

(16) V. J. Shiner, Jr., and R. D. Fisher, *J. Amer. Chem. Soc.*, **93**, 2553 (1971).

(17) RX and XR refer to different enantiomeric configurations about the asymmetric reaction center and SH is solvent. See ref 16 for additional comments interpreting some of the details of the reaction scheme.

(18) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, p 172.

(19) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362 (1969).

(20) The generalized scheme has many branches. In principle reaction *via* all paths is possible and, of course, each process occurs with some finite rate constant; however, for each specific reaction, most paths will not be stoichiometrically important. In the present case it is not possible to put a significant, low, upper limit on the amount of the reaction that could be going *via* the free carbonium ion or by attack on the tight ion pair; there is no evidence that requires any of either. On the other hand, evidence already cited requires that significant proportions of the reaction go *via* nucleophilic attack on the solvent-separated ion pair. As the argument develops we will explain all the results in these terms and do not need to postulate any reaction *via* the other pathways; it is a more difficult matter to put quantitative upper limits on their importance.

(21) B. L. Murr and M. F. Donnelly, *J. Amer. Chem. Soc.*, **92**, 6686 (1970).

TABLE V
STEREOCHEMICAL COURSE OF SOLVOLYSIS IN THE α-PHENETHYL SYSTEM

Compd	Reaction conditions	Inversion, %	Ref
α-Phenethyl tosylate	Acetolysis, room temp	12	*a*
α-Phenethyl chloride	Acetolysis, 50°	17	*b*
	EtOH, 70°	28	*c*
	MeOH, 70°	28	*c*
	80% Me_2CO–H_2O, 70°	4	*c*
	H_2O, 40°	24	*d*
	60% EtOH–H_2O, 40°	26.5 (alc)	*d*
	80% EtOH–H_2O, 40°	31.5 (alc)	*d*
	60% EtOH–H_2O, 25°	32.6 (alc)	*e*
	80% EtOH–H_2O, 25°	34.2 (alc)	*e*
	70% aq dioxane, 40°	6.0	*f*
	50% aq dioxane, 40°	10.3	*f*

[a] J. Kenyon, H. Phillips, and F. M. H. Taylor, *J. Chem. Soc.*, 173 (1933). [b] L. P. Hammett and J. Steigman, *J. Amer. Chem. Soc.*, **59**, 2536 (1937). [c] E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1201 (1937). [d] Reference 15. [e] This work. [f] Reference 9.

alkyl halide to solvolysis product that would be expected in the addition of HCl to styrene if the tight ion pair is produced as an intermediate. A steady-state treatment shows how the ratio k_p/k_c is determined by the ion pair partitioning rate constant ratios.[22]

In pure TFE the polarimetric rate (Table I) is about 10% faster than it is in 97 T. Although the precise measurement of solvolysis rates in pure TFE is not possible using our current conductance techniques, approximate rate determinations using nmr indicate that the solvolysis rates in 97 T and 100 T do not differ by more than about 10%. Thus, the added water in 97 T does not change the rate of solvolysis appreciably but does divert about 20% of the reaction to the formation of alcohol. This indicates that the product-forming step (rate constant k_6 in the above scheme) comes after the rate-determining step (rate constant, k_2). Since the reaction rates in 97 T and 100 T are nearly the same, the data from both of these solvents can be discussed in terms of the same relative rate constants for ion-pair partitioning. This is particularly useful because in pure TFE, important mechanistic information can be obtained from a study of the addition of HCl to styrene.

Since HCl is not appreciably dissociated in pure trifluoroethanol, the reactants involved are the olefin and molecular hydrogen chloride. Since solvolysis of 1-phenylethyl chloride does not yield appreciable amounts of styrene, any carbonium ion like intermediates in the solvolytic scheme that might also be formed in the acid addition reaction would not be expected to undergo return to olefin and acid reactants. In pure TFE the solvolysis of 1-phenylethyl chloride is reversible so that it and 1-phenylethyl trifluoroethyl ether are in equilibrium in the presence of HCl. However, at reasonable concentrations of HCl, the addition reaction is substantially faster than solvolysis and it is possible to observe from initial yields, determined by nmr, that the ratio of rates of formation of chloride and ether in the addition reaction itself is ~6:1. This indicates that the 1-phenylethyl cation–chloride ion pairs produced on transfer of H^+ from HCl to styrene covalently combine faster than they solvolyze by this same factor of ~6:1[23] and that, if this intermediate is the tight ion pair, k_2/k_{-1} is $^1/_6$ or 0.17. The observed value of k_p/k_c of 1.72 is consistent with this, a value of k_8/k_{-1} of 0.085 and a value of k_2/k_8 of about 2. Thus, we can conclude that in 97–100 T, for every 100 tight ion pairs formed, about 80 return, 13 solvolyze, and 7 invert configuration. The value of k_2/k_{-1} of 0.17 requires that k_2 is not completely rate determining and that the observed isotope effect is not precisely at the maximum that would be exhibited if $k_2 \ll k_{-1}$. If we make the assumption that the isotope effect in k_1 is 1.120 (this is a reasonable but probably not a precisely correct value),[5] then the observed value of $k_H/k_{\alpha\text{-}d}$ of 1.158 and the k_2/k_{-1} value of 0.17 requires that the limiting isotope effect when $k_2 \ll k_{-1}$ be 1.164. The small variations we have observed for the "maximum" α-d effect for different solvents and different reactants[2,5] may well be due to the fact that the ratios of k_2/k_{-1} are not sufficiently small to make the step labeled k_2 strictly "rate determining" in all cases. For example, the value of $k_H/k_{\alpha\text{-}d}$ in 60 E is only 1.151; this is consistent with the limits mentioned above and a k_2/k_{-1} for this solvent of 0.40. Further, the k_p/k_c value of 1.05 requires (for almost any reasonable value of k_2/k_{-1}; *i.e.*, between 1 and 0.1) that k_2/k_8 be about 20. Having these estimates of the change in the ratios of rate constants for ion pair partitioning on changing solvent from 97 T to 60 E it is of interest to speculate on how the individual rate constants are affected by this change in solvent. It appears to us that the most straightforward conclusion is that the higher dielectric constant of 60 E over 97 T causes about a tenfold increase in k_2; this reaction involves simply the further diffusion apart of ion pairs and should not be strongly influenced by nucleophilicity or hydrogen bonding; consistent with this conclusion is the intermediate value of k_p/k_c of 1.16 observed for 80 E. We would expect higher values of k_p/k_c for less aqueous ethanol solvents, as their dielectric constants would be near that for 97 T (ethanol and trifluoroethanol have nearly the same dielectric constant). However, in these solvents the reaction appears to be diverted owing to the lower solvent polarity and higher nucleophilicity to nucleophilic attack on the tight ion pair as indicated by lower α-d effects and larger yields of product of inverted configuration.[2,15] If we assume that the change of solvent from 97 T to 60 E causes about a tenfold increase in k_2, we must conclude, since k_2/k_{-1} only increases from 0.17 to 0.4, that k_{-1} must increase about fourfold. This seems unusual, since the dielectric constant effect would be expected to operate in the opposite sense. However, it is important to remember that, despite its dielectric constant, 97 T is an excellent solvolytic medium in which 1-phenylethyl chloride reacts about ten times faster than it does in 60 E. This is almost certainly due to the fact that TFE is about a 10^3–10^4 times stronger acid than ethanol, which allows it to hydrogen bond strongly to the departing chloride

(22) k_c (the first-order rate constant for solvolysis) $= k_1k_2/(k_{-1} + k_2)$. k_p (the first-order rate constant for change in optical activity) $= k_1(2k_8 + k_2)/(k_{-1} + 2k_8 + k_2)$.

$$k_p/k_c = \frac{(2k_8/k_{-1} + k_2/k_{-1})(1 + k_2/k_{-1})}{(1 + 2k_8/k_{-1} + k_2/k_{-1})k_2/k_{-1}} = \frac{(1 + 2k_8/k_2)(1 + k_{-1}/k_2)}{(k_{-1}/k_2 + 2k_8/k_2 + 1)}$$

(23) V. J. Shiner, Jr. and W. Dowd, *J. Amer. Chem. Soc.*, **91**, 6528 (1969).

ion making it effectively a better leaving group and a poorer nucleophile. It is probably this higher effective nucelophilicity of chloride ion in 60 E that causes internal return (k_{-1}) to be faster in this solvent than in 97 T. The tenfold higher value for k_2 and the fourfold higher value for k_{-1} of themselves would tend to make the solvolysis rate in 60 E about 2–5 times faster than in 97 T; the fact that the reaction is actually about ten times faster in 97 T would have to be explained by k_1 being faster in 97 T by a factor of about 25. In effect the above arguments are based on an implicit assumption that the inversion rate constant, k_8, for tight ion pairs is about the same in 97 T and 60 E. This may be approximately right, since such a reaction would not depend on solvent or counterion nucelophilicity and would probably involve only a small increase in dipole moment and therefore a small dependence on solvent dielectric constant.

The α-d and β-d_3 effect on the polarimetric rates (Table VI) are in general accord with this mechanistic

Table VI

Deuterium Effects on Rates of Reaction of 1-Phenylethyl Chloride at 25°

Solvent[a]	Method[b]	$k_H/k_{\alpha\text{-}d}$	$k_H/k_{\beta\text{-}d_3}$
60 E	C	1.151	1.225
60 E	P	1.17	1.27
97 T	C	1.157	1.218
97 T	P	1.20	1.24
97 T + Py	P	1.145	1.213
100 T	P	1.188	1.228
100 T + Py	P	1.171	1.279

[a,b] See footnotes for Table II.

picture but, unfortunately, are not sufficiently accurate to be as conclusive as hoped. Thus, the isotope effects on k_p are a mixture of those that would be expected if the steps with constants k_1, k_2, or k_8 were rate determining. If $k_p \gg k_c$, then $k_8 \gg k_2$; if also $k_{-1} \gg k_8$ then the isotope effects on k_p should be those that apply if the step with rate constant k_8, the inversion of the tight ion pairs, is rate determining.

The transition state for this process should involve a structure with the chloride ion in the plane of the carbonium ion (the nodal plane of the vacant p orbital) and no covalent bonding between the carbonium and chloride ions. Thus, the isotope effects should be at their maximum in this situation; we have suggested above that such a maximum ought also apply if k_2 is strictly rate determining and that the α effect would be near 1.164 under these conditions. In the solvents we have used, internal return and internal racemization are most dominant in 97–100 T. The polarimetric isotope effects for these reactions are in the range of 17 ± 2% for the α-d and 25 ± 4% for the β-d_3 compound. Within the experimental error involved these are the same as the corresponding effects observed in solvolysis.

The isotope effects in the acid-catalyzed racemization of 1-phenylethyl alcohol in TFE and TFE–water solvents provide interesting additional mechanistic information. In pure TFE the racemization rate is first order in active 1-phenylethyl alcohol concentration at a given stoichiometric HCl concentration. Although the rates were measured at only three HCl concentrations between 1×10^{-4} and 3×10^{-2} M, the plot of the logarithm of the first-order racemization rate constants *vs.* the logarithm of the HCl concentration has a slope in this region of about 0.5–0.6, indicating that the reaction is approximately 0.5 order in HCl. This is consistent with the rate-determining step in the racemization involving *dissociated* 1-phenylethyloxonium ions formed from HCl and 1-phenylethyl alcohol (ROH) *via* the following equation.

$$ROH + HCl \rightleftharpoons R\overset{+}{O}H_2\bar{C}l \rightleftharpoons R\overset{+}{O}H_2 + Cl^-$$
$$\downarrow$$
racemization

This behavior is expected only if the dominant molecular form of hydrogen chloride in the solution is undissociated (either as HCl or as ion pairs $^+ROH_2Cl^-$) and the reactive form of the alcohol is free ROH_2^+. It is probable that the proton-transfer equilibrium is largely in the un-ionized reactants (ROH is not a very strong base with respect to HCl) and the ionized acid is largely dissociated, since TFE is a reasonably good dissociating solvent. The nmr studies of product formation under conditions similar to these show that initially the alcohol is converted exclusively to the trifluoroethyl ether at a rate, within the rather large experimental error, equal to the rate of racemization and that 1-phenylethyl chloride is only subsequently produced by reverse reaction of the ether with HCl which ends in the establishment of appreciable concentrations of both chloride and ether at equilibrium. These results show that the free carbonium ion produced by heterolylic cleavage of the C–O bond in the free oxonium ion does not undergo a *kinetically* significant fraction of reaction with chloride ion to form alkyl chloride. This is consistent with all of the kinetic results in TFE–water and ethanol–water mixtures, which indicate no mass law effect in 1-phenylethyl chloride solvolysis. The racemizations of 1-phenylethyl alcohol in 97% TFE and 70% TFE as indicated in Table III require significantly higher concentrations of HCl. This is expected, since the water in the solvent partly neutralizes the acidity of HCl by converting it to hydronium and chloride ions. The racemizations in these solvents are first order in active alcohol. In 97% TFE the reaction is also first order in HCl, consistent with the reaction being a rate-determining conversion of the free protonated alkoxonium ion formed in small proportions in equilibrium with H_3O^+. In 70% TFE the reaction is not quite first order in HCl, probably because the concentrations of HCl required are sufficiently large that the value of the h_0 function is not equal to the stoichiometric concentration of HCl. Although h_0 was not measured in 70% TFE, the rates do correlate reasonably well with the h_0 functions for HCl in the same concentration in water (70% TFE–30% H_2O is about 70 mol % water). Thus, in all three TFE-containing solvents the racemization seems to be a reaction of the free conjugate acid of the alcohol. It is interesting that the α-d effects in these reactions [$k_H/k_{\alpha\text{-}d}$ = 1.15 (70% TFE), 1.19 (97% TFE)] are smaller than those expected for a limiting reaction with oxygen as the leaving group. Consider first the 15% effect in 70% TFE, a solvent in which most of the molecules are water. The rate-determining

step must generally be the breaking of the C–O bond to give a symetrically solvated carbonium ion.

$$H_2O + ROH_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2O\overset{+}{R}OH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2O\overset{+}{R} + H_2O$$

The C–O bond cleavage step *itself* must involve racemization. Therefore, the isotope effect refers to the transition state of the heterolytic step (rate constant k_1 in the general scheme) and is smaller than the maximum of ~1.23 characteristic of solvolytic reactions with oxygen leaving groups, found for processes which involve rate-determining formation of a second ion pair from the first product of ionization.[16] The 15% isotope effect is the same as that found for solvolysis of pinacolyl *p*-bromobenzenesulfonate in which formation of the tight ion pair is rate determining because of rapid Wagner–Meerwein rearrangement of the 3,3-dimethyl-2-butyl cation.[24] The α-*d* effect in 97% TFE is larger than in 70% TFE, probably because, in at least a significant proportion of the reaction, the molecule at the rear, after initial heterolysis of the C–O bond, is not a water molecule but trifluoroethanol. Thus, a

$$CF_3CH_2OH + R\overset{+}{O}H_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CF_3CH_2O\overset{H}{\overset{|}{\overset{+}{R}}}OH_2 \xrightarrow{k_2}$$

$$H_2O\overset{+}{R}OH_2 \longrightarrow H_2\overset{+}{O}R + H_2O$$

significant fraction of the carbonium ions initially formed would be expected to return to unracemized alcohol *via* k_{-1}; the further dissociation of the unsymmetrically solvated, initially formed carbonium ion would contribute to the rate-determining step and give a larger α-*d* effect, since this transition state involves no partial covalent bond between carbon and oxygen. In this way, it is similar to the rate-determining step in limiting solvolyses which show α-*d* effects in oxygen leaving groups around 1.23.

The 9.4% β-d_3 effect in racemization of the alcohol is small compared to the 22% effect characteristic of the solvolysis of the chloride. However, the latter process involves rate-determining interconversion of ion pairs (see above) in which it is believed that there is no covalent bond between oxygen and carbon. The partial covalent bond in the transition state for the C–O heterolysis step causes both β and α effects to be smaller when this step is rate determining than they are when the step is labeled k_2 is rate determining. The comparison of β-d_3 effects on the solvolysis of isopropyl brosylate in trifluoroacetic acid ($k_H/k_{\beta\text{-}d_3}$ = 1.46) and in 70% TFE ($k_H/k_{\beta\text{-}d_3}$ = 1.24) gives the best example of the change in a β-d_3 effect on changing rate-determining step from ion-pair interconversion to ion-pair formation. Since for the former case the β-d_3 effect for the 1-phenylethylcarbonium ion is 1.22, the above observed effect on the heterolysis step (1.10) is in line with previous results.

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Registry No.—1-Phenylethyl alcohol, 98-85-1; 1-phenylethyl-*1-d* alcohol, 3101-96-0; 1-phenylethyl-*2,2,2-d*$_3$ alcohol, 17537-32-5; 1-phenylethyl chloride, 672-65-1; 1-phenylethyl-*1-d* chloride, 41203-27-4; 1-phenylethyl-*2,2,2-d*$_3$ chloride, 40662-53-1.

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The Nature of Solvent Participation in the Restriction of Rotation about Single Bonds. II

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The activation enthalpy for the racemization of 2,2′-dimethoxy-6,6′-diphenamide decreases by 4.2 kcal/mol when the solvent is changed from acetone to acetic acid. It is shown that this is entirely due to a lowering of the transition state energy. Activation parameters have been determined for the racemization of *N*-benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroaniline in 26 solvents and heats of solution have been measured in nine of these solvents.

When one considers the fact that reaction rates and equilibrium constants may be altered by several powers of ten through changes in the reaction medium, it becomes obvious that the role of the medium must be understood if one is to arrive at a useful understanding of organic reactions as they take place in solution. A change in the solvent may increase the rate of a reaction either by decreasing the free energy of the transition state or by increasing the free energy of the ground state. It is, therefore, important in the understanding of solvent effects that one be able to tell just how much of the variation in the activation parameters is due to changes in ground-state solvation and how much is due to changes in transition-state solvation. This is conveniently done in the case of the activation enthalpy by measuring the heats of solution of the reactant in the solvent systems under investigation.[1-3] The difference in the heats of solution is the enthalpy difference between the two solvated ground states, $\delta_M \Delta\bar{H}^g$. The

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TABLE I

RACEMIZATION OF 2,2′-DIMETHOXY-6,6′-DIPHENAMIDE

Temp, °K	$k \times 10^3$, hr^{-1} Acetone	Acetic acid
363.7[a]	0.3448	1.656
382.1[a]	2.783	7.308
406.7[b]	53.0	127
411.7	77.98	222.8
432.7		904.8

[a] The kinetic data for 363.7 and 382.1°K is from ref 10. [b] The kinetic data for 406.7°K was obtained at 50 and 60 atm pressure by Kay R. Brower, New Mexico Institute of Mining and Technology.

enthalpy difference between the two solvated transition states, $\delta_M \Delta\bar{H}^t$, is then obtained by $\delta_M \Delta\bar{H}^t = \delta_M \Delta\bar{H}^g + \delta_M \Delta\bar{H}^{\pm}$, where $\delta_M \Delta\bar{H}^{\pm}$ is the difference in the activation enthalpies.[3]

Perhaps the simplest "reaction" subject to a solvent effect that an organic molecule can undergo is one involving nothing more than rotation about a single bond, *i.e.*, conformational change. That the solvent can indeed influence the height of the energy barriers between conformers was first demonstrated in 1932 by various workers,[4-6] who showed that the rates of racemization for several optically active biphenyls were solvent dependent. In 1959 Leffler and coworkers measured activation parameters for the racemization of several optically active biphenyls in as many as 26 different solvent systems.[7-10] They observed that the racemization of 2,2′-dimethoxy-6,6′-diphenamide (I) was particularly solvent dependent, having an activation enthalpy of 21.49 kcal/mol in acetic acid and 30.59 kcal/mol in acetone. This change of 9 kcal/mol in the activation enthalpy was significantly larger than the usual 2–4 kcal/mol observed by them for the other biphenyls studied. In the process of further investigations concerning this solvent effect it was found necessary to repeat this work. Rate data over a 69° temperature range was gathered from three independent research groups. These data, listed in Table I and shown graphically in Figure 1, give the activation enthalpies as being 33.31 kcal/mol in acetone and 29.08 kcal/mol in acetic acid. The corresponding entropies of activation are +0.48 and −8.22 eu, respectively. Thus the difference in activation enthalpies, $\delta_M \Delta\bar{H}^{\pm}$, is 4.23 kcal/mol. The previously reported values for the heats of solution of I in acetone and acetic acid are 2.98 and 1.98 kcal/mol, respectively, giving 1.0 kcal/mol as the enthalpy difference between the two solvated ground states, $\delta_M \Delta\bar{H}^g$.[11] Combining this with the $\delta_M \Delta\bar{H}^{\pm}$ value of 4.23 kcal/mol gives 5.2 kcal/mol as the enthalpy difference between the two solvated transition states. Clearly then the 4.2 kcal/mol change in the activation enthalpy observed for this solvent change is due entirely to a medium effect on the transition state. In an unsuccessful attempt to characterize the nature of this solvent effect, benzamide and several benzamide derivatives were prepared and their heats of solution were measured in acetone and acetic acid. It was reasoned that if crowding of the amide group in the transition state were responsible for the solvent effect then this should be reflected in the enthalpies of transfer for a series of 2,4,6-trisubstituted benzamides in which the steric requirements of the substituent groups were gradually increased. In this respect the results, shown in Table II, were inconclusive. Attempts at increasing the size of the substituent groups beyond that of the ethyl group were unsuccessful. Attempts to prepare 2,5-di-*tert*-butyl-3,6-dimethoxybenzamide failed when bromination of 2,5-dimethoxy-1,4-di-*tert*-butylbenzene gave 2,5-dimethoxy-1,4-dibromobenzene as the major product. The observation that *o*- and *p*-methoxybenzamide have essentially the same en-

TABLE II

HEATS OF SOLUTION FOR SOME SUBSTITUTED AMIDES IN ACETONE AND ACETIC ACID TOGETHER WITH THE ENTHALPIES OF TRANSFER FROM ACETIC ACID TO ACETONE

Compd	Registry no.	$\Delta\bar{H}_s$, kcal/mol Acetone	Acetic acid	$\delta\Delta\bar{H}_s$, kcal/mol
Benzene	71-43-2	0.11 ± 0.04	0.37 ± 0.04	−0.26
Benzamide	55-21-0	3.97 ± 0.11	2.51 ± 0.06	1.46
o-Methoxybenzamide	2439-77-2	5.18 ± 0.30	3.22 ± 0.14	1.96
m-Methoxybenzamide	5813-86-5	4.59 ± 0.15	3.88 ± 0.11	0.71
p-Methoxybenzamide	3424-93-9	4.70 ± 0.13	2.79 ± 0.20	1.91
2,6-Dimethoxybenzamide	21864-67-5	4.35 ± 0.51	3.04 ± 0.21	1.31
2,4,6-Trimethylbenzamide	4380-68-1	4.28 ± 0.17	2.90 ± 0.13	1.38
2,4,6-Triethylbenzamide	41214-94-2	3.76 ± 0.21	2.14 ± 0.14	1.62

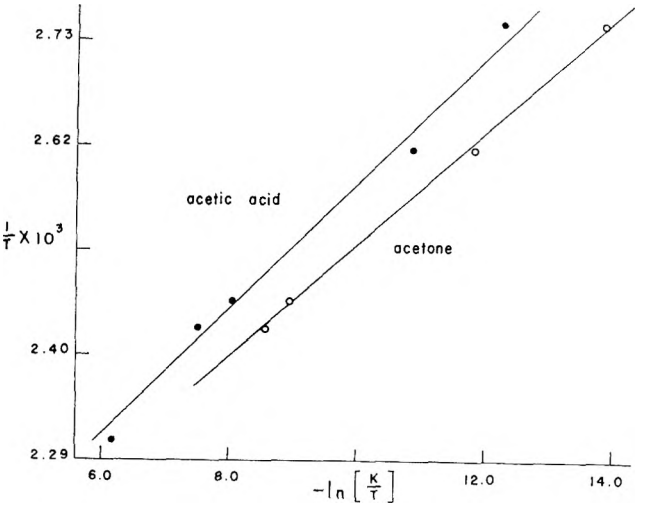

Figure 1.—A plot of $1/T$ *vs.* $-\ln(k/T)$ for the racemization of 2,2′-dimethoxy-6,6′-diphenamide in acetone and in acetic acid.

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Table III

Activation Parameters for the Racemization of *N*-Benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroaniline (II) in Various Solvents

Solvent	Registry no.	Temp, °C	$k \times 10^{-3}$, hr^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
Methanol	67-56-1	40	31.44 ± 0.56	21.8 ± 0.1	−13.5 ± 0.2
		60	268.9 ± 4.7		
		80	1878 ± 37		
Ethanol (95%)	64-17-5	40	26.80 ± 0.61	20.5 ± 0.7	−17.9 ± 2.2
		50	79.90 ± 1.6		
		57	153.4 ± 3.1		
Absolute ethanol	64-17-5	40	26.84 ± 0.51	22.9 ± 0.3	−10.3 ± 0.8
		57	171.7 ± 4.5		
		60	264.8 ± 4.7		
		80	1948 ± 40		
Isopropyl alcohol	67-63-0	40	27.38 ± 0.52	21.9 ± 0.4	−13.7 ± 1.1
		60	215.3 ± 4.1		
		80	1660 ± 32		
tert-Butyl alcohol	75-65-0	40	23.64 ± 0.71	22.5 ± 0.3	−11.8 ± 1.0
		60	201.0 ± 4.1		
		80	1619 ± 33		
Benzyl alcohol	100-51-6	40	18.86 ± 0.56	24.0 ± 0.2	−7.4 ± 0.6
		60	214.6 ± 3.9		
		80	1681 ± 30		
Acetone	67-64-1	40	37.92 ± 0.67	21.7 ± 0.3	−13.7 ± 0.8
		60	300.0 ± 6.0		
		80	2208 ± 40		
Diethyl ketone	96-22-0	40	31.09 ± 0.55	21.9 ± 0.1	−13.1 ± 0.3
		60	280.0 ± 4.9		
		80	1896 ± 34		
Diisopropyl ketone	565-80-0	40	22.68 ± 0.43	22.9 ± 0.3	−10.8 ± 0.8
		60	205.7 ± 3.8		
		80	1649 ± 29		
Cyclopentanone	120-92-3	40	33.27 ± 0.75	21.9 ± 0.4	−13.0 ± 1.1
		60	327.4 ± 5.6		
		80	2014 ± 39		
Tetrahydrofuran	109-99-9	40	30.14 ± 0.53	22.4 ± 0.4	−11.9 ± 1.3
		60	243.2 ± 4.9		
		80	2003 ± 36		
Dimethylformamide	68-12-2	40	51.58 ± 1.1	19.2 ± 1.0	−20.8 ± 3.2
		50	125.5 ± 2.4		
		57	273.6 ± 5.3		
Dimethyl sulfoxide	67-68-5	40	49.44 ± 0.96	20.3 ± 1.1	−17.2 ± 3.2
		60	552.8 ± 11		
		80	2319 ± 53		
Pyridine	100-86-1	40	48.69 ± 0.92	20.4 ± 0.9	−16.9 ± 2.8
		60	494.3 ± 10		
		80	2238 ± 42		
p-Dioxane	123-91-1	40	27.60 ± 0.59	22.3 ± 0.3	−12.1 ± 0.8
		60	274.8 ± 4.7		
		80	1808 ± 32		
Anisole	100-66-3	40	25.52 ± 0.49	21.9 ± 0.3	−13.5 ± 0.9
		60	246.6 ± 4.0		
		80	1551 ± 29		
Acetonitrile	75-05-8	40	42.72 ± 0.72	22.0 ± 0.1	−12.4 ± 0.2
		60	368.0 ± 7.1		
		80	2632 ± 46		
Benzonitrile	100-47-0	40	31.92 ± 0.71	21.3 ± 0.2	−15.1 ± 0.6
		60	259.2 ± 5.3		
		80	1740 ± 33		
Propionitrile	107-12-0	40	42.53 ± 0.73	21.0 ± 0.1	−15.3 ± 0.2
		60	343.2 ± 6.5		
		80	2210 ± 39		
Nitrobenzene	98-95-3	40	24.14 ± 3.7	21.0 ± 0.4	−16.6 ± 1.2
		60	172.8 ± 3.7		
		80	1258 ± 26		
Acetic acid	64-19-7	40	19.56 ± 0.39	22.4 ± 0.2	−12.4 ± 0.7
		60	193.8 ± 3.5		
		80	1290 ± 26		
1,2-Dichloroethane	107-06-2	40	20.36 ± 0.57	22.8 ± 0.2	−11.2 ± 0.5
		60	205.1 ± 3.6		
		80	1440 ± 27		

TABLE III (*Continued*)

Solvent	Registry no.	Temp, °C	$k \times 10^{-3}$, hr^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
Methyl acetate	79-20-9	40	29.60 ± 0.69	20.9 ± 0.6	−16.5 ± 1.8
		50	90.16 ± 1.9		
		57	175.0 ± 3.7		
Ethylene glycol	107-21-1	40	20.16 ± 0.49	23.0 ± 0.6	−10.7 ± 1.7
		60	166.4 ± 3.8		
		80	1508 ± 33		
Butyrolactone	96-48-0	40	34.74 ± 0.64	22.4 ± 0.3	−11.3 ± 1.0
		60	343.2 ± 7.2		
		80	2317 ± 43		
Ethyl malonate	105-53-3	40	26.42 ± 0.55	22.8 ± 0.2	−10.7 ± 0.5
		60	263.9 ± 4.5		
		80	1888 ± 35		

thalpy of transfer while that of the meta isomer is significantly different makes it seem likely that there is no steric inhibition of solvation in the ortho isomer despite the close proximity of the substituent groups, and that the differences in solvation between the ortho–para isomers and the meta isomer are due to differences in the electronic distributions caused by mesomeric effects.

N-Benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroaniline (II) was prepared and resolved. The activation parameters for the racemization of II in 26 different solvents were determined. These data are shown in Table III. Heats of solution were also measured in nine of these solvents. The heats of solution were then coupled with the activation enthalpies to give enthalpies of transfer for the transition state $\delta_M \Delta\bar{H}^t$. These enthalpies of transfer are from each of the nine solvents studied to acetonitrile. These data are shown in Table IV and a plot of $\delta_M \Delta\bar{H}^g$ *vs.* $\delta_M \Delta\bar{H}^t$ is

TABLE IV

ENTHALPIES OF TRANSFER FROM VARIOUS SOLVENTS TO ACETONITRILE FOR THE GROUND STATE AND THE TRANSITION STATE OF *N*-BENZENESULFONYL-*N*-CARBOXYMETHYL-1-AMINO-2,4-DIMETHYL-6-NITROBENZENE

Solvent	$\Delta H^{\pm}$, kcal/mol	$\Delta\bar{H}_s$, kcal/mol	$\delta_M \Delta\bar{H}^t$	$\delta_M \Delta\bar{H}^g$
DMF	19.2 ± 1.0	−0.17 ± 0.20	8.1	5.3
DMSO	20.3 ± 1.1	1.28 ± 0.12	5.5	3.8
Ethanol (95%)	20.5 ± 0.7	5.37 ± 0.29	1.2	−0.3
Acetone	21.7 ± 0.3	3.36 ± 0.12	2.0	1.7
Methanol	21.8 ± 0.1	5.20 ± 0.20	0.1	−0.1
Acetonitrile	22.0 ± 0.1	5.10 ± 0.24	0.0	0.0
p-Dioxane	22.3 ± 0.3	3.60 ± 0.12	1.2	1.5
Acetic Acid	22.4 ± 0.2	3.98 ± 0.12	0.7	1.1
1,2-Dichloroethane	22.8 ± 0.2	3.76 ± 0.37	0.5	1.3

shown in Figure 2. The most notable feature of Figure 2 is that all four of the dipolar aprotic solvents studied (acetonitrile, acetone, dimethyl sulfoxide, and dimethylformamide) are fairly well spread out and lie along a straight line while the other five solvents are bunched and randomly located about the line determined by the dipolar aprotic solvents. However, only ethanol is separated from this line by more than 0.5 kcal. The observation, for the dipolar aprotic solvents, that changes in solvent involvement in the transition state can be predicted from changes in solvent involvement in the ground state indicates that no solvent properties which are unimportant in the ground state are becoming important in the transition state. Solvation of the transition state can differ from that of the ground state because of two changes which take place during the transformation of ground state into transition state. Firstly, steric crowding in the transition state could lead to steric inhibition of solvation. Thus solvation of the interfering groups could be decreased in the transition state. Secondly, previous experiments have shown that the mesomeric effect of electron-withdrawing groups para to the nitrogen atom causes an increase in the rate of racemization by stabilization of the planar intermediate.[12] The same phenomenon should occur in the racemization of II and the resulting changes in polarization should be accompanied by changes in solvation. It is difficult to say which of these two solvent effects might be of more importance in this situation. It might be argued that steric inhibition of solvation in the transition state is unimportant, since this would bring into importance in the transition state a solvent property relatively unimportant in the ground state, that of solvent size. However this argument fails to the extent that the nine solvents studied resemble each other in steric requirements.

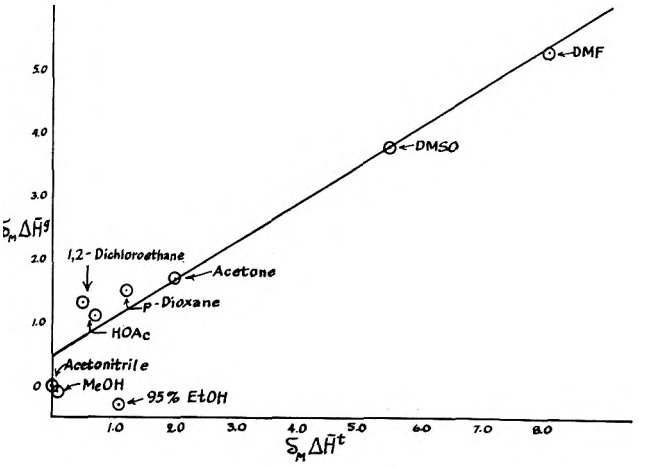

Figure 2.—A plot of $\delta_M \Delta\bar{H}^g$ *vs.* $\delta_M \Delta\bar{H}^t$ for the racemization of *N*-benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroaniline in various solvents.

Experimental Section

2,2′-Dimethoxy-6,6′-diphenamide (I) was prepared by the method of Leffler and Graybill[9] with the modifications described in ref 11.

(12) R. Adams and K. V. Y. Sundstrom, *J. Amer. Chem. Soc.*, **76**, 5474 (1954).

N-Benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroaniline (II) was prepared by the method of Adams and Gordon[13] as modified by Adams and Brower.[14]

Calorimetry.—The calorimeter used was similar to that already described by Arnett.[2] The errors reported with the heats of solution are 95% confidence limits. The relatively large errors are due to the extremely small temperature change resulting from the solution of 100 mg of sample in 175 ml of solvent. It was not practical to work with a larger sample size because of the slow rates of solution. In some solvents it was not possible to measure heats of solution because of the slow rates of solution.

Kinetics.—Resolved compound (0.1 g) was dissolved in 25 ml of solvent. Aliquots (2 ml) were placed in 12 13 × 100 mm Pyrex test tubes which were then flushed with nitrogen, sealed off, and placed in a constant-temperature bath. Temperature values known to within 0.1° were obtained with an N. B. S. calibrated thermometer. The 12 ampoules were removed in pairs over the course of the reaction and quenched by immersion in ice–water. After quenching the tubes were opened and the contents were placed in a polarimeter tube. A Rudolph photoelectric polarimeter (Model 520-M) equipped with a sodium vapor lamp was used to measure the optical rotation. Rates were measured at three different temperatures, usually 40, 60, and 80°. A least-squares program written by A. Ault of Cornell College was used to calculate the best values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ from the kinetic data. The errors listed are 95% confidence limits.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—I, 23306-01-6; II, 41391-02-0.

(13) R. Adams and J. R. Gordon, *J. Amer. Chem. Soc.*, **72**, 2458 (1950).
(14) R. Adams and K. R. Brower, *J. Amer. Chem. Soc.*, **78**, 663 (1956).

Notes

Synthesis of Trineopentylamine

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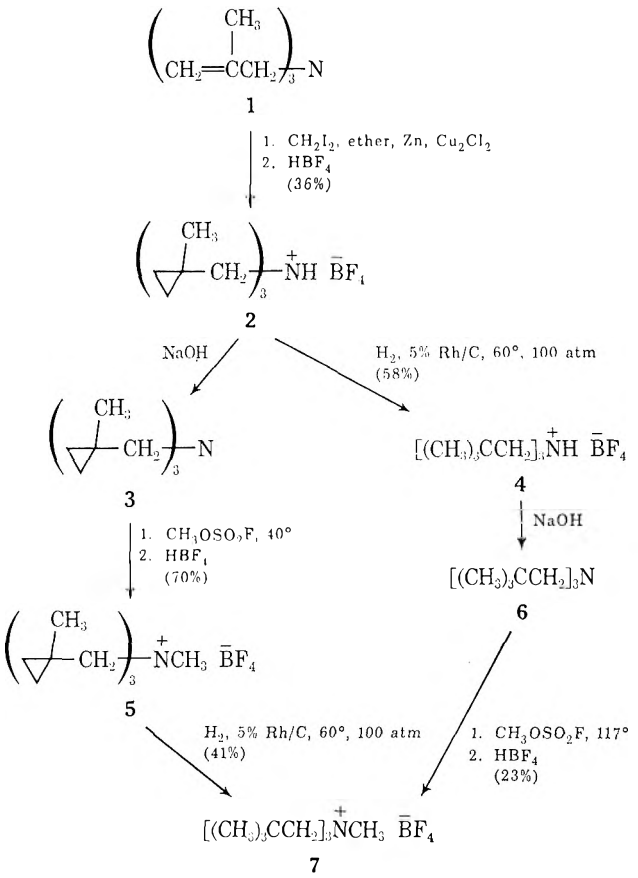
Received May 15, 1973

In attempts to prepare base-resistant quaternary ammonium ions, with tetraneopentylammonium ion as a fanciful goal, I have synthesized two new highly crowded tertiary amines, tris(1-methylcyclopropylmethyl)amine (**3**) and trineopentylamine (**6**), directly from tris(2-methylallyl)amine (**1**). The synthetic methods and results are summarized in Scheme I. Little effort has been made to optimize the yields.

Several features of the synthesis may be of general interest. (1) A modified Simmons–Smith reaction,[1] the triple cyclopropanation of **1**, proceeds readily in the presence of a tertiary amine in 36% yield. (2) Hydrogenations of hindered cyclopropanes **2** and **5** proceed under milder conditions with rhodium than with the previously used[2] palladium catalyst. With 5% palladium on carbon, hydrogenations of **2** and **5** at 100 atm required temperatures of 130–150° and gave poorer yields of less pure **4** and **7**. As with other 1,1-dialkylcyclopropanes, catalytic hydrogenation of **2** and **5** occurs exclusively at the unsubstituted cyclopropane bond.[3] (3) Tertiary amines and tetraalkylammonium ions were handled whenever possible as their tetrafluoroborate salts, which are in general more stable and easier to crystallize than the free amines or the halide salts.[4] Trifluoromethanesulfonates may serve as well as tetrafluoroborates for this purpose.[5]

SCHEME I



The highly crowded nature of amines **3** and **6** is demonstrated by their resistance to alkylation. Only methyl fluorosulfonate, at 40 and 117° respectively, gave reasonable yields of their corresponding methyl-

(1) R. J. Rawson and I. T. Harrison, *J. Org. Chem.*, **35**, 2057 (1970).
(2) A. L. Schultz, *J. Org. Chem.*, **36**, 383 (1971).
(3) C. W. Woodworth, V. Buss, and P. v. R. Schleyer, *Chem. Commun.*, 569 (1968).
(4) H. O. House, E. Feng, and N. P. Peet, *J. Org. Chem.*, **36**, 2371 (1971).
(5) K. Rousseau, G. C. Farrington, and D. Dolphin, *J. Org. Chem.*, **37**, 3968 (1972).

trialkylammonium salts, **5** and **7**. Attempts to methylate **3** and **6** with methyl iodide, methyl *p*-toluenesulfonate, and trimethyloxonium tetrafluoroborate all failed or gave much lower yields. All attempts to alkylate **3** and **6** with groups larger than methyl failed. Some of these experiments are reported briefly in the microfilm edition.

Experimental Section[6]

Materials.—Tris(2-methylallyl)amine (1) was prepared from 2-methylallyl chloride (Eastman) and aqueous ammonia,[7] bp 84–88° at 15 Torr (lit.[8] bp 83–85° at 15 Torr). Methyl fluorosulfonate (Aldrich) was distilled and stored over CaH_2 at −20°. Technical 2-methoxyethanol was distilled. *p*-Toluenesulfonyl chloride was purified.[9] All other chemicals were reagent grade and were used as obtained without further purification.

Tris(1-methylcyclopropylmethyl)ammonium Tetrafluoroborate (2).—A mixture of 58.8 g of zinc dust, 81.3 g of Cu_2Cl_2, and 150 ml of anhydrous ethyl ether was stirred for 30 min at reflux. A solution of 17.9 g of 1 and 10 ml of ethyl ether was added slowly, and 102.8 g of CH_2I_2 (Eastman) was added dropwise over 45 min. After 21 hr at reflux the mixture was cooled and poured into a mixture of 800 ml of saturated aqueous NH_4Cl and ice. The layers were separated, and the aqueous suspension was washed with 4 × 200 ml portions of ether. The combined ether extract was dried over $MgSO_4$ and distilled through a 30-cm Vigreux column until 150 ml of yellow solution remained. To the ethereal solution 9.7 g of 48–50% aqueous HBF_4 was added slowly with stirring. The resulting precipitate was collected, air dried, and crystallized from methanol–ethyl acetate to give 11.0 g (35.6%) of **2**:[10] white needles; mp 227–228.5° dec (gas evolution); pmr ($CDCl_3$) δ 0.63 (12 H, AA′BB′), 1.24 (9 H, s), 3.28 (6 H, d, J = 6 Hz). The pmr spectrum showed a trace of 2-methylallyl groups (<3% of the area of 1-methylcyclopropylmethyl groups) and showed no sign of ^+N–H. A second crop was obtained from acetone–ethyl acetate: 2.1 g, mp 224.5–226° dec.

Tris(1-methylcyclopropylmethyl)amine (3).—A 1.19-g sample of **2** was shaken with 6 ml of 1 *M* NaOH and extracted with 10 ml of 30–60° petroleum ether. The organic solution was dried over K_2CO_3 and distilled on a steam bath through a 15-cm Vigreux column. Cooling of the residual liquid formed white solid **3**:[11] 0.85 g; mp 35–41°; pmr (CCl_4) δ 0.25 (12 H, br s), 1.16 (9 H, s), 2.23 (6 H, s). The pmr spectrum also showed a trace of residual petroleum ether, but this slightly impure material was used for subsequent experiments because further attempted removal of petroleum ether by evacuation and by passing a stream of N_2 over the solid resulted in much loss of **3** by sublimation. A sample sublimed at 25° and 1 atm for 7 days from the bottom to the upper walls of a sealed flask had mp 46–46.5°.

***Methyltris(1-methylcyclopropylmethyl)ammonium* Tetrafluoroborate (5).**—A solution of 24.4 mmol of **3** and 46.5 mmol of methyl fluorosulfonate in 10 ml of CH_2Cl_2 was refluxed for 4.7 hr under N_2. The resulting dark CH_2Cl_2 solution was poured into 50 ml of water, extracted, washed with 50 ml of 1 *M* aqueous NaOH (which changed its color to beige), and washed with 4 × 25 ml portions of 3 *M* aqueous HBF_4. The combined aqueous wash solutions were extracted with 10 ml of CH_2Cl_2, and the combined CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated to a beige solid. Crystallization from methanol–ethyl acetate gave 5.48 g (70%) of **5**:[10] white needles; mp 188.5–189.5° dec (gas evolution); pmr ($CDCl_3$) δ 0.70 (12 H, AA′BB′), 1.33 (9 H, s), 3.40 (6 H, d, J = 6 Hz), 3.47 (3 H, s). A second crop was obtained: 0.76 g, mp 186–187° dec.

Trineopentylammonium Tetrafluoroborate (4).—To a solution of 5.05 g of **2** in 175 ml of 2-methoxyethanol in a glass liner was added 4.99 g of 5% rhodium on carbon (Engelhard Industries). The mixture was rocked for 48 hr at 60° and 100 atm of H_2. The catalyst was removed by gravity filtration and washed with methanol. The filtrate was evaporated to ~10 ml. Addition of 50 ml of ethyl ether and filtration of the resulting mixture gave crude white solid, 4.3 g, mp 191–199°, which was a mixture of two compounds having *tert*-butyl peaks in the pmr. A slurry of the crude solid in 15 ml of CH_2Cl_2 was filtered to give a solution of **4** and an insoluble solid which was not identified. Evaporation of the filtrate gave white solid, 3.51 g, mp 215–220°, which was crystallized three times from ethyl acetate to give **4**:[10] 2.97 g (58%); mp 221–224°; pmr (CH_2Cl_2) δ 1.15 (27 H, s), 3.34 (6 H, d, J = 5 Hz).

Trineopentylamine (6).—By the method described for conversion of **2** to **3**, 0.97 g of **4** was converted to liquid **6** contaminated with a trace of petroleum ether. Pure samples of **6**[10] for elemental analysis and spectra were collected by preparative glpc on a 10 ft × 0.25 in. column of 20% Apiezon L on 60–80 Chromosorb W at 190°: pmr (CH_2Cl_2) δ 0.93 (27 H, s), 2.21 (6 H, s); mass spectrum (Varian-MAT CH-5, 70 ev) *m/e* 227 (M^+), 212, 170 (base peak), 100, 71.

Methyltrineopentylammonium Tetrafluoroborate (7). A.—A mixture of 6.24 g of **5**, 5.9 g of 5% rhodium on carbon, and 250 ml of 2-methoxyethanol in a glass liner was rocked for 24 hr at 60° and 100 atm of H_2. The catalyst was removed by gravity filtration and washed with methanol. The filtrate was evaporated to a solid, which was crystallized from methanol–ethyl acetate to give **7**:[10] 2.62 g (41%); fine white flakes; mp 237–239°; pmr ($CDCl_3$) δ 1.25 (27 H, s), 3.32 (3 H, s), 3.44 (6 H, s).

B.—A solution of 0.474 g of **6**, 1.17 g of methyl fluorosulfonate, and 1.0 ml of CH_2Cl_2 was sealed in a heavy-wall glass tube and heated 2.5 hr at 117°. The contents of the tube were poured into 6 ml of 1 *M* aqueous HBF_4 and extracted with 6 × 1 ml portions of CH_2Cl_2. The combined CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated to a white paste, which was extracted with 3 ml of 1 *M* aqueous NaOH and 3 × 2 ml portions of 30–60° petroleum ether. The combined petroleum ether solution contained much unreacted **6** according to its pmr spectrum. The white solid which remained suspended in the aqueous phase during the petroleum ether extractions was isolated by filtration (0.29 g) and crystallized from methanol–ethyl acetate to give **7**, 0.144 g (23%), white needles, mp 234–237° dec, whose pmr spectrum was identical with that of **7** prepared by method A.

Acknowledgments.—I thank the U. S. Public Health Service (GM 16909) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support, Robert McNeil for technical assistance with the hydrogenations, and J. C. Martin for helpful discussion.

Registry No.—**1**, 6321-40-0; **2**, 41143-53-7; **3**, 41143-60-6; **4**, 41143-54-8; **5**, 41143-55-9; **6**, 13369-22-7; **7**, 41143-56-0.

Supplementary Material Available.—A supplementary experimental section will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20X reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-3614-73.

(6) All temperatures including melting points and boiling points are uncorrected. Pmr spectra were obtained on Varian A-60A and HA-100 spectrometers. Microanalyses were performed by J. Nemeth and associates.

(7) G. B. Butler and B. M. Benjamin, *J. Chem. Educ.*, **28**, 191 (1951).

(8) M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

(9) S. W. Pelletier, *Chem. Ind. (London)*, 1034 (1953).

(10) Satisfactory elemental analysis for C, H, and N (±0.3%) was obtained for this compound. The data appears in a supplementary table of this paper in the microfilm edition.

(11) No elemental analysis was obtained for this compound.

Synthesis of 2-Methylene-4-thiazolidinones

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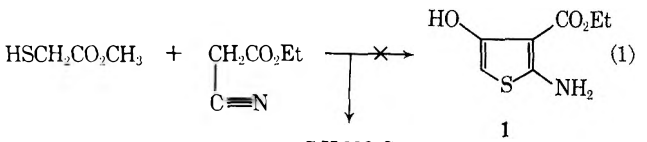
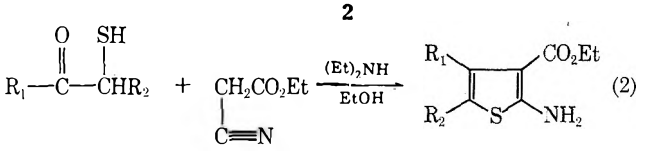
Received May 30, 1972

In recent synthetic work it was anticipated that the base-catalyzed condensation of α-mercapto esters with ethyl cyanoacetate would give 2-amino-3-carbethoxy-4-

hydroxythiophene (**1**, eq 1) by analogy with the documented formation of 2-amino-3-carbethoxythiophenes from the interaction of α-mercapto ketones with ethyl cyanoacetate (eq 2).[1,2]



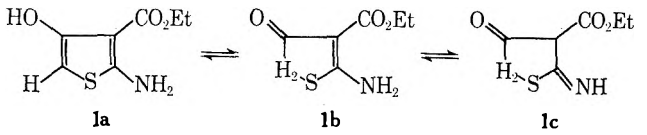
(1)



(2)

R_1 and R_2 = alkyl, aryl, and/or acyl

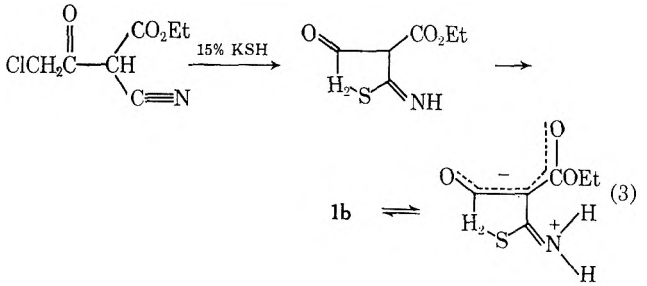
However, it was found that the interaction of methyl mercaptoacetate with ethyl cyanoacetate in diethylamine–ethanol gave a nearly quantitative yield of a product (**2**) whose empirical formula corresponded to **1**, but whose nmr spectrum was inconsistent with **1**. The nmr spectrum of **2** indicated the presence of a carbethoxy group, a singlet methylene absorption at 5.86 ppm, a one-hydrogen singlet that collapsed very slowly upon addition of D_2O, and one singlet hydrogen attached to nitrogen (^{14}N spin decoupled) at 11.50 ppm downfield from TMS. Of the three possible tautomeric forms for **1** (**1a**, **1b**, and **1c**) only **1c** could give rise to this



1a **1b** **1c**

spectrum. However, this tautomer is highly unlikely for **1**, and a large variety of 2-aminothiophenes have been shown to exist entirely in the amino rather than imino form.[3,4]

A subsequent literature search for **1** revealed a reported synthesis of **1c** from the treatment of ethyl chloroacetylcyanoacetate with aqueous potassium hydrosulfide (eq 3).[5–8] Repetition of this procedure gave



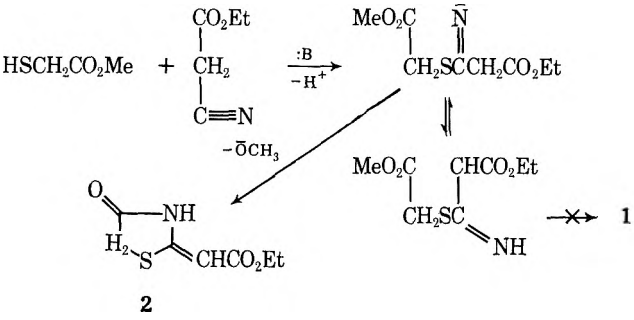
(3)

what appeared to be **1**, but as **1b** rather than **1c** from the nmr spectrum, and as expected, the ir, nmr, and mass spectrum of **1b** all differed from those given by the isomeric compound, **2**. It is interesting to note that the nmr spectrum of **1b** displays two different NH protons at room temperature, presumably owing to the rather unque steric arrangement of this vinylogous amide where restricted rotation about the C–N bond gives rise to two magnetically distinct amine hydrogens. The positive character of the nitrogen is evident from the unusually low shift values for the amine protons (8.87 and 9.40 ppm downfield from TMS).

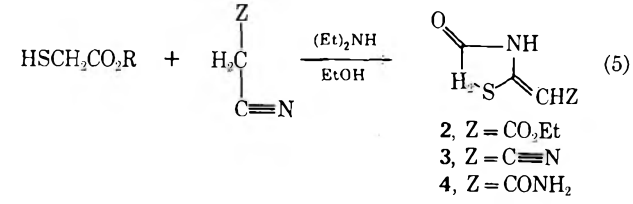
The identity of **2** was established by desulfurization with Raney nickel to give the ethyl ester of *N*-acetyl-β-alanine (eq 4). Reconstruction of **2** from the desulfurization process indicated that **2** is 2-carbethoxymethylene-4-thiazolidenone, resulting from sulfur attack at the nitrile carbon followed by lactam formation (Scheme I).

(4)

SCHEME I



It was subsequently found that this type of reaction with α-mercapto esters is general for methylene-active nitriles. Thus, the condensation of methyl mercaptoacetate with malononitrile and with 2-cyanoacetamide gave excellent yields of **3** and **4**, respectively, and constitues a new and facile synthesis of this biologically and industrially important ring system (eq 5).[9]



(5)

2, Z = CO_2Et
3, Z = C≡N
4, Z = $CONH_2$

A similar reaction has been previously observed in the thiazole system, where α-mercapto acids or esters react with Schiff bases to give 4-oxothiazolidines.[10,11] The method is restricted to Schiff bases, however, and good yields require preformation of the Schiff base.

Experimental Section

2-Carbethoxymethylene-4-thiazolidinone (**2**).—A solution consisting of 10.0 g (0.094 mol) of ethyl mercaptoacetate, 13.0 g

(1) K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).
(2) W. Ried and R. Giesse, *Justus Liebigs Ann. Chem.*, **713**, 143 (1968).
(3) M. C. Ford and D. McKay, *J. Chem. Soc.*, 4985 (1956).
(4) R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 515 (1961).
(5) Tohl and Eberhard, *Chem. Ber.*, **26**, 2945 (1893).
(6) W. Autenrieth and A. Bruning, *Chem. Ber.*, **36**, 3464 (1903).
(7) E. Benary, *Chem. Ber.*, **41**, 2399 (1908).
(8) E. Benary, *Chem. Ber.*, **43**, 1943 (1910).
(9) For a review of 4-thiazolidinones see F. C. Brown, *Chem. Rev.*, **61**, 463 (1961).
(10) A. R. Surrey, *J. Amer. Chem. Soc.*, **71**, 3105 (1949).
(11) H. D. Troutman and L. M. Long, *J. Amer. Chem. Soc.*, **70**, 3436 (1948).

(slight excess) of ethyl cyanoacetate, and 6 ml of acetic acid in 50 ml of absolute alcohol was stirred at room temperature. Then 10 ml of diethylamine was added in small portions. The temperature rose rapidly to 45°, then began to drop as the last of the diethylamine was added. After 15 min, a white, fluffy precipitate formed. Stirring was continued for an additional 1 hr, then the mixture was cooled in an ice bath for 30 min. The white crystals were filtered, washed with water, and then recrystallized from 95% ethanol to give 16.4 g (93%) of shiny, white flakes: mp 144–149°; ir (KBr) 3260, 3000, 1730, 1725, 1670, and 1575 cm^{-1}; nmr (DMSO-d_6) δ 1.20 (3 H, t, J = 6 Hz), 3.73 (2 H, s), 4.00 (2 H, q, J = 6 Hz), 5.86 (1 H, s), and 11.50 ppm (1 H, broad s, exchanged with D_2O); uv max (CH_3OH) 233 nm (ϵ 11,000) and 284 (22,000); mass spectrum (70 eV) m/e (rel intensity) 187 (60), 173 (7), 159 (18), 142 (82), 115 (100), and 86 (40).

Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.84; N, 7.49; S, 17.12. Found: C, 44.85; H, 4.76; N, 7.47; S, 17.06.

2-Cyanomethylene-4-thiazolidinone (3).—Five milliliters of piperidine was added to a stirred mixture consisting of 120.17 g (1.0 mol) of ethyl mercaptoacetate, 66.07 g (1.0 mol) of malononitrile, and 5 drops of acetic acid in 200 ml of absolute ethanol. The temperature quickly rose to 60° and was subsequently maintained between 50 and 60° by intermittent use of an ice bath. After a short time, a white precipitate formed a solid mass in the reaction vessel. An additional 100 ml of ethanol was then added and the mixture was stirred for 30 min more. The mixture was then filtered and the white solid was recrystallized from a mixture (v/v) of ethanol–acetonitrile (2:1) to give 80 g (57%) of a white powder that slowly decomposed over 200°: ir (KBr), 3115, 3090, 3000, 2880, 2218, 1770, 1730, and 1600 cm^{-1}; nmr (DMSO-d_6) δ 4.00 (2 H, s), 4.90 (1 H, s), and 11.75 ppm (1 H, broad s, exchanged with D_2O); mass spectrum (70 eV) m/e (rel intensity) 139 (39), 111 (12), 73 (20), 67 (100), 66 (53), 47 (35), 46 (78), 45 (61), and 42 (33).

Anal. Calcd for $C_5H_4N_2OS$: C, 42.87; H, 2.88; N, 20.00; S, 22.84. Found: C, 42.44; H, 2.94; N, 20.01; S, 22.37.

2-Carboxamidomethylene-4-thiazolidinone (4).—A mixture of 10.0 g (0.094 mol) of methyl mercaptoacetate, 13.0 g (slight excess) of 2-cyanoacetamide, 2.0 g of ammonium acetate, and 50 ml of ethanol was stirred at room temperature. Then 15 ml of diethylamine was added and stirring was continued for 1 hr, during which time the temperature gradually rose to 48°. At the end of 1 hr, the temperature began to drop and a tan powder came out of solution. After an additional 0.5 hr the solution was filtered and the very insoluble powder was washed liberally with ethanol, then ether. The residue after washing weighed 4.8 g (32%) as a light brown powder that decomposed at 260° and sublimed over 200°, and was homogeneous (tlc): ir (KBr) 3400, 3160, 2783, 1730, 1675, 1630, and 1590 cm^{-1}; nmr (DMSO-d_6) δ 3.60 (2 H, s), 5.59 (1 H, s), 6.60 (1 H, broad s), 7.10 (1 H, broad s), and 10.50 ppm (1 H, broad s); mass spectrum (70 eV) m/e (rel intensity) 158 (100), 142 (16), 115 (19), 84 (28), 73 (42), 68 (42), 46 (53), 44 (53), and 42 (56).

Anal. Calcd for $C_5H_6N_2O_2S$: C, 37.98; H, 3.82; N, 17.71; S, 20.24. Found: C, 37.98; H, 3.79; N, 17.49; S, 20.19.

Desulfurization of 2-Carbethoxymethylene-4-thiazolidinone (2).—Three grams of 2 was dissolved in 250 ml of absolute ethanol containing approximately 18 g of W2 Raney nickel and the mixture was stirred and refluxed for 44 hr. The solution was then cooled, filtered through an asbestos plug, and then filtered by gravity through fluted paper to give a clear, colorless filtrate. Removal of the ethanol by evaporation left a colorless oil that was distilled at 137–138° (6 mm) [lit. 136° (6 mm)]: ir (liquid film) 3260, 2950, 1740, and 1650 cm^{-1}; nmr (CCl_4) δ 1.23 (3 H, t, J = 6 Hz), and 2.05 (3 H, s), 2.48 (2 H, t, J = 6 Hz), 3.28 (2 H, q, J = 6 Hz), 4.00 (2 H, q, J = 6 Hz), 7.50 ppm (1, H, broad t). The ir, nmr, and elemental analyses indicated that the product was the ethyl ester of *N*-acetyl-β-alanine.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.57; H, 8.51; N, 9.06.

2-Amino-3-carbethoxy-4-hydroxythiophene (1b)[8].—Nine grams (0.048 mol) of ethyl chloroacetylcyanoacetate[7] was dissolved in 90 ml of a 15% aqueous potassium hydrosulfide solution. The mixture was warmed gently on a steam bath. After a few minutes, shiny plates began to appear. After 15 min the precipitate was collected, washed with water, and recrystallized from ethanol to give 4.2 g (45%) of shiny, white flakes: mp 219–202; ir (KBr) 3350, 3080, 1673, 1625, and 1490 cm^{-1}; nmr (DMSO-d_6) δ 1.20 (3 H, t, J = 6 Hz), 3.35 (2, H, s), 4.15 (2, H, q, J = Hz), 8.87 (1 H, broad s, sharpened upon ^{14}N spin decoupling), and 9.40 ppm (1, H, broad s, sharpened upon ^{14}N spin decoupling); mass spectrum (70 eV) m/e (rel intensity) 187 (100), 143 (100), 142 (100), 141 (69), 115 (100), 85 (69), 68 (100), and 60 (65).

Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.84; N, 17.49. Found: C, 45.00; H, 4.80; N, 17.38.

Registry No.—**1b**, 38555-67-8; **2**, 24146-36-9; **3**, 3364-82-7; **4**, 27653-83-4; ethyl mercaptoacetate, 623-51-8; ethyl cyanoacetate, 105-56-6; malononitrile, 109-77-3; 2-cyanoacetamide, 107-91-5; methyl mercaptoacetate, 2365-48-2; ethyl ester of *N*-acetyl-β-alanine, 33233-68-0; ethyl chloroacetylcyanoacetate, 26390-99-8.

The Synthesis of the Fluorinated Ethers "Perfluoroglyme" and "Perfluorodiglyme" by Direct Fluorination

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The synthesis of perfluorinated ethers and polyethers using existing technology is often difficult and in many cases impossible to accomplish. A facile general synthesis with possible commercial importance has been developed in our laboratory by employing modified[1] LaMar[2] direct fluorination techniques. Perfluorinated polyethers are of interest as potential high stability fluids and as solvents. Of the reported products, only "perfluoroglyme" (perfluoro-1,2-dimethoxyethane) has been prepared in 4% yield based on the electrolytic fluorination and cleavage of 1,4-dioxane.[3]

Experimental Section

Perfluoro-1,2-dimethoxyethane.—1,2-Dimethoxyethane (4.015 g, 0.045 mol) was evaporated employing a flow of 50–100 cc of helium into gradient reactor containing four distinct zones which were maintained at −78°, a temperature below the freezing point of the ether (−58°). An initial flow of 0.5 cc/min of fluorine and 20 cc/min of helium was started and after 12 hr the fluorine was increased to 1.0 cc/min. After an additional 12 hr, zone 1 was allowed to run out of Dry Ice. Twelve hours after zone 1 was clear of Dry Ice the fluorine was increased to 1.5 cc/min while helium flow still was maintained at 20 cc/min. The fluorine flow was maintained at 1.5 cc/min. On alternate days the helium was reduced to 10 cc/min, followed by one additional zone being allowed to clear of Dry Ice. Subsequent reductions to 5-, then to 0-cc/min helium flow were followed each time by warming of one additional zone.[4] Finally, as the reactor warmed under a flow of pure fluorine, the fluorinated ether was passed through a metal trap filled with sodium fluoride pellets and into a glass trap maintained at −78°. The raw fluorocarbon ethers collected represented a mass which corresponded to between 50 and 100% of the expected yield based on moles of the parent ether. This mixture contained several hydrofluoro ethers and

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(2) R. J. Lagow and J. L. Margrave, "The Reaction of Polynuclear Hydrocarbons with Elemental Fluorine," in press; R. J. Lagow and J. L. Margrave, *Chem. Eng. News*, 40 (Jan 12, 1970).

(3) J. H. Simons, U. S. Patent 2,500,388 (1950).

(4) Warmings of successive zones allowed renewal of the reactant surface inside the reactor.

other hydrolytically unstable and corrosive products along with a smaller amount of perfluorinated fragments. The yield of the hydrofluoro ethers in most cases exceeded the yield of perfluoro ethers owing to incomplete reaction. These products were removed by aqueous alkali hydrolysis and the hydrolytically stable ethers fractionated. The bulk of the desired products was collected in the −95 and −130° traps (combined weight 2.48 g, 20.6%). Final purification was accomplished using gas–liquid chromatography using a fluorosilicone (QF-1-0065, 13% on Chromosorb p, 80–100 mesh) column.

Perfluoro-1,2-dimethoxyethane is a gas at room temperature (bp 16.7°). The molecular weight determined by the ideal gas method was 269 (*cf.* 270 for $C_4F_{10}O_2$). The ^{19}F nmr consisted of a triplet at +59.54 and a quartet at +94.19 ppm relative to $CFCl_3$[5] with coupling constant 9.2 Hz and relative intensities of 3:2. The ir spectrum exhibited bands at 1410 (w), 1295 (s), 1250 (s), 1200 (w), 1170 (sh), 1155 (s), 1105 (w), 923 (w), 887 (m), 865 (w), 819 (w), 690 (w) wavenumbers. The mass spectrum contained no parent peak but showed strong peaks at *m/e* 135 corresponding to the symmetrical cleavage of the molecule, (CF_3–O–CF_2). Other strong peaks were at *m/e* 119 (C_2F_5), 100 (C_2F_4), 69 (CF_3), 50 (CF_2), 47 (CFO). *Anal.* Calcd for $C_4F_{10}O_2$: F, 70.36. Found: C, 17.41; F, 70.08. The yield was 21%.

1-Hydrononafluoro-2,5-dioxahexane.—If the products of the previously described reaction were not hydrolyzed, a second major product may be isolated which in some cases exceeds the amount of perfluoro-1,2-dimethoxyethane. This ether was a liquid with a disagreeable odor and may be quite toxic. Its molecular weight was determined to be 251 (*cf.* 252 for $C_4HF_9O_2$). Its ^{19}F nmr spectrum exhibited a triplet at +59.22 and a quartet at +93.63 with a coupling constant of 9.4 hz and relative intensities of 2:2, a doublet centered at +88.36 (J = 70.0 Hz) split into triplets (J = 4.4 Hz), and a triplet at +92.47 ppm (J = 4.6 Hz) relative to $CFCl_3$ with relative integrals of 2:2. The proton nmr consisted of a triplet at −6.26 ppm relative to TMS (external standard) with coupling constant equal to 68.6 Hz, in good agreement with the doublet splitting in the ^{19}F nmr. If the proton was irradiated, the ^{19}F doublet decayed into a singlet. This information is consistent with a structure containing a proton in the 1 position (Chart I). The mass spectrum supports this

CHART I

^1H AND ^{19}F NUCLEAR MAGNETIC RESONANCE SPECTRA[a]

Perfluoro-1,2-dimethoxyethane

$$\underset{+59.54}{CF_3}—O—\underset{+94.19}{CF_2}—\underset{+94.19}{CF_2}—O—\underset{+59.54}{CF_3}$$
(9.2)

1-Hydrononafluoro-2,5-dioxahexane

$$\underset{+59.22}{CF_3}——O——\underset{+93.63}{CF_2}——\underset{+92.47}{CF_2}——O——\underset{+88.36}{CF_2}——\underset{-6.26^b}{H}$$
(9.2) (<1) (4.5) (69.3)

Perfluorobis(2-methoxyethyl) Ether

$$\underset{+59.30}{CF_3}—O—\underset{+93.84}{CF_2}——\underset{+91.64}{CF_2}—O—\underset{+91.64}{CF_2}—\underset{+93.84}{CF_2}—O—\underset{+59.30}{CF_3}$$
(9.4) (<1)

[a] ϕ in parts per million (J in hertz). $\phi_{CFCl_3(ext)} = 0$. [b] ^1H [TMS (external standard)].

conclusion. The two peaks corresponding to "symmetrical" cleavage at *m/e* 135 (C_2F_5O) and 117 (C_2HF_4O) were both strong with relative intensities of 1:1.5 as were the very strong peaks at *m/e* 69 (CF_3) and 51 (CHF_2) of relative intensties of 1:1.5. Other, less intense peaks support this conclusion. The ir spectrum contained a weak proton absorption at 3028 cm^{-1} in addition to carbon–fluorine and carbon–oxygen bands at 1400 (w, b), 1370 (w), 1295 (s), 1250 (s), 1192 (m), 1179 (sh), 1159 (s), 1125 (s), 1040 (m), 910 (m), 853 (w), 818 (w), 700 (w) cm^{-1}. The yield was 0–25%.

Perfluorobis(2-methoxyethyl) Ether.—Bis(2-methoxyethyl) ether (1.79 g, 0.0134 mol) was evaporated at 50° into the four-zone cryogenic factor (zone 1, −40°; zones 2, 3, and 4 at −78°) using a 80–100-cc/min flow of helium gas. After 6 to 8 hr the helium flow was reduced to 20 cc/min and a 0.5-cc/min flow of fluorine was started. A similar procedure to that used for 1,2-dimethoxyethane was used to complete the reaction. The raw products were fractionated through −63, −78, −95, and −196° traps. Perfluorobis(2-methoxyethyl) ether was collected from the −78 and −95° traps (yield 0.83 g, 16.1%). Perfluorobis(2-methoxyethyl) ether is a volatile liquid, bp 60–63°). Its molecular weight was determined to be 385 (*cf.* 386 for $C_6F_{14}O_3$). The ^{19}F nmr exhibited a triplet at +59.30 and a quartet at +93.84 (J = 9.4 Hz) and a singlet at +91.64 ppm relative to $CFCl_3$. The relative integrals of the absorptions are 3:2:2. The spectrum exhibited bands at 1385 (w), 1295 (s), 1250 (s), 1220 (sh, w), 1200 (w), 1165 (s), 1145 (s), 920 (sh), 910 (m), 770 (m), 697 (w), 681 (sh) wavenumbers. The mass spectrum exhibited strong peaks at *m/e* 185 (C_3F_7O), 135 (C_2F_5O), 119 (C_2F_5), 100 (C_2F_4), 69 (CF_3), 50 (CF_2). *Anal.* Calcd for $C_6F_{14}O_3$: C, 18.67; F, 68.90. Found: C, 18.64; F, 69.94. The yield was 16%.

Discussion

The yields of perfluorinated ethers reported are not to be considered optimum. Obviously the partially fluorinated material could be recycled. A new variable temperature reactor[6] which enables reactions to be studied at temperatures other than −78° may also greatly improve the yields.

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Registry No.—Perfluoro-1,2-dimethoxyethane, 378-11-0; 1,2-dimethoxyethane, 110-71-4; fluorine, 7782-41-4; 1-hydrononafluoro-2,5-dioxahexane, 40891-98-3; perfluorobis(2-methoxyethyl) ether, 40891-99-4; bis(2-methoxyethyl) ether, 111-96-6.

(5) Nmr samples were condensed into capillary tubes, sealed, and immersed in a solution of $CFCl_3$ (30%), tetramethylsilane (5%), and carbon tetrachloride (65%) contained in a standard nmr tube.

(6) To be published.

Carbon-13 Magnetic Resonance Study of Terpenoids. I. An Application of Heteronuclear Selective Decoupling Experiments to the Spectral Assignments of Nonproton-Bearing Carbon-13 Resonances of a Germacranolide, Melampodin

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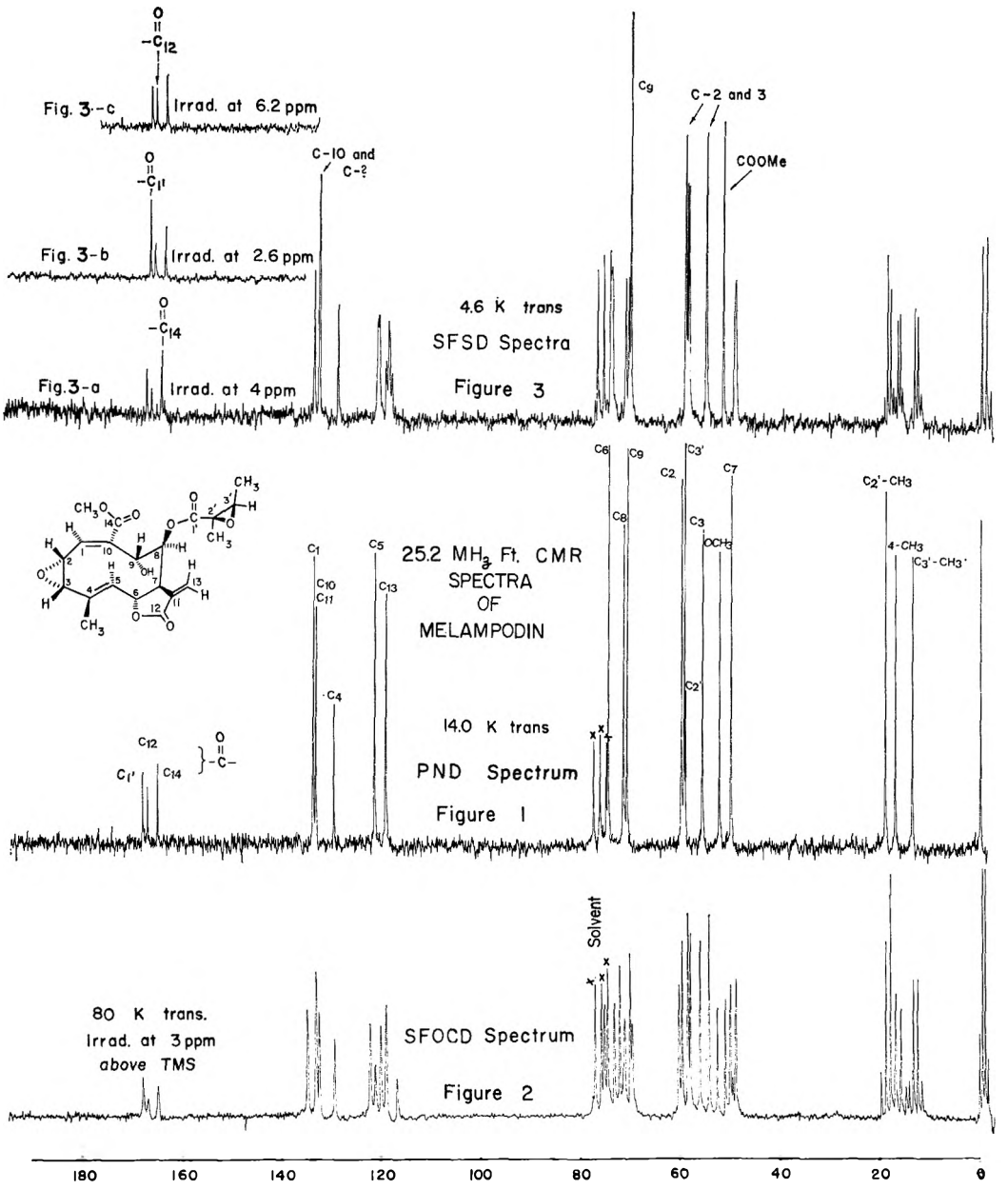
We recently reported[2] the isolation and structure elucidation of melampodin, a new sesquiterpene lactone from *Melampodium leucanthum* Torr. & Gray. Single-crystal X-ray diffraction[3] and neutron diffraction[4] of this highly oxygenated medium-ring compound revealed that melampodin represents a new and novel germacranolide-type sesquiterpene lactone, which, in contrast to the well-known *trans,trans*-cyclodeca-1,5-

(1) (a) Louisiana State University. (b) Varian AG.

(2) N. H. Fischer, R. Wiley, and J. D. Wander, *J. Chem. Soc. Chem. Commun.*, 137 (1972).

(3) S. Neidle and D. Rogers, *J. Chem. Soc. Chem. Commun.*, 140 (1972).

(4) I. Bernal and S. F. Watkins, *Science*, **178**, 1282 (1972).



Figures 1–3.

diene germacrolides, represents a *cis,trans*-cyclodeca-1,5-diene melampolide ($\Delta^{1(10)}$ cis double bond).[5] Limited amounts of material and inconclusive results in a number of chemical reactions of melampodin and other new, highly oxygenated sesquiterpene lactones suggest that nuclear magnetic resonance (nmr) studies in general and ^{13}C magnetic resonance (cmr) in particular offered the best prospects for the structural elucidation of new malampolides and their derivatives. The cmr investigation of melampodin was conducted by dissolving the compound in $CDCl_3$ containing ~2% tetramethylsilane to act as an internal reference, and then recording cmr spectra of the sample under the experimental conditions as described below.

The initial cmr spectrum of melampodin was obtained on an nmr spectrometer operating at 23.4 kG or 25.2 MHz for ^{13}C and simultaneous proton noise decoupling (PND) at 100 MHz. The utilization of this technique leads to the elimination of all ^{13}C–^{1}H spin–spin splittings yielding just one line per carbon atom. The resultant cmr spectrum of the compound ($C_{21}H_{24}O_9$) consists of 20 sharp singlets representing 21 carbon atoms in the molecule (Figure 1).

The singlet resonances occurring in the PND spectrum were assigned to methyl, methylene, and methine groups and nonproton-bearing carbons by obtaining a second ^{13}C spectrum of the sample under slightly modified conditions. Namely, in the place of a PND frequency, a single-frequency (coherent) decoupling field was applied which was tuned to a frequency several hundred hertz (usually 300 to 500 Hz) farther away from all proton resonances that are coupled to the ^{13}C nuclei under observation. Since $J_{^{13}C-^{1}H}$ values are relatively large (120–250 Hz), a partially decoupled spectrum results under single-frequency off-center decoupled (SFOCD) experimental conditions. This spectrum (Figure 2) exhibits small residual splittings in the form of a quartet for methyl carbons, a triplet for methylene carbons, a doublet for tertiary carbons, and unchanged singlets for nonproton-bearing carbon

(5) D. Rogers, G. P. Moss, and S. Neidle, *J. Chem. Soc. Chem. Commun.*, 142 (1972).

TABLE I[a]

Chemical shift (PND spectrum)	No. of lines (SFOCD spectra)	Inference deduced from PND and SFOCD spectra	Comparison of ^{13}C resonances in PND and SFSD spectra)	^{13}C assignment
167.0	Singlet	Lowest field resonances, carbonyl signals	SE when C-2′ Me or C-3′ PM are irradiated (Figure 3b)	C-1′
166.0	Singlet		SE when C-13 pm is irradiated (Figure 3c)	C-12
164.0	Singlet		SE when COOMe PM is irradiated (Figure 3a)	C-14
133.0	Doublet	Lowest field $^{H}>C=$, β to carbonyl, ∴ C-1		C-1
132.5	Singlet	Two >C=, ∵ twice the intensity of singlet at 128.9	SE when COOMe, or C-13 PM are irradiated (Figure 3a)	C-10 and C-11
128.9	Singlet	One >C=	SE when C-4 PM is irradiated	C-4
120.7	Doublet	$^{H}>C$, by process of elimination C-5	SE when C-5 PM is irradiated	C-5
118.5	Triplet	$^{H}_{H}>C=$, ∴ C-13		C-13
74.2	Doublet	H–C–O probably present in medium ring	SE when C-6 PM is irradiated	C-6
71.2	Doublet		SE when C-8 PM is irradiated	C-8
70.2	Doublet		SE when C-9 PM is irradiated (Figure 3a)	C-9
59.5	Doublet	H–C–O probably present in the epoxide ring	SE when C-2 and C-3 PM are irradiated (Figure 3a)	C-2 or 3
59.0	Doublet		SE when C-3′ PM is irradiated	C-3′
58.7	Singlet	–C–O, ∴ C-2′	SE when C-3′ PM is irradiated	C-2′
55.3	Doublet	H–C–O (probably epoxide)	SE when C-2 and C-3 PM are irradiated (Figure 3a)	C-3 or C-2
51.9	Quartet	Me at O–C(=O)–, ∴ COOMe		COOMe
49.7	Doublet	H–C–O or H–C–	SE when C-7 PM is irradiated	C-7
18.9	Quartet	Me, ∴ C-2′ Me, C-3′ Me, or C-4 Me	SE when C-2′ methyl PM is irradiated	C-2′ Me
16.9	Quartet		SE when C-4 methyl PM is irradiated	C-4 Me
13.4	Quartet		SE when C-3′ Me PM is irradiated	C-3′ Me

[a] Chemical shift recorded in parts per million relative to TMS. PND, proton noise-decoupled spectrum; SFOCD, single-frequency off-center decoupled spectrum; SFSD, selectively decoupled spectrum; SE, signal enhanced; PM, proton–carbon-13 multiplet.

atoms. The spectral data obtained from these two experimental conditions and the interpretation of these data are recorded in the first three columns of Table I.

The definitive designation of the unassigned and partially assigned ^{13}C resonances of melampodin was obtained from selective single-frequency heteronuclear-decoupled (SFSD) cmr spectra[6] and the correlation of chemical shifts of the ^{13}C signals from the PND spectrum with the assigned proton signals in the proton magnetic resonance (pmr) spectrum (Figure 4). In a SFOCD spectrum, all ^{13}C–^{1}H splittings caused by the direct spin–spin interactions of ^{13}C and ^{1}H nuclei are greatly reduced. The magnitude of this residual splitting (J_{res}) may be described by the following expression: J_{res}^{obsd} in a given ^{13}C resonance $= \Delta f J/(\gamma_{H_2}/2\pi)$, where J = the magnitude of true ^{13}C–^{1}H coupling, $\gamma_{H_2}/2\pi$ = the strength of the decoupling field in hertz, and Δf = the frequency difference (in hertz) between the decoupling frequency and the resonance frequency of proton(s) attached to the ^{13}C nucleus under investigation.

In the SFSD experiment, $\Delta f = 0$ for the ^{13}C nucleus under investigation and the value of $\gamma_{H_2}/2\pi$ was reduced by approximately one half or one third of the intensity employed during the SFOCD experiments. The strength of $\gamma_{H_2}/2\pi$ employed in the SFSD experiments depends upon the width of the multiplet of the proton that is directly bonded to the carbon atom to be assigned. The irradiated proton spectral region is not a relative narrow multiplet composed of ^{1}H–^{1}H couplings, but a spectral pattern caused by the combined ^{1}H–^{1}H and ^{1}H–^{13}C splittings and thus may be ~120 to 250 Hz wide. Although in the pmr spectra of even moderately complex molecules ^{1}H–^{1}H–^{13}C multiplets inevitable overlap, the SFSD technique may still be successfully employed to assign ^{13}C resonances, provided that their corresponding ^{1}H–^{1}H multiplets are separated from each other by at least 5 Hz. Therefore, when the single frequency decoupling radiofrequency field was centered at the absorption frequency of H-9 at δ 4.00 in the pmr spectrum of melam-

(6) (a) A. J. Jones, T. D. Alger, D. M. Grant, and W. M. Lichtman, *J. Amer. Chem. Soc.*, **92**, 2396 (1970); (b) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *ibid.*, **91**, 7445 (1969).

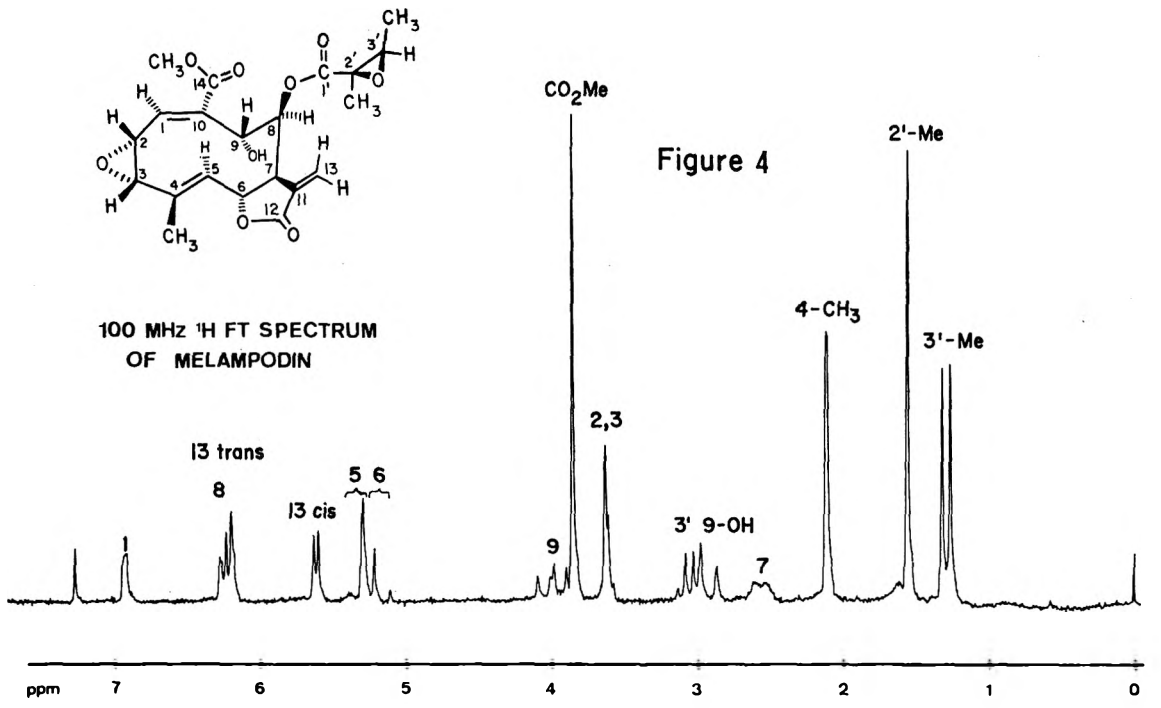


Figure 4.

podin (see Figure 4), the ^{13}C–^{1}H splittings associated with the respective interacting nuclei were totally eliminated and the completely decoupled ^{13}C resonance of C-9 appeared as the sharpest singlet in the SFSD spectrum (Figure 3a). Comparison of this SFSD spectrum with those obtained under PND and SFOCD spectra (Figures 1 and 2) showed that, besides the C-9 multiplet, other ^{13}C–^{1}H multiplets occurring in the SFOCD spectrum as shown in Figure 2 also collapsed into singlets in the SFSD spectrum (Figure 3a). The magnitude of intensities and the degree of sharpness observed in these ^{13}C singlets in the SFSD spectrum are directly related to the proximity of the resonance frequencies of the protons attached to the corresponding ^{13}C nuclei, to the proton frequency at which the maximum intensity of the perturbing radiofrequency field is aligned. Thus, when the decoupling radiofrequency field was aligned at the center of the H-9 ^{13}C–^{1}H multiplet at δ 4.00, other ^{13}C–^{1}H multiplets representing COOMe and H-2 and H-3 in the pmr spectrum were also considerably perturbed. As a direct consequence of this irradiation the quartet at 51.9 ppm and the doublets at 55.3 and 59.5 ppm observed in the SFOCD spectrum of melampodin were transformed into singlets in the SFSD trace (Figure 3a). In the SFSD spectrum the COOMe singlet was sharper than the two C-2 and C-3 singlets because the COOMe pmr signal at 3.94 ppm is nearer to the maximum intensity of the perturbing radiofrequency field at δ 4.00 than the overlapping absorptions of H-2 and H-3 at 3.63 ppm. Previously partially designated methyl ^{13}C signals at 13.4, 16.9, and 18.9 ppm as well as the methine ^{13}C resonances at 49.7, 59.0, and 71.2 ppm were assigned to C-3′ Me, C-4 Me, C-2′ Me, C-7, C-3′, C-8, and C-6, respectively, by performing similar selective decoupling experiments. (See the last two columns in Table I.)

The ^{13}C signals at 128.9 and 132.5 ppm corresponding to nonproton-bearing olefinic carbon atoms as well as the carbonyl carbon atoms at 164.0, 166.0, and 167.0 ppm were sorted out during the SFSD experiments by observing the enhancements in the intensities of the resonances of the nonproton-bearing ^{13}C nuclei. When in the pmr spectrum of melampodin the maximum intensity of the decoupling field was set at the resonance frequency of the C-3′ methyl group at δ 1.3, not only the splittings of the directly bonded nuclei (^{13}C–^{1}H) of the C-3′ methyl multiplet and to a lesser extent the C-2′ methyl signal at δ 1.58 were perturbed, but the long range couplings (^{13}C–C–^{1}H and ^{13}C–C–C–^{1}H) occurring in their resonances were also affected. As a direct result of this decoupling, the intensities of the nonproton-bearing C-2′ carbon and the C-1′ carbonyl carbon singlets at 58.7 and 167.0 ppm, respectively, increased in the SFSD spectrum. Similarly, when in the pmr spectrum the decoupling frequency was aligned at δ 2.6, the proton resonances of the C-2′ methyl at δ 1.58 and H-3′ at δ 3.1 were perturbed and the C-1′ carbonyl ^{13}C signal exhibited even greater intensity enhancement (compare Figures 3b and 1). Thus by observing the small but definite increment in their intensity in the selectively decoupled spectra, the C-12 and C-14 carbonyl ^{13}C resonances (see Figures 3a and 3c) as well as the nonproton-bearing olefinic C-4, C-10, and C-11 ^{13}C signals were assigned. This appears to be the first reported example[7] for the assignment of the ^{13}C resonances representing nonproton-bearing carbonyl and olefinic carbon atoms in a complex natural product with the aid of SFSD experiments. This technique may be generally useful for the assignment of nonproton-bearing ^{13}C signals in other related systems.

The resonance of the epoxide carbon atoms 2 and 3 were distinguished on the basis of their distinctive chemical shifts. The model of melampodin derived

(7) Jones, *et al.*,[6a] used in 1970 the same SFSD technique toward the spectral assignment of ^{13}C resonances in cmr spectra of nonalternating hydrocarbons.

from neutron diffraction data[4] indicates a definite steric interaction between the C-4 methyl protons and H-3, whereas no such interaction exists between H-2 and H-1. Since it is well known that such steric interaction causes an upfield shift in resonances of interacting ^{13}C nuclei, the high field signal at 55.3 is assigned to C-3 while the lower field absorption at 59.5 to C-2.

The above methodology employed for the cmr spectral analysis will be particularly useful in the structure elucidation of other new, structurally related melampolides and complex natural products in general. After accumulating data from other sesquiterpene lactones we hope to correlate the ^{13}C chemical shift data with stereochemical and conformational features of the melampolides. The availability of accurate conformational information of melampolides in solution will help to better understand the biogenesis of these highly strained medium rings. Furthermore, the newly obtained data will be used extensively in our biochemical systematic studies of the three white-rayed species of the genus *Melampodium*.[2,8]

Experimental Section

The nmr spectral data were obtained on a Varian XL-100-15 spectrometer operating Fourier transform mode with proton decoupling. Data were accumulated in a Varian 620F computer using 5000-Hz sweep width in 8192 points. Data acquisition and pulse delay times were 0.8 and 0.9 sec. The number of pulses (transients) employed were varied and are recorded on respective cmr traces. Melampodin (300 mg) dissolved in 2 ml of $CDCl_3$ was employed for the nmr study. The chemical shifts are relative to internal tetramethylsilane and are estimated to be accurate to ± 0.04 ppm.

Acknowledgment is made to the University Council on Research, Louisiana State University, for partial support of this work. We thank Dr. T. F. Stuessy for collecting and authenticating the plant collections.

Registry No.—Melampodin, 35852-26-7.

(8) T. F. Stuessy, *Brittonia*, **23**, 177 (1971).

Nucleosides. LXXXIV. Total Synthesis of Pentopyranine C, a Nucleoside Elaborated by *Streptomyces griseochromogenes*[1]

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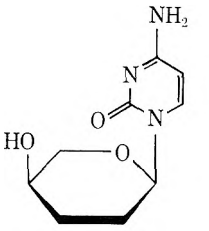
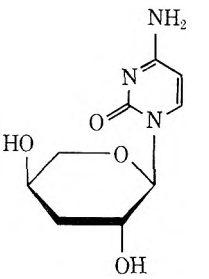
Received April 18, 1973

Recently, Seto, *et al.*,[2] isolated two cytosine nucleosides, pentopyranine A and C, from the fermentation broth of *Streptomyces griseochromogenes*, the blasticidin S-producing microorganism.[3] The structures of these nucleosides were given as 1-(2,3-dideoxy-α-L-*glycero*-pentopyranosyl)cytosine (**1**) and 1-(3-deoxy-α-L-*threo*-pentopyranosyl)cytosine (**2**). Pentopyranine A and C are therefore the first naturally occurring nucleosides possessing the α-L configuration.



1, pentopyranine A



2, pentopyranine C

We now report the total synthesis of pentopyranine C (**2**) and its furanosyl isomer (**13**) by condensation of bis(trimethylsilyl)-N^4-acetylcytosine with tri-*O*-acetyl-3-deoxy-L-*threo*-pentoses (**9** and **10**) in the presence of stannic chloride.[4]

The starting material, 3-deoxy-1,2-*O*-isopropylidene-α-L-*threo*-pentose (**6**), was prepared by the procedure of Prokop and Murray[5] as shown in Chart I from 3-deoxy-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**3**).[5,6] Acid hydrolysis of **6** afforded the aldopentose (**8**) which was acetylated to give a mixture of **9** and **10**. This mixture of triacetates (**9** and **10**) was not separated, but condensed directly with bis(trimethylsilyl)-N^4-benzoylcytosine to afford the mixture **11a** and **12a**, which was saponified and acetylated to **11b** and **12b**. The latter mixture was separated easily by fractional crystallization from methanol. The physical constants (melting point, uv, ir, and nmr) of **11b** were identical with those reported[2] for the triacetyl derivative of pentopyranine C. After deacetylation of **11b**, a product (**2**) was obtained which was identical with pentopyranine C with respect to melting point, optical rotation, and uv, ir spectral characteristics.

The structure of compound **12b** was established by an unambiguous synthesis. Acetylation of **6** gave compound **7** which was acetolyzed to the triacetate (**9**). Condensation of **9** with bis(trimethylsilyl)-N^4-acetylcytosine gave a nucleoside identical in all respects with **12b**. After deacetylation of **12b**, the free nucleoside (**13**) was obtained. The α-L configuration for **13** was established by comparison of its ORD curve (in water) with that of 1-(α-L-arabinofuranosyl)cytosine (**14**).[7] Both **13** and **14** showed positive Cotton effects with two extrema at 273 and 218 mμ (the amplitudes being 180 and 230, respectively).

The total synthesis of pentopyranine C provides conclusive proof of the structure of this natural product which is believed to be a shunt pathway product[2] in the synthesis of the important anti rice blast disease agent, Blasticidin S.[3]

Experimental Section

Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

(2) H. Seto, N. Otake, and H. Yonehara, *Tetrahedron Lett.*, 3991 (1972).

(3) S. Takeuchi, K. Hirayama, K. Ueda, H. Sakai, and H. Yonehara, *J. Antibiot. Ser. A*, **11**, 1 (1958); For recent reviews, see J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966); R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley, New York, N. Y., 1970).

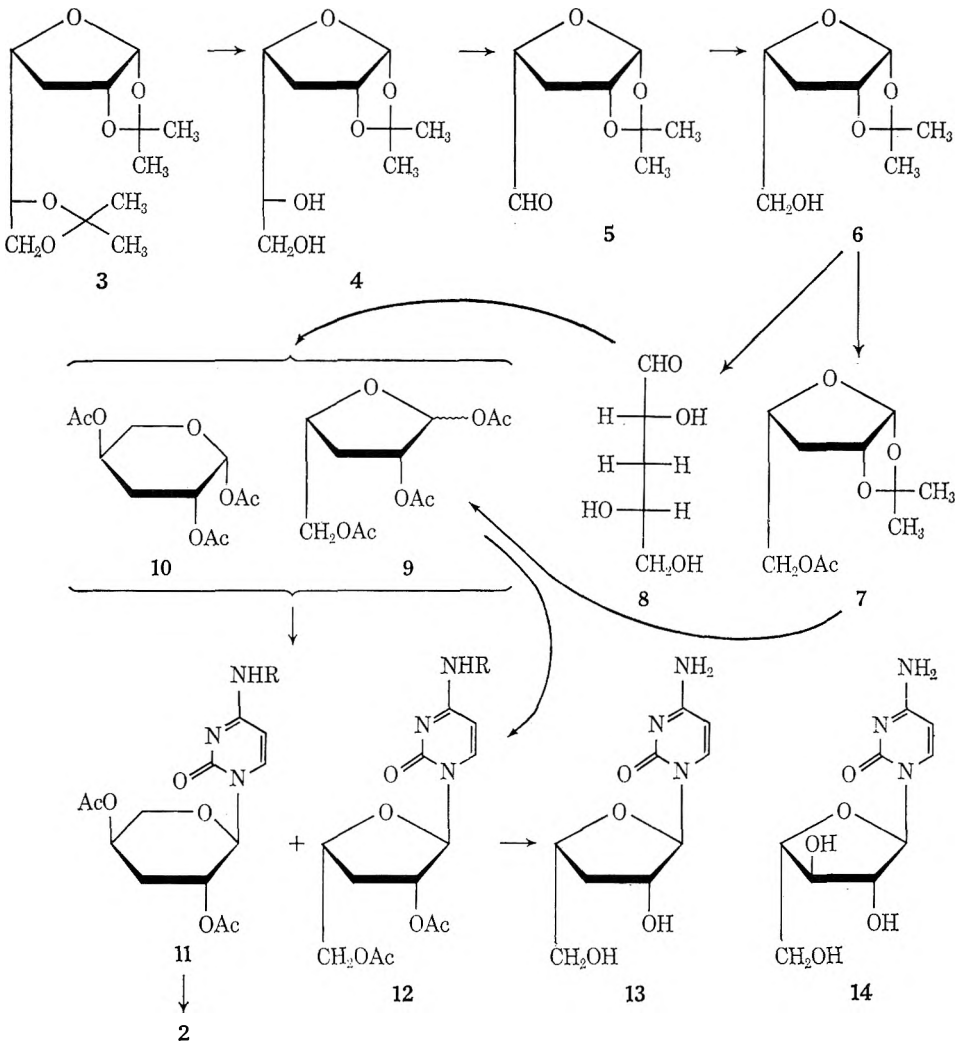
(4) U. Niedballa and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **9**, 461 (1970); K. A. Watanabe, I. Wempen, and J. J. Fox, *Carbohyd. Res.*, **21**, 148 (1972).

(5) J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(6) T. Chiu, K. A. Watanabe, and J. J. Fox, *Carbohyd. Res.*, in press.

(7) N. Yamaoka, B. A. Otter, and J. J. Fox, *J. Med. Chem.*, **11**, 55 (1968).

CHART I



3-Deoxy-L-*threo*-pentose (8).—A mixture of compound 6 (7.0 g) and Dowex 50 (H^+) (~5 ml) in water (70 ml) was stirred for 1.5 hr. The resin was filtered, and the filtrate was concentrated to a syrup (5.0 g) which was free of isopropylidene group (nmr). This product was not characterized further, but used directly in the next step.

Tri-*O*-acetyl-3-deoxy-L-*threo*-pentofuranose (9) and -β-L-*threo*-pentopyranose (10).—Compound 8 (5.0 g) was acetylated in pyridine (26 ml) and acetic anhydride (20 ml) overnight. The mixture was poured into ice–water (300 ml) and extracted with dichloromethane (5 × 60 ml). The organic extracts were washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, and condensed to dryness. The residue was coevaporated several times with toluene. The nmr spectrum in $CDCl_3$ showed that the product consists mainly of 9 and 10 about 1:1 ratio (H-1 for 9, δ 6.19, singlet; H-1 for 10, δ 5.78, doublet $J_{1,2} \cong 3.5$ Hz). This product was used directly in the next step.

1-(2,4-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentopyranosyl)-N^4-acetylcytosine (11b) and 1-(2,5-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentofuranosyl)-N^4-acetylcytosine (12b).—To a solution of the above mixture of 9 and 10 (4.5 g) and tin tetrachloride (8 ml) in 1,2-dichloroethane (250 ml) was added a 1,2-dichloroethane solution (100 ml) of bis(trimethylsilyl)-N^4-benzoylcytosine[8] prepared from 12 g of N^4-benzoylcytosine. The mixture was stirred overnight at room temperature and then poured into a cold, saturated sodium bicarbonate solution (400 ml). The organic layer was washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was crystallized from ethanol. Compounds 11a and 12a cocrystallized. Both 11a and 12a had identical mobilities on tlc in several solvent systems.

The mixture of 11a and 12a (4.2 g) was treated with methanolic ammonia saturated at 0° (~120 ml) overnight. After evaporation, the residue was partitioned between water and ether (50 ml each). The organic layer was washed with chloroform (2 × 50 ml) and evaporated to give a mixture of 2 and 13 as a glass. All attempts to separate 2 and 13 by fractional crystallization or column chromatography failed.

The mixture of 2 and 13 (1 g) was dissolved in pyridine (5 ml) and acetylated with acetic anhydride overnight. The mixture was poured into ice–water (60 ml) and extracted with chloroform (2 × 50 ml). The combined extracts were washed with water, saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residue was coevaporated several times with ethanol to remove traces of pyridine and then dissolved in methanol (~5 ml), and the mixture was kept at 0° overnight. Compound 12b (180 mg) crystallized as needles: mp 179–181°; $[\alpha]^{27}D$ +43° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$, TMS internal standard) OAc δ 2.17 (6 H), NAc 2.27 (3 H), H-5′,5″ 4.2 (doublet, 2 H), H-4′ 4.83 (multiplet), H-2′ 5.58 (multiplet), H-1′ 5.87 (doublet $J_{1',2'} = 1.5$ Hz).

Anal. Calcd for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.42; N, 11.89. Found: C, 51.05; H, 5.60; N, 11.83.

The mother liquor of crystallization of 12a was kept at 0° for 2 days. Compound 11b (121 mg) crystallized as cubes: mp 204–205° (lit.[2] mp 203–205°); $[\alpha]^{27}D$ 0° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$; TMS internal standard) OAc δ 1.96 (3 H), 2.16 (3 H), NAc 2.28 (3 H), H-5′,5″ 4.01 (2 H, quartet $J_{5',5''} \cong 13.0$ Hz), H-4′ 5.11 (narrow multiplet), H-2′ 5.29 (broad multiplet), H-1′ 5.91 (doublet $J_{1',2'} = 9.5$ Hz), H-5, H-6 7.51 and 7.82 (doublets $J_{5,6} = 7.5$ Hz).

(8) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.*, **11**, 1470 (1963).

1-(3-Deoxy-α-L-*threo*-pentopyranosyl)cytosine (2) (Pentopyranine C).—Compound **11b** (98 mg) was treated overnight with methanolic ammonia (~10 ml) saturated at 0°. After evaporation of the solvent, the residue was triturated with ether (2 × 10 ml) and chloroform (2 × 10 ml), and the residue was crystallized from ethanol to give compound **2**: 49 mg; mp 144–145°; $[\alpha]^{27}D$ +19° (*c* 1.0, H_2O) (lit.[2] mp 143–145°, $[\alpha]^{21}D$ +20°).

1-(3-Deoxy-α-L-*threo*-pentofuranosyl)cytosine (13).—Compound **12a** (110 mg) was deacetylated with methanolic ammonia as described for the synthesis of **2** from **11a**. Compound **13** (42 mg) was obtained as needles after recrystallization from methanol: mp 160–163°, $[\alpha]^{27}D$ +19° (*c* 1.0, H_2O).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.43; H, 5.66; N, 18.20.

5-*O*-Acetyl-3-deoxy-1,2-di-*O*-isopropylidene-β-L-*threo*-pentose (7).—Compound **6**[5] (5 g) was acetylated in pyridine (20 ml) with acetic anhydride (5 ml) overnight. The crude acetyl derivative **7** (5 g) was obtained as a syrup which was chromatographically homogeneous and sufficiently pure for the next step.

Tri-*O*-acetyl-3-deoxy-β-L-*threo*-pentofuranose (9).—To a cooled and stirred solution of **7** (5 g) in acetic acid (20 ml) and acetic anhydride (10 ml) was added sulfuric acid (1 ml). The mixture was kept overnight at room temperature, then partitioned between dichloromethane (100 ml) and ice–water (100 ml). The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 100 ml), water, dried over sodium sulfate, and evaporated to dryness. The residue was coevaporated several times with toluene to remove traces of acetic acid. This syrup was contaminated with a small amount of the α anomer: nmr ($CDCl_3$, TMS internal standard) β-H-1 δ 6.18 (singlet), α-H-1 6.80 (doublet, $J_{1,2}$ = 3.5 Hz). No anomeric signal corresponding to the pyranose isomers was detected by nmr.

1-(2,5-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentofuranosyl)cytosine (12b).—The anomeric mixture of **9** was condensed with bis(trimethylsilyl)-N^4-acetylcytosine[8] (prepared from 5 g of N^4-acetylcytosine) in 1,2-dichloroethane (250 ml) in the presence of stannic chloride (8 ml). Compound **12b** (2.2 g) was obtained after two recrystallizations from methanol: mp 179–181°, $[\alpha]^{27}D$ +43° (*c* 1, $CHCl_3$). A mixture melting point of this sample with **12b** prepared as described previously in this paper was undepressed. Ir and nmr spectra of both samples were identical.

Registry No.—**2**, 39007-97-1; **7**, 41107-64-6; **8**, 41107-43-1; **9**, 41107-68-0; **10**, 41164-55-0; **11b**, 41164-56-1; **12b**, 41164-57-2; **13**, 41164-58-3.

Conversion of 1,2-*O*-Isopropylidene-α-D-xylofuranose into 3-*O*-Benzoyl-5-bromo- and -5-iodo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose *via* a Cyclic *N,N*-Dimethylbenzamide Acetal Derivative

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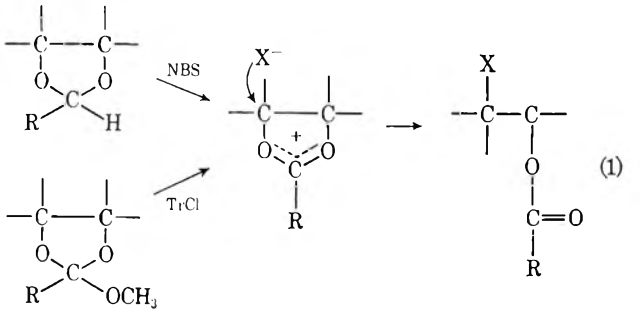
Received March 27, 1973

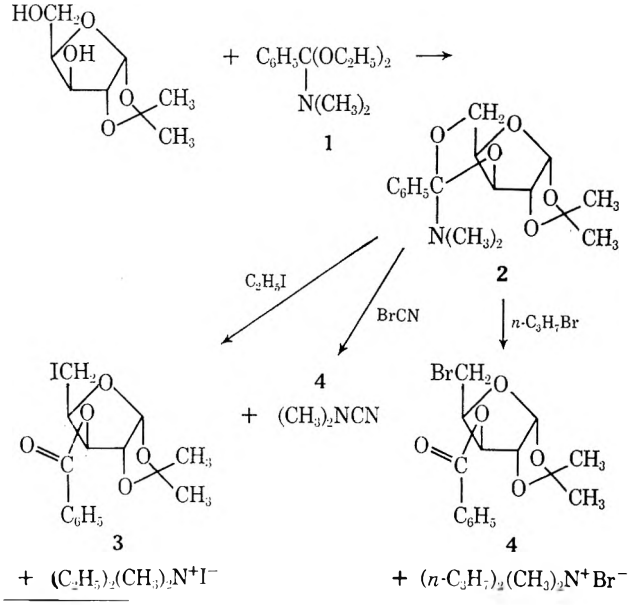
We wish to report a new method for converting glycols into esters of halohydrins under very mild conditions requiring no acid or base catalyst. Previously, cyclic benzylidene acetals of carbohydrates have been opened with *N*-bromosuccinimide to form bromodeoxy benzoate derivatives.[1] For example, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was converted into methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside. Recently, it has been reported that acetates of simple aliphatic chlorohydrins are readily prepared by the reaction of cyclic ortho esters with trityl chloride.[2] Both of these reactions are regioselective and stereospecific and it has been proposed that they proceed by a nucleophilic attack by halide ion on an acyloxonium ion intermediate (eq 1).



(1)

The dimethyl acetal of *N,N*-dimethylbenzamide is reported to react with methyl β-D-ribofuranoside to give a 2,3-cyclic amide acetal derivative.[3] We have found that 1,2-*O*-isopropylidene-α-D-xylofuranose reacts on standing with a dichloromethane solution of *N,N*-dimethylbenzamide diethyl acetal **1** to give 3,5-*O*-[α-(dimethylamino)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**). The compound, isolated by distillation, slowly crystallized after standing a few weeks at room temperature and was recrystallized from pentane, mp 74–75.5°. Gas chromatography showed only one peak, but the nmr spectrum indicated the presence of two compounds. Three singlets for the *C*-methyls (δ 1.33, 1.43, and 1.50), two singlets for *N*-methyl (2.07 and 2.27, ratio of 6:1), and two doublets for the C-1 hydrogen (5.97 and 6.07) suggested two isomers differing only in the chirality of the benzyl carbon atom.

When **2** was refluxed with methyl or ethyl iodide a quaternary ammonium iodide salt precipitated. Evaporation of the filtrate gave a colorless syrup (**3**): $C_{15}H_{17}IO_5$. The ir spectrum (liquid film) showed absorption at 1727 cm^{-1}, indicative of a benzoate ester. The nmr spectrum was compatible with 3-*O*-benzoyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose. A two-proton doublet appeared at δ 3.33 ($J_{4,5}$ = 7 Hz) upfield from a one-proton doublet at 5.58 ($J_{3,4}$ = 3 Hz, $J_{2,3}$ = 0); consequently the iodine substitution was assigned



(1) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035, 1045, 1053 (1969).

(2) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, **95**, 278 (1973).

(3) S. Hanessian and E. Moralioglu, *Tetrahedron Lett.*, 813 (1971).

to the C-5 methylene while the more electronegative benzoate ester was placed at C-3.

The preparation of 3-*O*-benzoyl-5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (4) was carried out by refluxing 2 either in *n*-propyl bromide solution or in a chloroform solution containing cyanogen bromide. In this case the two-proton doublet for the C-5 hydrogens appeared at δ 3.55 ($J_{4,5}$ = 7 Hz) with the C-3 one-proton doublet at 5.58 ($J_{3,4}$ = 3 Hz, $J_{2,3}$ = 0). The reaction with cyanogen bromide appears to be a special case of the von Braun reaction[4] whereby bromide ion attacks the C-5 position either simultaneously or after elimination of dimethylcyanamide.

Cyclic α-(dimethylamino)benzylidene acetals are useful intermediates for functionalizing glycols under very mild conditions. It would appear that the reaction could be carried out with any reagent which would cause elimination of the dimethylamino moiety and supply a suitable nucleophile to open the resulting acyloxonium ion intermediate.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus. Ir spectra were measured on a Beckman IR-9 spectrometer. Nmr spectra were measured on a Varian Associates A-60 instrument with tetramethylsilane as the internal standard. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Gas chromatography was performed with an F & M 810 chromatograph equipped with a 4 ft × 0.25 in. glass column containing 100–120 mesh 3% OV-17 Gas-Chrom Q and programmed for 150–300° at 10°/min and 25 ml/min. Tlc was carried out on silica gel Quanta/Gram plates obtained from Quantum Industries. Silica gel for column chromatography was 70–325 mesh from EM Reagents, distributed by Brinkman Instruments.

3,5-*O*-[α-(Dimethylamino)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (2).—A solution of 5.00 g of 1,2-*O*-isopropylidene-α-D-xylofuranose[5] and *N*,*N*-dimethylbenzamide diethyl acetal[6] in 25 ml of CH_2Cl_2 was allowed to stand overnight at room temperature. After evaporation of the solvent the residual oil was distilled at reduced pressure to yield 7.12 g (84%) of a thick syrup: bp 143–145° (0.1 mm); $[\alpha]^{25}D$ +25.4° (*c* 1.01, $CHCl_3$); nmr ($CDCl_3$) δ 1.33 (3 H, s, $CHCH_3$), 1.43 and 1.50 (3 H combined, s, s, partially resolved, ratio of ~1:5, respectively, *C*-CH_3), 2.08 and 2.27 (6 H combined, s, s, resolved, ratio of 6:1, *N*-CH_3), 3.80–4.75 (5 H, m, H-2, -3, -4, and -5), 5.97 and 6.07 (1 H combined, d, d, H-1), 7.4 (5 H, m, C_6H_5). The product crystallized after standing for several weeks at room temperature and was recrystallized from pentane: mp 74–75.5°; $[\alpha]^{25}D$ +30.6° (*c* 1.04, $CHCl_3$). The nmr was the same as for the distilled product. Gas chromatography showed only one peak at 8.5-min retention time.

Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.58; H, 7.12; N, 4.42.

3-*O*-Benzoyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose (3).—A solution of 0.62 g of 3,5-*O*-[α-(dimethylamino)-benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (2) in 15 ml ethyl iodide was refluxed for 5 hr. Filtration afforded a white solid which was very water soluble and precipitated AgI on addition of $AgNO_3$ solution. Tlc ($CHCl_3$) of the filtrate showed two spots,[7] R_f 0.8 (major) and 0.1 (minor). Evaporation to a syrup and chromatography on a column of 15 g of silica gel with $CHCl_3$ gave 0.67 g (82%) of a colorless syrup (only R_f 0.8 spot by tlc): $[\alpha]^{25}D$ −50.8° (*c* 1.02, $CHCl_3$); ir (liquid film) 1727 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (3 H, s, *C*-CH_3), 1.56 (3 H, s, *C*-CH_3), 3.33 (2 H, d, $J_{4,5}$ = 7 Hz, CH_2I), 4.68 (sextet, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 7 Hz, H-4), 4.70 (d, overlaid on the H-4 signal, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 0, H-2; 2 H for H-2 plus H-4), 5.58 (1 H, d, $J_{3,4}$ = 3 Hz, $CHOCOC_6H_5$), 6.03 (1 H, d, $J_{1,2}$ = 4 Hz, H-1), 7.35–8.15 (5 H, m, $CO_2C_6H_5$).

Anal. Calcd for $C_{15}H_{17}IO_5$: C, 44.57; H, 4.24; I, 31.39. Found: C, 44.48; H, 4.29; I, 31.60.

3-*O*-Benzoyl-5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (4). Method A.—A solution of 0.50 g of 2 and 0.30 g of cyanogen bromide in 15 ml of $CHCl_3$ was refluxed for 17 hr. Tlc ($CHCl_3$) showed a major spot at R_f 0.6 and two minor spots at 0.1 and 0.5.[7] The major spot also moved at R_f 0.3 with toluene. After concentrating the mixture to a syrup it was chromatographed on a column of 10 g of silica gel with toluene. Combining fractions with only the major spot and evaporating gave 0.30 g of a syrup: $[\alpha]^{25}D$ −46.6° (*c* 1.00, $CHCl_3$); ir (liquid film) 1734 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (3 H, s, *C*-CH_3), 1.55 (3 H, s, *C*-CH_3), 3.55 (2 H, d, $J_{4,5}$ = 7 Hz, CH_2Br), 4.68 (d, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 0, H-2; superposed sextet, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 7 Hz, H-4; total of 2 H), 5.58 (1 H, d, $J_{3,4}$ = 3 Hz, $CHOCOC_6H_5$), 6.03 (1 H, d, $J_{1,2}$ = 4 Hz, H-1), 7.3–8.2 (5 H, m, C_6H_5).

Anal. Calcd for $C_{15}H_{17}BrO_5$: C, 50.44; H, 4.80; Br, 22.37. Found: C, 50.54; H, 4.83; Br, 22.28.

Method B.—A solution of 2 in 5 ml of *n*-propyl bromide was refluxed overnight and filtered from the insoluble dimethyldi-*n*-propylammonium bromide. Gas chromatography showed only one peak with a retention time of 9.8 min, the same as for the product from method A.

Registry No.—1, 19429-87-9; 2, 41164-23-2; 3, 41164-24-3; 4, 41164-25-4; 1,2-*O*-isopropylidene-α-D-xylofuranose, 20031-21-4.

(4) H. A. Hageman, in *Org. React.*, **7**, 198 (1953).

(5) P. A. Levene and A. L. Raymond, *J. Chem. Soc.*, **102**, 317 (1933).

(6) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **96**, 2671 (1963).

(7) Plates were sprayed with a solution prepared from 5 g of ammonium molybdate, 5 ml of concentrated H_2SO_4, and 5 ml of 86% H_3PO_4 in 100 ml of water and heated at 120°. Gray spots turned blue on standing at room temperature: S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 2163 (1969).

γ Substitution of Allyl Ylides in the Wittig Reaction

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Received December 26, 1972

There are several reports in the literature describing electrophilic capture of phosphonate- or phosphonamide-stabilized allylic anions by ketones or aldehydes at both the α and γ carbons.[3] Also, allylidenetriphenylphosphorane reacts at the α and γ carbons with ethyl chloroformate, and cinnamyltriphenylphosphonium salt undergoes deuterium exchange in basic solution at both allylic positions.[4] A further example of γ substitution has been reported by Buchi and Wuest in the course of attempted Wittig reaction of allylidenetriphenylphosphorane and an enone,[5] but this appears to be a special case since 1,4 addition to the enone occurs as well. To our knowledge, there is no previously reported instance of γ substitution in a typical Wittig reaction.

We have found that allyltriphenylphosphonium fluoroborate reacts with benzaldehyde and diazabicycloundecene (DBU) in refluxing tetrahydrofuran to form a dienol 1 (26%) in addition to the expected Wittig product 1-phenylbutadiene. The structure of 1 is proved by the nmr spectrum [δ 7.2–7.5 (10 H),

(1) Alfred P. Sloan Fellow, 1971–1973.

(2) Support of this work by the National Science Foundation is acknowledged.

(3) E. J. Corey and D. E. Cane, *J. Org. Chem.*, **34**, 3053 (1969); G. Lavielle, *C. R. Acad. Sci.*, **270**, 86 (1970).

(4) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 27 (1961); H. J. Bestmann and H. Schulz, *Justus Liebigs Ann. Chem.*, **674**, 11 (1964).

(5) G. Buchi and H. Wuest, *Helv. Chim. Acta*, **54**, 1767 (1971).

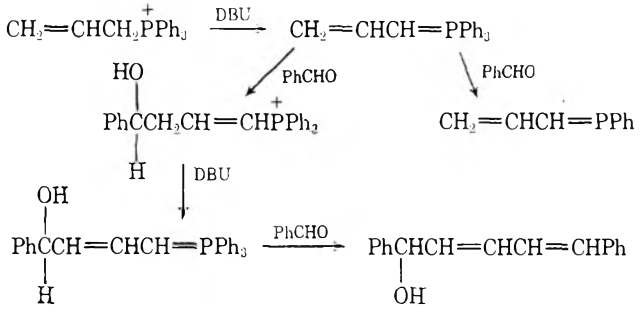
TABLE I

REACTION OF BENZALDEHYDE WITH ALLYLIC PHOSPHONIUM FLUOROBORATES AND DBU IN TETRAHYDROFURAN

Registry no.	Salt	Conditions	Yield of Wittig diene, %	Yield of dienol, %
		DBU		
41143-49-1	$CH_2{=}CHCH_2\overset{+}{P}Ph_3$	18-hr reflux	59	26
	$CH_2{=}CHCH_2\overset{+}{P}Ph_3$	50 hr, 25°	49	35
41143-50-4	$CH_3CH{=}CHCH_2\overset{+}{P}Ph_3$	18-hr reflux	67	13
41143-51-5	$PhCH{=}CHCH_2\overset{+}{P}Ph_3$	18-hr reflux	67	0
41143-52-6	$CH_3CH{=}C(CH_3)\overset{+}{P}Ph_3$	18-hr reflux	5	42
41187-93-3	$CH_3CH{=}C(CH_3)\overset{+}{P}CH_3Ph_2$	18-hr reflux	30	24
		Methanolic DBU		
	$CH_2{=}CHCH_2\overset{+}{P}Ph_3$	18-hr reflux	5	49
	$CH_3CH{=}CHCH_2\overset{+}{P}Ph_3$	18-hr reflux	19	39
	$CH_3CH{=}C(CH_3)PCH_3Ph_2$	18-hr reflux	0.4	28

5.8–7.2 (4 H), 5.26 (1 H, dd, J = 7, 2.5 Hz), 2.15 (1 OH)] and conversion into 1,5-diphenylpenta-2,4-dienone[6] with activated manganese dioxide. The dienol results from γ substitution of the allyl ylide followed by proton transfer to form a new ylide and normal Wittig reaction with a second mole of benzaldehyde.

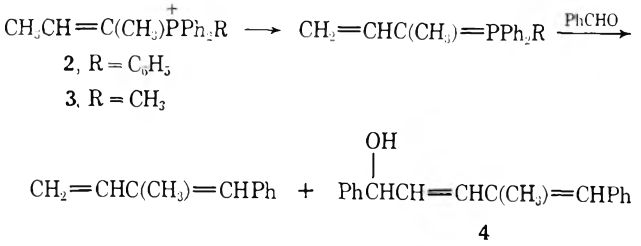
SCHEME I



1

Under similar conditions, crotyltriphenylphosphonium fluoroborate gives relatively less dienol (Table I). Cinnamyltriphenylphosphonium fluoroborate produces only the normal Wittig product, indicating that the ratio of α:γ ylide substitution increases with steric crowding at the γ carbon.

As expected, increased hindrance at the α carbon favors γ substitution. 2-Butenyltriphenylphosphonium fluoroborate[7] (2), benzaldehyde, and DBU afford the dienol 4 (42%) and only 5% of the Wittig product,

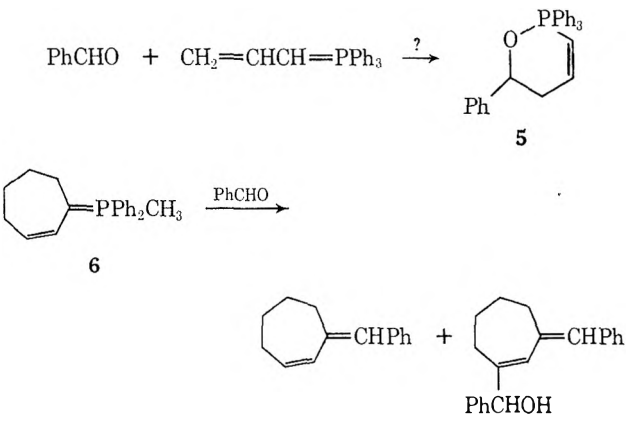


4

1-phenyl-2-methylbuta-1,3-diene. Approximately equal amounts of diene and dienol are obtained using 2-butenylmethyldiphenylphosphonium fluoroborate[8] (3) as the ylide precursor; so reduced hindrance by the phosphorus substituents favors α substitution.

A dramatic increase in the ratio of γ:α substitution product is observed when allylic ylides are generated with DBU in refluxing methanol (Table I). The ratio of dienol:diene is *ca.* 10:1 for allyltriphenylphosphonium fluoroborate and 2:1 for the crotyl analog. No significant solvent effect is observed when the allylidene ylide reaction is performed using excess methanolic sodium methoxide as the base in place of DBU. These observations are in accord with the simple ionic mechanism of Scheme I. Proton transfer to the developing negative charge on the aldehyde oxygen is more important for γ attack than for α attack owing to greater charge separation in the former, and the γ:α ratio increases in methanol relative to THF. In the presence of excess methoxide, the medium is too basic to exert as strong a catalytic effect.[9]

The solvent effects are inconsistent with a Diels–Alder mechanism for γ substitution *via* the pentavalent phosphorane 5. Also, we have observed formation of a dienol from reaction of benzaldehyde and the



(6) J. T. Thomas and G. Branch, *J. Amer. Chem. Soc.*, **76**, 4793 (1953).

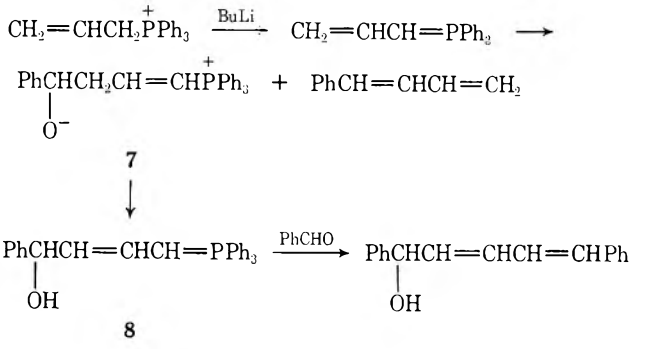
(7) D. Seyferth and J. Fogel, *J. Organometal. Chem.*, **6**, 205 (1966).

(8) Prepared from 2-butenyllithium and chlorodiphenylphosphine followed by methyl iodide and excess sodium fluoroborate. The noncrystalline product is characterized by the nmr spectrum ($CDCl_3$): δ 7.4–7.9 (10 H, m), 6.5–6.8 (1 H, m), 2.65 (3 H, d, J = 13 Hz), 2.07 (3 H, br, d, J = 14 Hz), 1.47 (3 H, m).

(9) Methanolic methoxide does affect the γ:α ratio in the reaction of **3** with benzaldehyde. The ratio changes from *ca.* 1:1 in THF–DBU to 9:1 in methanol–sodium methoxide.

transoid allylic ylide 6[10] which is incapable of a cycloaddition process.

To determine the generality of γ substitution, we have examined the reaction of allylidenetriphenylphosphorane and benzaldehyde under more typical Wittig conditions. Treatment of allyltriphenylphosphonium fluoroborate with a small excess of *n*-butyllithium (positive Gilman test) in tetrahydrofuran followed by benzaldehyde and aqueous work-up affords 1-phenylbutadiene (65%). Under these conditions, 1,5-diphenylpenta-2,4-dien-1-ol is not formed in amounts detectable by thin layer chromatography. However, the dienol is formed in 11% yield in addition to 1-phenylbutadiene if the same experiment is performed without aqueous work-up and the THF solution is treated with DBU, benzaldehyde, and the fluroroboric acid salt of DBU to approximate the latter stages of reactions listed in Table I. Clearly, the γ-substituted vinylphosphonium salt **7** is formed to a small extent even under aprotic Wittig conditions, but requires a proton transfer agent (DBU·HBF_4 or methanol) in order to be converted into the hydroxyl ylide **8**.[11]



Allyl- or crotyltriphenylphosphonium salts also react with isobutyraldehyde (DBU, THF at reflux) to form dienols (10–20%) in addition to the dienes. We conclude that γ substitution of allyl ylides is general and probably has not been observed previously in the Wittig reaction because the initially formed salt (*i.e.*, **7**) is not converted to dienol under aprotic conditions, and is discarded along with other polar byproducts in the course of aqueous work-up.

Experimental Section

2-(2-Butenyl)methyldiphenylphosphonium Fluoroborate.—A 250-ml three-neck flask was equipped with mechanical stirring and argon inlet and outlet. Lithium wire (1.3 g, 0.185 mol) cut into small pieces was added together with dry ether (60 ml) under argon and the mixture was cooled to −30° and stirred vigorously. (*E*)-2-bromobut-2-ene (5.4 g, 0.04 mol) was added dropwise over 20 min and the mixture was stirred for an additional 1 hr at −30°. The ether solution was transferred at −30° by syringe to a second flask, unreacted lithium being left behind. To this solution was added chlorodiphenylphosphine (Aldrich, distilled, 5.5 g, 0.025 mol) and the reaction mixture was stirred at −30° for 3 hr. Excess methyl iodide (17 g) was then added under argon and the reaction was allowed to stand at room temperature for 18 hr. The ether was evaporated to dryness, and the residue was taken up in methanol (*ca.* 100 ml) and stirred vigorously with a large excess of aqueous sodium fluoroborate. The product was then extracted into chloroform (3 × 50 ml), and the chloroform was dried over magnesium sulfate and evaporated under high vacuum. The residual yellow oil could not be crystallized but the nmr spectrum indicated <90% 2-(2-butenyl)methyldiphenylphosphonium fluoroborate, nmr ($CDCl_3$) δ 7.4–8 (10 H, m), 6.2–6.8 (1 H, m), 2.7 (3 H, d, J = 14 Hz), 2.1 (3 H, m), 1.6 (3 H, m).

Reaction of Allylic Phosphonium Salts with Benzaldehyde. General Procedure.—The phosphonium salt (0.005 mol), DBU (0.0055 mol), and benzaldehyde (0.025 mol) were dissolved in the appropriate solvent (dry tetrahydrofuran or reagent grade methanol, 10 ml) and allowed to react under nitrogen as indicated in Table I. The products were then extracted by aqueous pentane work-up. The pentane layer was concentrated, an internal standard (toluene) was added, and the diene yields were determined by glpc on 5 ft × 0.25 in. SE-30. The aqueous layer and all pentane—insoluble residues were then extracted with chloroform, and all of the organic fractions were combined and evaporated. The crude product was separated by preparative layer chromatography over silica gel using 4:1 hexane–ether. Three zones were observed in addition to polar base line material, R_f 0.8 (diene), 0.6–0.7 (recovered benzaldehyde), and 0.2–0.3 (dienol). All dienol products were oils and were characterized by nmr and exact mass. Elution of the base-line material with chloroform–ether afforded the phosphine oxide, generally in 3–8% higher yield than the combined yields of diene and dienol.

γ Substitution under Aprotic Conditions.—Allyltriphenylphosphonium fluoroborate (1.8 g, 0.0045 mol) suspended in dry tetrahydrofuran (25 ml) was treated dropwise with *n*-butyllithium (0.0046 mol) in hexane (3 ml) at 0°. Benzaldehyde (2.38 g, 0.0225 mol, freshly distilled) was then added to the homogeneous red solution and the reaction mixture was stored under nitrogen for 18 hr at 25°. Work-up as above afforded phenylbutadiene (65%, cis:trans 1:3) but no dienol by tlc analysis.

The above experiment was repeated. After overnight reaction of benzaldehyde with the ylide, 0.0045 mol each of DBU, DBU·$H^+BF_4^-$, and benzaldehyde was added, and the mixture was heated at reflux for 18 hr. Work-up as before afforded phenylbutadiene (52%) and 1-phenylpenta-2,4-dienol (11%). Addition of 3,4-dichlorobenzaldehyde after the initial Wittig condensation did not alter the product ratios and produced no new products by tlc or glpc analysis.

Registry No.—Benzaldehyde, 100-52-7; (*E*)-2-bromobut-2-ene, 3017-71-8; chlorodiphenylphosphine, 1079-66-9; methyl iodide, 74-88-4; sodium fluoroborate, 13755-29-8.

(10) E. Vedejs, K. A. J. Snoble, and P. L. Fuchs, *J. Org. Chem.*, **38**, 1178 (1973).

(11) It is conceivable that **7** is not formed initially if the Wittig betaine has not completely decomposed to phenylbutadiene at the time that benzaldehyde, DBU, and DBU·HBF_4 are added. Dissociation of the betaine under protic conditions followed by readdition to form **7** could then explain formation of the dienol. To exclude this possibility, we have conducted a crossover experiment where 3,4-dichlorobenzaldehyde is added instead of benzaldehyde after the initial Wittig condensation. The products contain no trace of 3,4-dichlorophenylbutadiene, which would have to be formed if dissociation of the betaine plays any role in the reaction.

The Reaction of Triethylamine with *N*-*p*-Toluenesulfonylarylhydrazidoyl Chlorides

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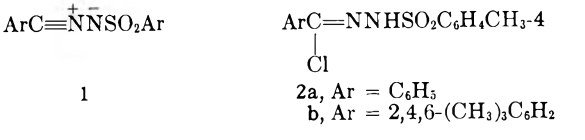
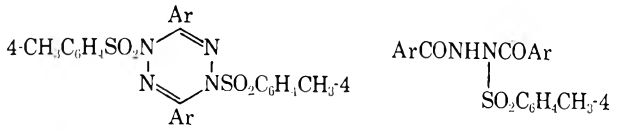
Received February 13, 1973

The reaction of triethylamine with *N*-*p*-toluenesulfonylhydrazidoyl chlorides (**2**) was investigated as a method for preparing nitrilesulfonimides (**1**).

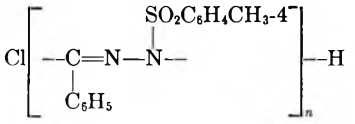


(1) Abstracted in part from the Ph.D. Thesis of J. N. K., 1973.

Triethylamine in tetrahydrofuran converted **2** into the 1,4-dihydro-3,6-diaryl-1,4-bis(*p*-toluenesulfonyl)-*s*-tetrazines (**3**). The reaction involving **2a** gave in addition small amounts of 1,2-dibenzoyl-1-*p*-toluenesulfonylhydrazine (**4a**) and two other compounds for which structures **5a** and **5b** were assigned upon the basis of their ir and nmr spectra and elemental analysis.



3a, Ar = C_6H_5 **4a**, Ar = C_6H_5
b, Ar = 2,4,6-$(CH_3)_3C_6H_2$ **b**, Ar = 2,4,6-$(CH_3)_2C_6H_2$

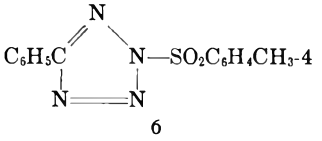


5a, $n = 2$
b, $n = 3$

In agreement with the structure proposed compound **5a**, when refluxed with aqueous ethanol, gave **3a**, the related 3,5-diphenyltetrazine, and **4a**. This reaction confirms the intermediacy of **5a** in the formation of **3a** and **4a** with the latter probably resulting from the action of moisture.

The only by-product isolated when **2b** was treated with triethylamine was **4b**.

The same dihydrotetrazine **3a** has been isolated in the reaction of *p*-toluenesulfonyl chloride with 5-phenyltetrazole in pyridine and has been ascribed to the dimerization of the intermediate nitrile imide (**1**).[2] An alternate and more likely reaction for the formation of the dimer **3a** is the conversion of the nitrile imide **1** by the pyridine hydrochloride into the chloride **2a** which is then converted into the dimer **3a** by pyridine. Evidence for such a pathway was obtained by preparing 2-*p*-toluenesulfonyl-5-phenyltetrazole (**6**) and studying its thermolysis. This labile tetrazole (**6**) decomposed in the presence of water and gave the hydration product of the intermediate nitrile imide (**1**), 1-benzoyl-2-*p*-toluenesulfonylhydrazine, the hydrolysis product of **6**, 5-phenyltetrazole, and trace amounts of 3,6-diphenyl-*s*-tetrazine.

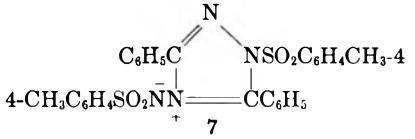


6

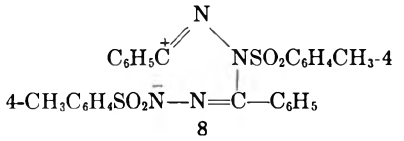
Thermal decomposition of the tetrazole (**6**) in anhydrous benzene was complex and gave 1,2-dibenzoyl-1-*p*-toluenesulfonylhydrazine (**4a**), *S*-*p*-tolyl thiobenzoate, *S*-*p*-tolyl *p*-toluenethiosulfonate and *p*-tolyl disulfide as the main products together with traces (less than 2 mg) of 3,6-diphenyl-*s*-tetrazine, the dimer **3a**, and *sym*-dibenzoylhydrazine.

The precursor of the disulfide and toluenethiosulfonate is *p*-toluenesulfinic acid[3] which would arise from the conversion of the dimer **3a** into 3,6-diphenyl-*s*-tetrazine.[2] The total amount of the latter actually isolated was very small and precludes this reaction as the only possibility involved in the formation of *p*-toluenesulfinic acid.

1,2-Dibenzoyl-1-*p*-toluenesulfonylhydrazine (**4a**) is probably formed by the action of traces of moisture on a dimer of the nitrile imide **1**. This dimer may be the [4 + 2] cycloaddition product **7** or the dipolar ion **8**.



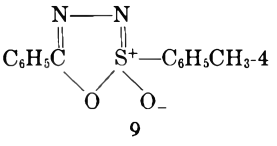
7



8

Either one of these could form the dimer **3a** and may be the precursors of *sym*-dibenzoylhydrazine.

The source of *S*-*p*-tolyl thiobenzoate is not known. The dimers **7** and **8** postulated are unlikely intermediates for this compound. A remote possibility which might lead to this compound is the cyclic form **9** of the nitrile imide **1**.



9

Experimental Section[4]

1-Benzoyl-2-*p*-toluenesulfonylhydrazine.—A solution of *p*-toluenesulfonyl chloride (85.5 g) in pyridine (175 ml) was added dropwise to a solution of benzhydrazide[5] (61.2 g) in pyridine (200 ml) at 10–15°. The reaction mixture was allowed to come to room temperature and was added to a mixture of 30% hydrochloric acid and ice. The resulting light yellow solid upon crystallization from 70% ethanol melted at 175.5–178.5° (lit.[6] mp 175–176°): yield 106.2 g; ir (Nujol) 3400 (NH), 1670 (CO), 1155 cm^{-1} (SO_2); nmr (pyridine-d_5) δ 11.68 (s, 1, $NHSO_2$), 8.64 (s, 1, CONH), 6.84 (m, 9, C_6H_5, C_6H_4), 2.04 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.86; N, 9.65. Found: C, 58.25; H, 4.92; N, 9.51.

***N*-(*p*-Toluenesulfonyl)benzhydrazidoyl Chloride (2a).**—A solution of 1-benzoyl-2-*p*-toluenesulfonylhydrazine (130.0 g) in thionyl chloride (800 ml) was refluxed for 2 hr. Removal of the thionyl chloride followed by the addition of ethanol (120 ml) and cooling gave a yellow solid. Successive recrystallizations from benzene–hexane and from absolute ethanol gave white crystals melting at 114.5–115.5°: yield 77.2 g (55.5%); ir (Nujol) 3380 (NH), 1595 (C=N), 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.36 (s, 1, NH), 7.52 (m, 9, C_6H_5, C_6H_4), 2.34 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{13}N_2O_2SCl$: C, 54.45; H, 4.24; N, 9.07. Found: C, 54.47; H, 4.29; N, 8.79.

Reaction of *N*-(*p*-Toluenesulfonyl)benzhydrazidoyl Chloride with Triethylamine.—A solution of the chloride (2.0 g) in dry tetrahydrofuran (20 ml) was added to a vigorously stirred solution of triethylamine (1.0 g) in tetrahydrofuran (80 ml) at −10 to 5° over the course of 1 hr. The resulting solution was stirred for 12 hr at room temperature, and the triethylamine hydrochloride was filtered. Removal of the solvent followed by the addition of absolute ethanol (10 ml) gave a yellow solid which after recrystallization from ethanol melted at 153.5–154.5° (lit.[2] mp 156.7°), yield 1.56 g. This compound was identified as 1,4-dihydro-3,6-diphenyl-1,4-bis(*p*-toluenesulfonyl)-5-tetrazene (**3a**) by comparison with an authentic sample.

(2) R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.*, **94**, 1555 (1961).
(3) E. Vinkler, F. Klivengi, and J. Szabo, *Acta Chim. Acad. Sci. Hung.*, **16**, 384 (1958).
(4) Melting points are corrected. Infrared spectra were obtained using a Perkin-Elmer 137B infrared spectrophotometer and nmr spectra were recorded with a Varian A-60 nmr spectrometer.
(5) G. Struve, *J. Prakt. Chem.*, **50**, 295 (1894).
(6) G. P. Schiemenz and H. Engelhard, *Chem. Ber.*, **92**, 1336 (1959).

The alcohol filtrate upon cooling gave a white solid which after recrystallization from ethanol gave white crystals of the trimer (**5b**) melting at 142–143° dec: yield 0.19 g; ir (Nujol) 3290 (NH), 1565 (C=N), 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ, 8.98 (s, 1, NH), 7.35 (m, 27, 3 C_6H_5, 3 C_6H_4), 2.45 (s, 3, CH_3), 2.37 (s, 3, CH_3), 2.23 (s, 3, CH_3).

Anal. Calcd for $C_{42}H_{37}N_6O_6S_3Cl$: C, 59.11; H, 4.37; N, 9.85; S, 11.27; Cl, 4.17. Found: C, 59.16; H, 4.24; N, 9.83; S, 11.22; Cl, 4.18.

Evaporation of the alcohol filtrate gave a solid which upon recrystallization from alcohol gave the dimer (**5a**) melting at 144.5–145.5° dec: yield 0.07 g; ir (Nujol) 3310 (NH), 1560 (C=N), 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.65 (s, 1, NH), 7.54 (m, 18, 2 C_6H_5, 2 C_6H_4), 2.41 (s, 3, CH_3), 2.35 (s, 3, CH_3).

Anal. Calcd for $C_{28}H_{25}N_4O_4S_2Cl$: C, 57.87; H, 4.34; N, 9.64; S, 11.04; Cl, 6.10. Found: C, 57.63; H, 4.38; N, 9.55; S, 10.96; Cl, 6.08.

Analysis by tlc on silica gel using chloroform of the ethanol filtrate from the last compound showed the presence of a trace of 1,2-dibenzoyl-2-(*p*-toluenesulfonyl)hydrazine (**4a**). Identification was based on a similar retention time to that of an authentic sample.

1,2-Dibenzoyl-1-(*p*-toluenesulfonyl)hydrazine (**4a**).—A mixture of sodium benzoate (0.5 g) and *N*-*p*-toluenesulfonylbenzhydrazidoyl chloride (1.0 g) in tetrahydrofuran (100 ml) was refluxed for 5 hr. Filtration of the solution followed by removal of the solvent gave a solid which was extracted first with chloroform and water and then recrystallized from absolute ethanol. The white crystals obtained melted at 225° dec: yield 0.31 g; ir (Nujol) 3400 (NH), 1705, 1655 (CO), 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 11.93 (s, 1, NH), 7.82 (m, 14, 2 C_6H_5, C_6H_4), 2.43 (s, 3, CH_3).

Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10. Found: C, 64.23; H, 4.56; N, 7.07.

Dehydrohalogenation of Dimer (**5a**).—A solution of the dimer (**5a**) (0.061 g) in 95% ethanol (10 ml) was refluxed for 12 hr. The solution became red in color which indicated the formation of 3,6-diphenyl-*s*-tetrazine. Analysis by tlc on alumina using chloroform indicated the presence of 3,6-diphenyl-*s*-tetrazine, 1,4-dihydro-3,6-diphenyl-1,4-bis(*p*-toluenesulfonyl)-*s*-tetrazine (**3a**), dimer (**5a**), and 1,2-dibenzoyl-1-(*p*-toluenesulfonyl)hydrazine (**4a**).

1-(2,4,6-Trimethylbenzoyl)-2-(*p*-toluenesulfonyl)hydrazine.—This compound was prepared from 2,4,6-trimethylbenzhydrazide[7] and *p*-toluenesulfonyl chloride using the procedure given for 1-benzoyl-2-*p*-toluenesulfonylhydrazide. Recrystallization from aqueous ethanol gave white crystals melting at 206–270°: yield 91.7%; ir (Nujol) 3420, 3200 (NH), 1670 (CO), 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 10.22 (s, 1, $NHSO_2$), 10.02 (s, 1, NHCO), 7.60 (q, 4, C_6H_4), 6.78 (s, 2, C_6H_2), 6.78 (s, 3, C_6H_4-CH_3), 2.18 (s, 3, $C_6H_2CH_3$), 2.07 (s, 6, $C_6H_2(CH_3)_2$).

Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43. Found: C, 61.49; H, 6.10; N, 8.19.

***N*-(*p*-Toluenesulfonyl)-2,4,6-trimethylbenzhydrazidoyl Chloride** (**2b**).—A solution of 1-(2,4,6-trimethylbenzoyl)-2-(*p*-toluenesulfonyl)hydrazine (38.0 g) in thionyl chloride (250 ml) was refluxed for 4 hr. Cooling gave white crystals melting at 185–186° dec: yield 19.1 g; ir (Nujol) 3225 (NH), 1620 (C=N), 1170 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.20 (s, 1, NH), 7.58 (q, 4, C_6H_4), 6.82 (s, 2, C_6H_2), 2.44 (s, 3, $C_6H_4CH_3$), 2.28 (s, 3, $C_6H_2CH_3$), 2.00 [s, 6, $C_6H_2(CH_3)_2$].

Anal. Calcd for $C_{17}H_{19}N_2O_2SCl$: C, 58.19; H, 5.46; N, 7.99. Found: C, 58.46; H, 5.35; N, 7.93.

Reaction of *N*-*p*-Toluenesulfonyl-2,4,6-trimethylbenzhydrazidoyl Chloride with Triethylamine.—A solution of triethylamine (1.52 g) in tetrahydrofuran (250 ml) was treated with the chloride (5.26 g) in tetrahydrofuran (150 ml) dropwise at −5 to 0°. The resulting mixture was stirred at room temperature for 12 hr and filtered. Removal of the solvent followed by the addition of absolute ethanol (20 ml) gave a white solid (**3b**, 1.71 g) melting at 230° dec: ir (Nujol) 1605 (C=N), 1180 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 7.31 (q, 8, 2 C_6H_4), 6.82 (s, 4, 2 C_6H_2), 2.40 (s, 6, 2 $C_6H_4CH_3$), 2.32 (s, 6, 2 $C_6H_2CH_3$), 1.90 [s, 12, 2 C_6H_2-$(CH_3)_2$].

Anal. Calcd for $C_{34}H_{36}N_4O_4S_2$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.87; H, 5.78; N, 9.12.

Removal of the ethanol from the filtrate followed by the addition of chloroform gave 1,2-di(2,4,6-trimethylbenzoyl)-2-*p*-toluenesulfonylhydrazine (**4b**, 2.13 g) melting at 221–222°. The ir and nmr spectra were similar to those of an authentic sample.

Evaporation of the chloroform filtrate gave an oil from which no crystalline compounds could be isolated.

1,2-Di(2,4,6-trimethylbenzoyl)-2-*p*-toluenesulfonylhydrazine (**4b**).—A mixture of sodium 2,4,6-trimethylbenzoate (0.47 g) and *N*-*p*-toluenesulfonyl)-2,4,6-trimethylbenzhydrazidoyl chloride (0.88 g) in tetrahydrofuran (100 ml) was refluxed for 2 hr. Filtration followed by removal of the solvent gave a solid which was dissolved in chloroform. The resulting solution was washed with water and upon removal of the chloroform gave a solid which was recrystallized from absolute ethanol: mp 221.5–223.5°; yield 1.0 g; ir (Nujol) 3360 (NH); 1705, 1685 (CO), 1165 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 11.27 (s, 1, NH), 7.82 (q, 4, C_6H_4), 6.80 (s, 4, 2 C_6H_2), 2.05 [m, 21, 2 $C_6H_2(CH_3)_3$, $C_6H_4CH_3$].

Anal. Calcd for $C_{27}H_{30}N_2O_4S$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.79; H, 6.51; N, 5.84.

2-*p*-Toluenesulfonyl-5-phenyltetrazole (**6**).—A solution of 5-phenyltetrazole (0.73 g) and *p*-toluenesulfonyl chloride (0.95 g) in tetrahydrofuran (25 ml) at 5–10° was treated with triethylamine (1.4 ml) in tetrahydrofuran (20 ml), and the resulting solution was stirred for 5 hr. The resulting triethylamine hydrochloride (0.64 g) was filtered and the filtrate was evaporated to dryness under reduced pressure at room temperature. The resulting solid was extracted with absolute ether and filtered. Concentration of the ether under reduced pressure gave 2-*p*-toluenesulfonyl-5-phenyltetrazole (**6**, 1.12 g): mp 92° (explosive); ir (Nujol) 1530 (C=N), 1180, 1190 cm^{-1} (SO_2); nmr ($CDCl_3$)[8] δ 2.46 (s, 3, CH_3), 7.56 (m, 7, C_6H_5, $CH_3C_6H_2$), 8.17 (d, 2, $C_6H_2SO_2$).

Anal. Calcd for $C_{14}H_{12}N_4SO_2$: C, 56.00; H, 4.00; N, 18.66. Found: C, 55.93; H, 4.55; N, 18.51.

Thermolysis of 2-*p*-Toluenesulfonyl-5-phenyltetrazole (**6**). **A**.—A solution of **6** (0.99 g) in a mixture of tetrahydrofuran (50 ml) and water (45 ml) was refluxed for 40 min. Partial removal of the solvent gave a pink solid (0.52 g) which was treated with a small amount of benzene and filtered. The solid (0.36 g) obtained had a wide melting point range, 145–185°, and was extracted with hot benzene. The insoluble portion (0.087 g) melted at 210–212° dec and was identified as 5-phenyltetrazole by its ir spectrum. The benzene filtrate upon cooling gave crystals (0.187 g) which upon crystallization from water gave 1-benzoyl-2-*p*-toluenesulfonylhydrazide (0.1 g), mp 174.5–176.5°. The residue obtained from the first benzene extraction was extracted with petroleum ether (bp 60–68°) and gave 3,6-diphenyl-*s*-tetrazine which upon recrystallization from methanol melted at 190–192°, yield 0.002 g. The mixture melting point with an authentic sample[2] melted at the same point.

B.—A solution of **6** (1.022 g) in dry benzene (100 ml) was refluxed for 10 min. Removal of the benzene under reduced pressure followed by the addition of dry methanol to the residue gave 0.1 g of 1,2-dibenzoyl-1-*p*-toluenesulfonylhydrazine, mp 214–215° dec. The methanol filtrate was evaporated to dryness and the resulting residue was dissolved in benzene and chromatographed on silica using benzene as the eluent. The first fraction was an oil (0.01 g) which was identified as *p*-tolyl disulfide by its mass and ir spectra. The second fraction was *S*-*p*-tolyl benzoate (0.05 g), mp 75–76° (lit.[9] mp 75°). This structure was substantiated by its mass spectrum. This fraction was contaminated with 3,6-diphenyl-*s*-tetrazine. The third fraction consisted of *S*-*p*-tolyl thio-*p*-toluenesulfonate (0.08 g), mp 73–74° (lit.[3] mp 74–75°). Identification was made by comparison with an authentic sample.

Fractions which did not migrate to any extent with benzene were removed from the silica by extraction with chloroform. Concentration of the chloroform gave a small amount of solid melting at 238–240°. This solid was identified as *sym*-dibenzoylhydrazine by its mass spectrum and comparison of its ir spectrum with that of an authentic sample. Chromatography of the chloroform extract on silica using chloroform as the eluent gave a small amount of the dimer **3a**. Identification was made by its migration time on silica and its decomposition at its melting point to the tetrazine. The other fractions obtained were present in insufficient amounts to be identified.

(7) M. S. Newman and E. G. Caflisch, Jr., *J. Amer. Chem. Soc.*, **80**, 862 (1958).

(8) Nitrogen was evolved slowly during the analysis.

(9) R. Schiller and R. Otto, *Chem. Ber.*, **9**, 1634 (1876).

Registry No.—2a, 31910-69-7; 2b, 41262-87-7; 3b, 41262-88-8; 4a, 41262-89-9; 4b, 41262-90-2; 5a, 41262-91-3; 5b, 41262-92-4; 6, 41262-93-5; 1-benzoyl-2-*p*-toluenesulfonylhydrazine, 3064-19-5; *p*-toluenesulfonyl chloride, 98-59-9; benzhydrazide, 613-94-5; triethylamine, 121-44-8; sodium benzoate, 532-32-1; 1-(2,4,6-trimethylbenzoyl)-2-(*p*-toluenesulfonyl)hydrazine, 41262-95-7; sodium 2,4,6-trimethylbenzoate, 32642-28-7; 5-phenyltetrazole, 18039-42-4; 3,6-diphenyl-s-tetrazine, 6830-78-0; *sym*-dibenzoylhydrazine, 787-84-8.

Reactions of Hydroxide Tetrakis(2-hydroxyethyl)ammonium

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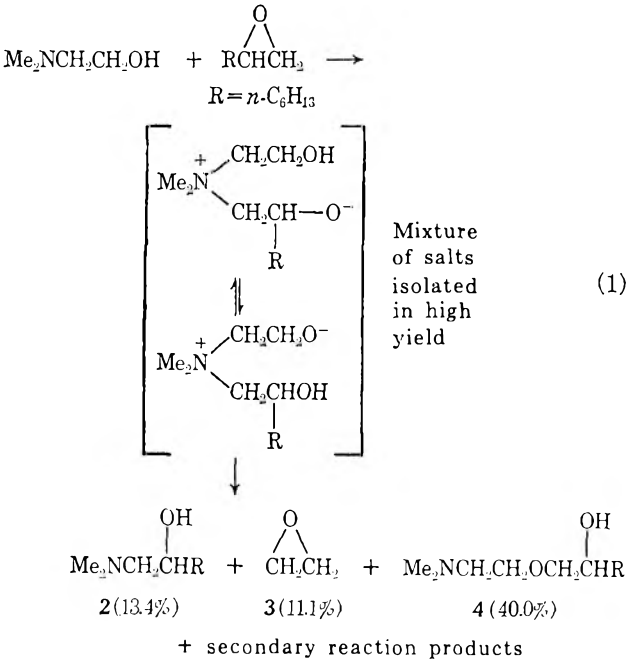
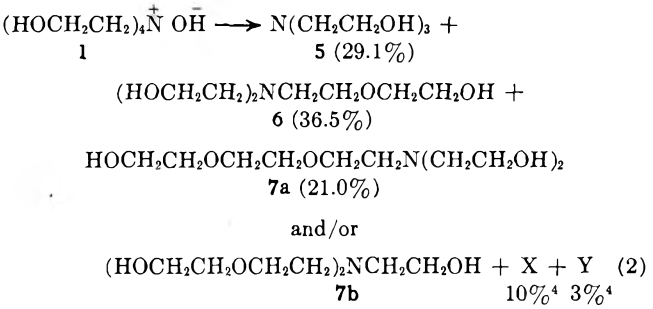
Usually quaternary ammonium hydroxides are considered synthetically useful for olefin formation *via* the Hofmann elimination.[1] However, quaternary ammonium hydroxides bearing one β-hydroxy-substituted side chain thermally decompose to give epoxides, in most cases in high yield to the exclusion of the desired olefin.[1] A paucity of information is available for the chemical reactions and the thermal decomposition of quaternary ammonium hydroxides with more than one β-hydroxy-substituted side chain. Tobler has reported the thermal decomposition of the mixture of quaternary ammonium alkoxides formed by the reaction of 2-(*N*,*N*-dimethylamino)ethanol with 1,2-epoxyoctane.[2] The thermal decomposition of this mixture of quaternary ammonium salts, each species bearing two β-hydroxy-substituted side chains, yields products postulated as occurring *via* intramolecular rearrangements as shown in eq 1.[2] Acetaldehyde formation by a Hofmann-type reaction was not observed.



(1)

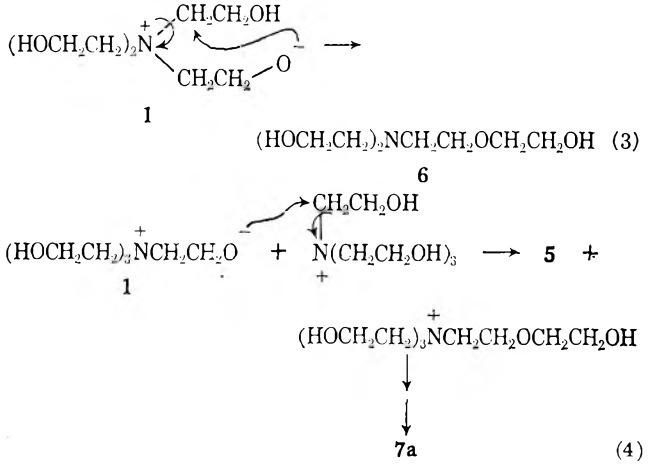
In contrast to the reactions of alkyl-substituted quaternary ammonium salts containing one or two 2-hydroxyalkyl groups, tetrakis(2-hydroxyethyl)-ammonium hydroxide, an easily prepared, stable, white, crystalline compound, behaves somewhat differently. Ethylene oxide and acetaldehyde, expected decomposition products, were not detected in significant quantities under any conditions. Instead the decomposition of **1** was found to take place largely by intermolecular SN2 processes as outlined below.

Thermal decomposition of neat tetrakis(2-hydroxyethyl)ammonium hydroxide (**1**) under nitrogen or high vacuum gives 2,2′,2″-nitrilotriethanol (**5**), 2-(2-hydroxyethoxy)ethyldi(2-hydroxyethyl)amine (**6**), 2-[(2-hydroxyethoxy)ethoxy]ethyldi(2-hydroxyethyl)-amine (**7a**), or di[2-(2-hydroxyethoxy)ethyl]-2-hydroxyethylamine (**7b**), and higher homologs (X, Y) as illustrated by eq 2.[3]



(2)

Formation of **6** could occur *via* an intramolecular pathway (eq 3). However, the isolation of the higher ethoxylated products, **7a** and **7b**, provides evidence for the decomposition proceeding at least partially by an intermolecular route (eq 4). In fact, recent work



(3)

(4)

by Eschenmoser, *et al.*,[5] and earlier work by House and Pitt[6] have shown that, although an endocyclic SN2 displacement reaction is more appealing, the reaction actually proceeds by an intermolecular pathway in many cases. Similar examples of intermolecular attack by various nucleophiles on quaternary am-

(1) A. C. Cope and E. R. Trumbull in "Organic Reactions," Vol. 11, Wiley, New York, N. Y., 1960, Chapter 5.

(2) E. Tobler, *Helv. Chim. Acta*, **52**, 408 (1969).

(3) For simplification **5** will be referred to as NTE and **6**, **7a** and **7b** as the NTE-1-mol and NTE-2-mol ethoxylates, respectively, in the remainder of the text.

(4) Identification of X, Y unknown; yields based on area per cent by vpc.

(5) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

(6) H. O. House, and C. G. Pitt, *J. Org. Chem.*, **31**, 1062 (1966).

TABLE I

DECOMPOSITION OF TETRAKIS(2-HYDROXYETHYL)AMMONIUM HYDROXIDE. PRODUCT MOLE RATIO

Solvent	Solvent:1 ratio	Mole ratio of products based on NTE = 1 NTE ethoxylates NTE	1-Mol	2-Mol	3-Mol	Other
None (vacuum 100 mm)		1	0.87	0.37	0.12	
None (vacuum 0.44–0.08 mm)		1	0.75	0.28	0.08	
Water	211:1	1	0.73	0.24	0.05	
2-Ethoxyethanol	54:1	1	0.32	0.04		0.27[a]
2,2′,2″-Nitrilotriethanol (NTE)	7:1	1	2.57	0.21		
2,2′,2″-Nitrilotriethanol	30:1	1	1.01	0.03		
2,2′-Iminodiethanol	39:1	1[b]				
2-Aminoethanol	9:1	1				1.06[c]
Ethylene glycol	20:1	1	0.06			0.52[d]

[a] 2-(2-Ethoxyethoxy)ethanol. [b] Only product. [c] 2,2′-Iminodiethanol. [d] Diethylene glycol.

monium salts having various β substituents other than hydroxyl groups have been reported.[7]

To distinguish between the extent of intermolecular *vs.* intramolecular SN2 reactions, the thermal decomposition of **1** was carried out in various solvents: water, 2-ethoxyethanol, ethylene glycol, 2-aminoethanol, 2,2′-iminodiethanol, and 2,2′,2″-nitrilotriethanol at 100° (Table I).

Evidence for the intermolecular decomposition of **1** was provided by the isolation of 2-(2-ethoxyethoxy)-ethanol (**8**) when 2-ethoxyethanol was used as the solvent (eq 5). Some of the NTE-1-mol and -2-mol

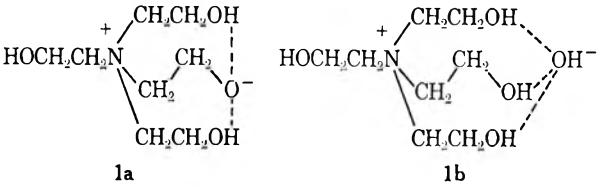
$$EtOCH_2CH_2OH + 1 \longrightarrow \underset{\mathbf{8}}{EtOCH_2CH_2OCH_2CH_2OH} + 5 + 6 + \mathbf{7a,b} \quad (5)$$

ethoxylates were also formed. The reactions of 2,2′-iminodiethanol (**9**) and 2-aminoethanol with **1** supplied conclusive evidence for the intermolecular nature of this reaction. The respective ethoxylation products **5** and **9** were isolated (eq 6 and 7). None of the ethoxylates of **5** were detected by vpc. Products corresponding to attack by the hydroxyl groups of 2,2′-iminodiethanol or 2-aminoethanol to produce the O-ethoxylation products **10** and **11** were not observed. Thus **1** acts as a discriminatory ethoxylation reagent for primary and secondary amines in the presence of hydroxyl groups.

$$(HOCH_2CH_2)_2NH + 1 \longrightarrow \begin{cases} \underset{\mathbf{5}}{2N(CH_2CH_2OH)_3} \\ \underset{\mathbf{10}}{HOCH_2CH_2OCH_2CH_2NHCH_2CH_2OH} \end{cases} \quad (6)$$

$$HOCH_2CH_2NH_2 + 1 \longrightarrow 5 + \underset{\mathbf{9}}{(HOCH_2CH_2)_2NH} + \underset{\mathbf{11}}{HOCH_2CH_2OCH_2CH_2NH_2} \quad (7)$$

The ratio of **5** to the NTE ethoxylates formed on decomposition of **1** in water was essentially identical with the ratio of products obtained by decomposing **1** in the absence of solvent. Ethylene glycol, the expected intermolecular SN2 product, was not detected. A possible explanation for the apparent inertness of water as a reactant with **1** can be attributed to the relative acidity of water in comparison to the hydroxyl groups of the quaternary salt or of **5**. In any given solvent the hydrogen bonding shown in structures **1a** and **1b** postulated for the quaternary salt might



1a **1b**

stabilize the anion to such an extent that as a consequence the effectve basicity of the anion would be significantly reduced. If this is the case, water apparently is not a strong enough acid and the equilibrium represented by eq 8 (R = H) lies far to the left. De-

$$\mathbf{1a} + ROH \rightleftharpoons \mathbf{1b} + RO^- \quad (8)$$

composition of **1** in water would then take place preferentially between two molecules of **1** as shown previously in eq 4. In an alcohol solvent, water is a weak acid in comparison to various alcohols such as 2-ethoxyethanol, ethylene glycol, or 2,2′-2″-nitrilotriethanol.[8] With the more acidic alcohols, such as those mentioned, the equilibrium shown by eq 8 should shift to the right, producing a nucleophile capable of decomposing **1**. In agreement with this suggestion, the most acidic alcohols, ethylene glycol and **5**, are ethoxylated to diethylene glycol and **6**, respectively, almost to the total exclusion of the higher NTE-ethoxylates. Less acidic than ethylene glycol or 2,2′,2″-nitrilotriethanol, but more acidic than water, 2-ethoxyethanol did not compete as effectively and the NTE-ethoxylates are produced in addition to **8**, the desired ethoxylation product.

The stability of **1** is attributed to the internal hydrogen bonding possible from the β-hydroxyethyl side chains present. As one replaces these β-hydroxyethyl groups with alkyl substituents, the stability of the corresponding quaternary ammonium salt would be expected to decrease, as has already been observed. Further, the chemical reactivity of such a series of

(7) (a) C. Bled-Charreton and A. Gaudemer, *C. R. Acad. Sci., Ser. C*, **272**, 1241 (1971); (b) E. Kitatsuji, N. Masuda, E. Yoshii, and T. Iida, *Yakugaku Zasshi*, **91**, 732 (1971); *Chem. Abstr.*, **75** 117837t (1971); (c) S. H. Pine, B. A. Catto, and F. G. Yamagishi, *J. Org. Chem.*, **35**, 3663 (1970); (d) M. Mori, *Kagaku No Ryoiki*, **25**, 872 (1971); *Chem. Abstr.*, **75**, 140376a (1971); (e) E. C. F. Ko and K. T. Leffek, *Can. J. Chem.*, **49**, 129 (1971); **50**, 1297 (1972); (f) S. Bogdal, *Rocz. Chem.*, **44**, 121 (1970); *Chem. Abstr.*, **73**, 44672g (1970); (g) N. D. V. Wilson and J. A. Joule, *Tetrahedron*, **24**, 5493 (1968); (h) J. E. Gordon and P. Varughese, *J. Chem. Soc., Chem. Commun.*, 1160 (1971); (i) C. L. Bumgardner and H. Iwerks, *ibid.*, 431 (1968); (j) G. Costa, A. Puxeddu, and E. Reisenhofer, *Tetrahedron Lett.*, 2167 (1972).

(8) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).

quaternary ammonium salts should change. These possibilities are under active investigation and will be reported later.

Experimental Section[9]

Preparation of Tetrakis(2-hydroxyethyl)ammonium Hydroxide (1).—A solution of tetrakis(2-hydroxyethyl)ammonium chloride (68.8 g, 0.3 mol) in water (22 ml) and methanol (200 ml) was kept under nitrogen with stirring (magnetic). Silver oxide freshly prepared from silver nitrate (102 g, 0.6 mol) was added as rapidly as possible (5). After stirring for 2 hr the thick slurry was filtered under nitrogen. The filter cake was washed once with methanol (50 ml). Solvent was removed under reduced pressure at room temperature. Ethanol (200 ml) was added to the thick syrup and the solvent was again removed under reduced pressure. The white, crystalline mass was dissolved in ethanol, placed under nitrogen, and cooled. The product was filtered and dried under reduced pressure (37.0 g, mp 150–155°). *Note:* On occasion the solution of product will assume a purple coloration, probably indicative of the decomposition of a soluble silver complex. A gentle treatment with activated charcoal will remove all coloration.

A lower melting species may be obtained by dissolving 1 in the minimum amount of water, then adding ethanol (ten times the amount of water used to dissolve 1). On cooling, large, white crystals are obtained, mp 120–125°.

Elemental analyses indicate that the structure of the higher melting quaternary salt is $C_8H_{19}O_4N$ and that of the lower melting form is $C_8H_{21}O_5N$. *Anal.* [high-melting form (1a)]. Calcd for $C_8H_{19}O_4N$: C, 49.72; H, 9.91; N, 7.25. Found: C, 49.52, 49.50; H, 9.92, 10.01; N, 7.05, 7.10. *Anal.* [low-melting form (1b)]. Calcd for $C_8H_{21}O_5N$: C, 45.48; H, 10.02; N, 6.63. Found: C, 45.51, 45.33; H, 10.10, 10.22; N, 6.57, 6.49.

Procedure 1. Thermal Decomposition of 1 without Solvent.—Tetrakis(2-hydroxyethyl)ammonium hydroxide (10.0 g, 99% pure, mp 144–150°) was placed in a 100-ml kettle equipped with a nitrogen inlet, thermowell, and gas outlet and heated to 184° for 4 hr. Vpc analysis of a small amount of the residue derivatized with Regisil [12 ft × 0.125 in. Al, 5% polyphenyl ether (five ring, OS-138) on Chromosorb G, 100–200° and hold, 10°/min; detector, 290°; injector, 270° He]. Three yeaks were collected and identified as the trimethylsilyl derivatives.

A.—2,2′,2″-Nitrilotriethanol (5) had nmr ($CDCl_3$) δ 0.09 (s, 27, $CH_3Si\lessgtr$), 2.67 (t, 6, $-CH_2N\lessgtr$), 3.57 (t, 6, $-CH_2O-$). *Anal.* Calcd for $C_{15}H_{39}NO_3Si_3$: C, 49.26; H, 10.74; N, 3.82. Found: C, 49.34; H, 10.48; N, 3.81.

B.—*N*-[2-(Hydroxyethoxy)ethyl]-*N*,*N*-di(2-hydroxyethyl)-amine (6) had nmr ($CDCl_3$) δ 0.08 (s, 27, $CH_3Si\lessgtr$), 2.74 (q, 6, $-CH_2N\lessgtr$), 3.60 (mm, 10, CH_2O). *Anal.* Calcd for $C_{17}H_{43}NO_4Si_3$: C, 49.82; H, 10.58; N, 3.42. Found: C, 49.99; H, 10.87; N, 3.34.

C.—*N*,*N*-Di[(2-Hydroxyethoxy)ethyl]-*N*-(2-hydroxyethyl)-amine (7a,b) had nmr ($CDCl_3$) δ 0.09 (s, 27, $CH_3Si\lessgtr$), 2.74 (q, 6, $-CH_2N\lessgtr$), 3.60 (mm, 14, $-CH_2O-$). *Anal.* Calcd for $C_{19}H_{47}NO_5Si_3$: C, 50.28; H, 10.43; N, 3.08. Found: C, 50.06; H, 10.76; N, 3.12.

Procedure 2. Decomposition of 1 in Solvent.—The quaternary ammonium hydroxide was dissolved in the minimum amount of water, diluted with the solvent, and heated to 100° until a pH of 10 was obtained. The reaction mixture was analyzed by distillation in conjunction with vpc.

Acknowledgments.—The author is indebted to Mr. C. B. Strow, Jr., Mr. W. H. Joyce, and Mr. J. T. Hildebrand for analytical data and interpretation and to Mr. R. L. Bailey for technical assistance.

Registry No.—**1a**, 41120-05-2; **1b**, 631-41-4; **5** trimethylsilyl derivative, 20836-42-4; **6** trimethylsilyl derivative, 41120-08-5; **7a** trimethylsilyl derivative, 41120-09-6; **7b** trimethylsilyl derivative, 41120-10-9; tetrakis(2-hydroxyethyl)ammonium chloride, 13269-66-4.

(9) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The nmr spectra were recorded on a Varian HA-100 nmr spectrometer. Elemental analyses were determined on a Perkin-Elmer 240 elemental analyzer.

The Preparation of 1,3,4-Thiadiazoline-2,5-dione and Its Use as a Dienophilic Reagent

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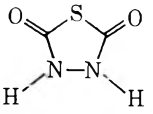
Received May 25, 1973

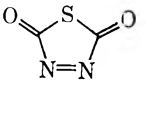
Over the past 10 years triazolinediones have been used as dienophiles with increasing frequency.[1,2] The use of these reagents suffers from the disadvantage that the resulting urazoles are very difficult to convert to hydrazines. Typically, prolonged treatment with potassium hydroxide in refluxing water–ethylene glycol[3] or lithium aluminum hydride in refluxing tetrahydrofuran[4] is necessary to effect hydrolysis. A need for a highly reactive dienophile that can be easily cleaved to a 1,2-disubstituted hydrazine led us to study the oxidation of 1,3,4-thiadiazolidine-2,5-dione (I).[5] It was found that I could be oxidized to the desired azo reagent II with lead tetraacetate in 2:1 tetrahydrofuran–dimethylformamide containing *ca.* 1% acetic acid (as stabilizer) at −78° giving a dark brown colored solution. When this solution was warmed to −20°, it became light yellow, indicating the decomposition of II. However, when the oxidation was run in the presence of an excess of a 1,3-diene, good yields of Diels–Alder products III could be isolated. The results are shown in Table I. Lower yields are obtained with the less reactive dienes owing mainly to concurrent decomposition of II.

TABLE I

Registry no.	Diene	Yield, % (adduct)
542-92-7	Cyclopentadiene	96 (IIIa)
592-57-4	Cyclohexadiene	92 (IIIb)
78-79-5	Isoprene	35 (IIIc)
2004-70-8	*trans*-Piperylene	55 (IIId)
513-81-5	2,3-Dimethylbutadiene	49 (IIIe)



I



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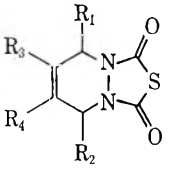
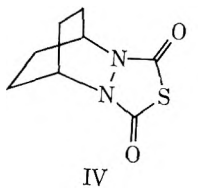


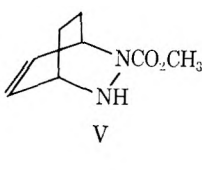
IIIa, $R_1 + R_2 = CH_2$; $R_3 = R_4 = H$
b, $R_1 + R_2 = CH_2CH_2$; $R_3 = R_4 = H$
c, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
d, $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$
e, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$

(1) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).
(2) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).
(3) L. A. Paquette, *J. Amer. Chem. Soc.*, **92**, 5765 (1970).
(4) D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *Chem. Commun.*, 939 (1970).
(5) K. Rufenact, *Helv. Chim. Acta*, **51**, 518 (1968).

No Diels–Alder adduct was found with anthracene or 1,4-diphenylbutadiene, and no ene adduct was observed with 2,3-dimethyl-2-butene. As expected, it was found that IIIb could be hydrolyzed by base under mild conditions. For example, reaction of IIIb in the presence of air with 0.1 *N* lithium hydroxide in water–diglyme for 2 hr at 25° gave cyclohexadiene and nitrogen. The adduct IIIb could be reduced to the dihydro derivative IV by hydrogen with 5% palladium-on-carbon catalyst in ethyl acetate at 1 atm. Hydrolysis of this compound under conditions described above gave 2,3-diaza[2.2.2]bicyclooct-2-ene.[6] Treatment of IIIb with methanolic potassium carbonate gave V.



IV



V

In conclusion, 1,3,4-thiadiazoline-2,5-dione can be used to form Diels–Alder adducts with moderately reactive dienes. The resulting adducts can readily be converted to hydrazine derivatives under mild conditions.[7]

Experimental Section

All Diels–Alder adducts were prepared by identical procedures. The reaction with cyclopentadiene is given as an example. Molecular weight measurements were by mass spectrometer.

Preparation of Adduct IIIa.—1,3,4-Thiadiazolidine-2,5-dione[5] (1.18 g, 10 mmol) was dissolved in 20 ml of dimethylformamide, 30 ml of tetrahydrofuran, and 0.5 ml of acetic acid. Cyclopentadiene (1.92 g, 30 mmol) was added, and the solution was cooled to −78°. Lead tetraacetate (7 g, 15 mmol) was added, and the solution was stirred for 4 hr at −78°. Then 1 ml of ethylene glycol was added, and the solution was allowed to warm to 25°. It was then poured into 100 ml of water, which was extracted with 4 × 50 ml of methylene chloride. The methylene chloride was extracted with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give a brown oil. Drying *in vacuo* (0.1 mm) for 18 hr gave 1.75 g (96%) of crystals. The product was recrystallized from benzene–cyclohexane: mp 83.5–84.5°; ir ($CHCl_3$) 5.80 and 6.00 μ; nmr ($CDCl_3$) δ 6.58 (2 H, d of d, J = 2, 2 Hz, CH=), 5.20 (2 H, m, CH), 2.38 (1 H, t of d, J = 9, 1.6 Hz, CHH), and 2.07 (1 H, t of d, J = 9, 1.8 Hz, CHH); mol wt (calcd for $C_7H_6N_2O_2S$, 182.0150) 182.0153.

Preparation of Adduct IIIb.—Adduct IIIb was similarly prepared in 92% yield from 1,3-cyclohexadiene. The product was recrystallized from benzene–cyclohexane: mp 139.5–140°; ir ($CHCl_3$) 3.40, 5.84, 6.02 μ; nmr ($CDCl_3$) δ 6.60 (2 H, d of d, J = 1.8, 2.4 Hz, CH=), 5.18 (2 H, m, CH), and 1.5–2.4 (4 H, m, CH_2); mol wt (calcd for $C_8H_8N_2O_2S$, 196.0307) 196.0307.

Preparation of Adduct IIIc.—Adduct IIIc was similarly prepared in 35% yield from isoprene. The product was recrystallized from ether–petroleum ether (bp 30–60°) at −78°: mp 99–100°; ir (neat) 5.80, 6.00 μ; nmr ($CDCl_3$) δ 5.65 (2 H, m, CH=), 4.25 (4 H, m, CH_2), and 1.92 (3 H, s, CH_3); mol wt (calcd for $C_7H_8N_2O_2S$, 184.0307) 184.0311.

Preparation of Adduct IIIe.—Adduct IIIe was similarly prepared in 50% yield from 2,3-dimethylbutadiene. The product was recrystallized from benzene–cyclohexane: mp 153.5–154.4°; ir ($CHCl_3$) 5.80 and 6.00 μ; nmr ($CDCl_3$) δ 4.10 (s, 4 H, CH_2), and 1.75 (6 H, s, CH_3); mol wt (calcd for $C_8H_{10}N_2O_2S$, 198.0463) 198.0460.

Preparation of Adduct IIId.—Adduct IIId was similarly prepared in 55% yield from *trans*-piperylene. The product was recrystallized from ether–pentane at −78°: mp 65–66°; ir (neat) 5.78 and 6.00 μ; nmr ($CDCl_3$ δ 5.89 (2 H, m, CH=), 4.8 (1 H, m, CH), 4.34 and 4.20 (2 H, 2 m, CH_2), and 1.38 (3 H, d, J = 6.5 Hz, CH_3); mol wt (calcd for $C_7H_8N_2O_2S$, 184.0307) 184.0311.

Preparation of 2-Carbomethoxy-2,3-diazabicyclooct-5-ene (V).—To a solution of 50 mg of anhydrous potassium carbonate in 1 ml of methanol was added 26 mg of IIIb. After stirring for 1.5 hr the solution was acidified with 10% hydrochloric acid and then made basic with potassium hydroxide. The solution was extracted with 4 × 10 ml of methylene chloride which was dried over sodium sulfate and evaporated to give 21 mg (95%) of colorless oil which was pure by tlc: ir (neat) 2.90, 3.11, 5.90, and 8.91 μ; nmr ($CDCl_3$) δ 6.53 (2 H, d of d, J = 3.6, 3.5 Hz, CH=), 4.80 (1 H, br, CH), 3.85 (1 H, br, CH), 3.73 (3 H, s, CH_3), 3.50 (1 H, br, NH), and 1.3–2.3 (4 H, m, CH_2CH_2).

Reduction of Adduct IIIb.—IIIb (196 mg) was dissolved in 5 ml of ethyl acetate containing 200 mg of 5% palladium on carbon, and the solution was stirred under hydrogen. After 4 hr the solution was filtered and evaporated, giving 190 mg (95%) of crystalline product (IV). Recrystallization from cyclohexane gave pure product: mp 129–131°; ir ($CHCl_3$) 5.85 and 6.05 μ; nmr ($CDCl_3$) δ 4.68 (2 H, br, CH) and 2.02 (8 H, br, CH_2).

2,3-Diaza[2.2.2]bicyclooct-2-ene.—To a solution of 50 mg of lithium hydroxide in 40 ml of 1:2 tetrahydrofuran–water was added 110 mg of IV. After stirring for 6 hr under air, the solution was exhaustively extracted with dichloromethane which was dried and evaporated to give 49 mg (81%) of 2,3-diaza[2.2.2]-bicyclooct-2-ene. Recrystallization from pentane–ether at −35° gave solid product: mp 136–138° (lit. mp 142°);[6] nmr ($CDCl_3$) δ 5.13 (2 H, br, CH) and 1.1–1.8 (8 H, br, CH_2); ir and uv data were as described.[6]

Hydrolysis of IIIb.—To a solution of 49 mg of IIIb in 3 ml of diglyme was added 3 ml of 0.2 *M* lithium hydroxide solution. After stirring for 2 hr at 25°, gc analysis (10 ft, 10% TCEP, 30°) indicated that cyclohexadiene had been formed. In a similar experiment using cyclohexane as an internal standard, gc analysis indicated that cyclohexadiene was formed in 95% yield.

Registry No.—I, 41316-13-6; II, 41316-14-7; IIIa, 41316-15-8; IIIb, 41316-16-9; IIIc, 41316-17-0; IIId, 41316-18-1; IIIe, 41316-19-2; IV, 41316-20-5; V, 41316-21-6; 2,3-diaza[2.2.2]-bicyclooct-2-ene, 3310-62-1.

(6) S. G. Cohen and R. Zand, *J. Amer. Chem. Soc.*, **84**, 586 (1962).

(7) This work was assisted financially by the National Institutes of Health and the National Science Foundation.

Carbonylation of Saturated Hydrocarbons Catalyzed by Copper(I) Carbonyl

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Several studies of reactions catalyzed by copper(I) carbonyl have been reported. Olefins react with carbon monoxide at room temperature and atmospheric pressure with the catalysis of copper(I) carbonyl, and *tert*-carboxylic acids were obtained in high yield.[1] Similarly *tert*-carboxylic acids were prepared from the carbonylation of alcohol with the catalysis of copper(I) carbonyl.[2] The pathway for formation of copper(I) carbonyl has been described.[1,2] Haff and Koch have found the synthesis of *tert*-carboxylic acid from paraffin *via* hydride transfer using formic acid.[3] Other studies were performed using different acid catalysts. Friedmann[4] reported the hydrogen fluoride catalyzed reactions of hydrocarbons and carbon monoxide at elevated

(1) Y. Souma, H. Sano, and J. Iyoda, *J. Org. Chem.*, **38**, 2016 (1973).

(2) Y. Souma and H. Sano, *Bull. Chem. Soc. Jap.*, in press; Y. Souma and H. Sano, *Kogyo Kagaku Zasshi*, **73**, 2723 (1970).

(3) W. Haff and H. Koch, *Justus Liebigs Ann. Chem.*, **638**, 122 (1960).

(4) B. S. Friedman and S. M. Cotton, *J. Org. Chem.*, **27**, 481 (1962).

TABLE I

tert-CARBOXYLIC ACID FROM SATURATED HYDROCARBON BY COPPER(I) CARBONYL CATALYST[a]

Saturated compd	Olefin or alcohol	Products	Yield, %
Methylcyclohexane (108-87-2)	1-Hexene (592-41-6)	Methylcyclohexanecarboxylic acid (1123-25-7),	5.5[b]
		t-C_7 acids[c]	1.5[b]
2-Methylpentane (107-83-5)	1-Octene (111-66-0)	2,2-Dimethylpentanoic acid (1185-39-3)	40
		2-Methyl-2-ethylbutanoic acid (19889-37-3),	20
		t-C_9 acids[d]	30
2-Methylbutane (78-78-4)	1-Octene	2,2-Dimethylbutanoic acid (595-37-9),	30
		t-C_9 acids[d]	60
		2,2-Dimethylpropionic acid (75-98-9)	5
Methylcyclopentane (96-37-7)	1-Octene	Methylcyclopentanecarboxylic acid (5217-05-0),	55
		t-C_9 acids[d]	26
Methylcyclohexane	1-Hexene	Methylcyclohexanecarboxylic acid,	51
		t-C_7 acids[c]	30
Methylcyclohexane	1-Octene	Methylcyclohexanecarboxylic acid,	65
		t-C_9 acids[d]	30
Methylcyclohexane	2-Propanol (67-63-0)	Methylcyclohexanecarboxylic acid	20
		2-Methylpropionic acid (79-31-2)	5
Methylcyclohexane	*tert*-Butyl alcohol (75-65-0)	Methylcyclohexanecarboxylic acid,	33
		2,2-dimethylpropionic acid	10
Methylcyclohexane	1-Hexanol (111-27-3)	Methylcyclohexanecarboxylic acid,	43
		t-C_7 acids[c]	29
Methylcyclohexane	1-Octanol (111-87-5)	Methylcyclohexanecarboxylic acid,	70
		t-C_9 acids[d]	10
1,4-Dimethylcyclohexane (589-90-2)	1-Hexene	1,4-Dimethylcyclohexanecarboxylic acid [cis (24097-71-0) to trans (24097-70-9), 1:1]	55
		t-C_7 acid[c]	26
Octane (111-65-9)	1-Hexene	*t*-C_9 acids[d]	0
		t-C_7 acids[c]	64
2,2,4-Trimethylpentane (540-84-1)	1-Hexene	*t*-C_9 acids[d]	1
		t-C_7 acids[c]	85
Cyclohexane (110-82-7)	1-Hexene	*t*-C_7 acids[c]	80

[a] In most cases, 0.2 mol of saturated hydrocarbon, 0.2 mol of olefin or alcohol, 0.02 mol of Cu_2O, and 105 ml of 98% H_2SO_4 were used. The reaction temperature was ~30°, and the reaction time varied from 1 to 2 hr. The pressure of carbon monoxide was 1 atm. The alkenes and alcohols in the reaction mixtures yield *tert*-carboxylic acids too. Registry numbers are given in parentheses. [b] Copper(I) compound was not used. [c] The ratio of 2,2-dimethylpentanoic acid to 2-methyl-2-ethylbutanoic acid was 2:1. [d] The ratio of 2,2-dimethylheptanoic acid (14250-73-8) to 2-methyl-2-ethylhexanoic acid (1185-29-1) to 2-methyl-2-propylpentanoic acid (31113-56-1) was 4:2:1.

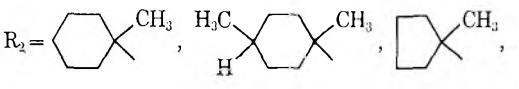
pressures. Matsubara[5] reported the carboxylic acid synthesis from paraffins in $BF_3 \cdot H_2O$ at 20 atm of carbon monoxide pressure.

In this paper, we describe the carbonylation of saturated hydrocarbons using copper(I) carbonyl catalyst in concentrated H_2SO_4 at room temperature and atmospheric pressure. A hydride transfer mechanism can account for this reaction.

$$R_1^+ + R_2H \longrightarrow R_1H + R_2^+$$

$$R_2^+ + CO \xrightarrow{Cu(CO)_3^+} R_2CO^+ \xrightarrow{H_2O} R_2COOH$$

R_1 = general alkyl (*n*-, *sec*-, *tert*-)

R_2 = 

$CH_3 \cdot (CH_2)_2 \cdot C(CH_3)_2-$, $CH_3CH_2C(CH_3)_2-$

Results and Discussion

Copper(I) carbonyl catalyst was prepared from copper(I) compounds and carbon monoxide in concentrated H_2SO_4. Alcohols or olefins were used as the sources of alkyl cations. As soon as the mixtures of saturated hydrocarbon and alkyl cation source were dropped into the copper(I) carbonyl suspension, carbon monoxide was absorbed and reacted immediately. The results of the carbonylation of saturated hydrocarbons using copper(I) carbonyl catalyst are shown in Table I. The yield of carboxylic acid was 7% in the absence of copper(I) compounds.

Alcohol or olefin gives carbonium ion in concentrated H_2SO_4. This cation abstracts hydride ion from saturated hydrocarbon. Then a new alkyl cation is formed from saturated hydrocarbon and reacted with carbon monoxide. Only the saturated hydrocarbons which contain *t*-H atom undergo hydride ion abstract. Octane or cyclohexane does not react with carbon monoxide. In Koch reaction, the products were obtained even for unbranched paraffins.[3] When the copper(I) carbonyl catalyst is used, the rate of carbonylation is very rapid. In the mixture of unbranched paraffin and olefin, the rate of carbonylation of olefins is more rapid than that of hydride abstract ion from unbranched paraffins. Carbonylation of 2,2,4-trimethylpentane does not occur, although it has *t*-H atom in the molecule (owing to steric hindrance of neopentyl group). In the comparison of alkyl cation sources, better results were obtained in longer chain alcohols (or olefins).

The influence of H_2SO_4 concentration on hydride transfer was examined in the reaction of methylcyclohexane and carbon monoxide in the presence of 1-

(5) M. Matsubara, M. Goto, K. Aomura, and H. Ohtsuka, *Kogyo Kagaku Zasshi*, **72**, 1290 (1969); M. Matsubara, M. Goto, K. Aomura, and H. Ohtsuka, *ibid.*, **72**, 1999 (1969).

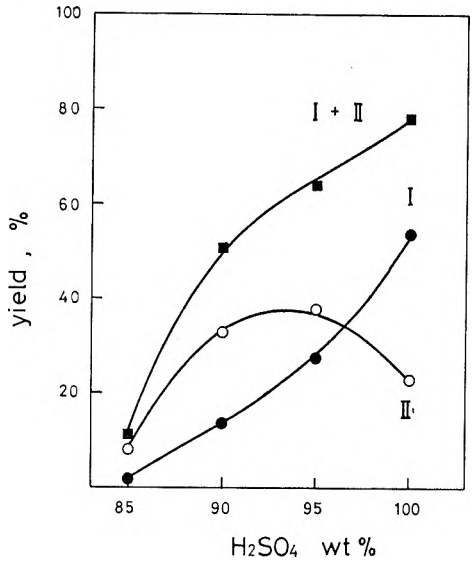


Figure 1.—The influence of H_2SO_4 concentration, with Cu_2O (0.02 mol), methylcyclohexane (0.2 mol), and hexene (0.2 mol) at 30° (2,2-dimethylpentanoic acid to 2-methyl-2-ethylbutanoic acid, 2:1).

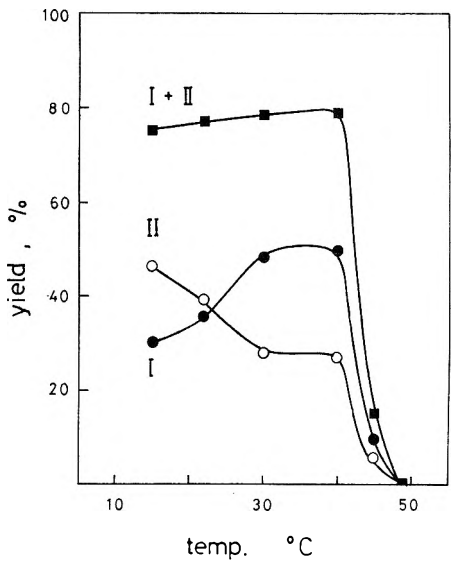
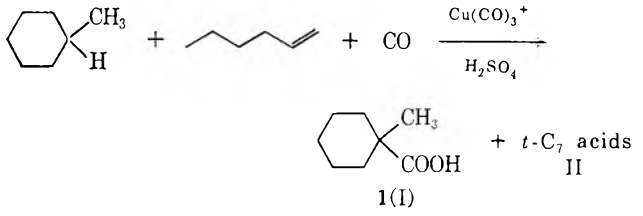


Figure 2.—The influence of reaction temperature. Cu_2O (0.02 mol), 98% H_2SO_4 (105 ml), methylcyclohexane (0.2 mol), and hexene (0.2 mol) were used.

hexene. The results are shown in Figure 1. The ratio of the product **1** *via* hydride transfer increased



with the increase of H_2SO_4 concentration. At the H_2SO_4 concentration of <80%, no reaction occurred. It is known that $Cu(CO)_3^+$ does not exist in the H_2SO_4 <80%.[6]

The influence of the reaction temperature was examined in the carbonylation of methylcyclohexane. The results are shown in Figure 2. The ratio of the product **1** *via* hydride transfer increases with an increase in temperature. However, no reaction occurred above 50°, since $Cu(CO)_3^+$, which acts as catalyst, can not exist in the reaction system above 50° at 1 atm of carbon monoxide pressure.

Experimental Section

The ir spectra were taken as neat samples using a Hitachi EPI-S2 spectrometer. ^1H nmr spectra were taken on a JEOL PS-100 at 100 MHz in CCl_4 solvent. Chemical shifts are given in δ units (parts per million) downfield from internal TMS. Glpc analyses were performed using a 3M FFAP column (10% on Chromosorb WAW). Elemental analyses were done on a Yanagimoto CHN MT-2.

Reagent.—Methylcyclohexane, methylcyclopentane, 1,4-dimethylcyclohexane, 2-methylpentane, 2-methylbutane, octane, 2,2,4-trimethylpentane, cyclohexane, 1-hexene, 1-octene, 2-propanol, *tert*-butyl alcohol, 1-hexanol, and 1-octanol were all commercial reagents and purified by distillation.

Cu_2O, CO, and H_2SO_4 were all commercial reagents, which were used without further purification.

Preparation of copper(I) carbonyl was carried out as described in previous papers.[1,6]

Carbonylation of Saturated Hydrocarbons.—The mixtures of 0.2 mol of saturated hydrocarbon and 0.2 mol of olefin (or alcohol) were added dropwise during 50 minutes to the copper(I) carbonyl suspension. Carbon monoxide was soon absorbed and reacted with carbonium ion. CO absorption was finished in 1 to 2 hr, and the reaction mixture was poured over ice-water. The products were extracted by benzene. Excess alkali was added to the benzene extract. The water phase was acidified by concentrated H_2SO_4. Carboxylic acids were again extracted by benzene and isolated by preparative glpc. The structures of products were determined by ir, nmr, and elemental analysis.

Methylcyclohexanecarboxylic acid was obtained by the carbonylation of methylcyclohexane: ir 2950, 1700 (C=O), 1460, 1250; nmr δ 1.13 (s, 3, CH_3CCOOH), 1.20~1.80 (m, 8, CH_2, HCH), 1.95~2.24 (m, 2, HCHCCOOH), 11.72 (br s, 1, COOH).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.74; H, 10.20.

Methylcyclopentanecarboxylic acid was obtained by the carbonylation of methylcyclopentane: ir 2980, 1705 (C=O), 1460, 1280, 1200; nmr δ 1.28 (s, 3, CH_3CCOOH), 1.70 (m, 6, CH_2, HCH), 2.16 (m, 2, HCHCCOOH), 11.78 (br s, 1, COOH).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 66.02, H, 9.57.

All identifications of 1,4-dimethylcyclohexanecarboxylic acid, 2-methylpropionic acid, 2,2-dimethylpentanoic acid, 2,2-dimethylbutanoic acid, 2-methyl-2-ethylbutanoic acid, and *t*-C_9 acid were made by comparison of retention time and "spiking" with authentic samples. Authentic samples were prepared by the carbonylations of olefins[1] or alcohols.[2]

Registry No.—$Cu(CO)_3^+$, 28990-05-8.

(6) Y. Souma and H. Sano, *Nihon Kagaku Zasshi*, **91**, 625 (1970).

A Photochemical Synthesis of Tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane

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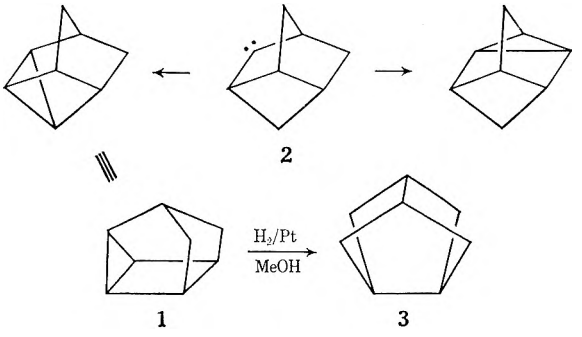
Received April 25, 1973

The synthesis of tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (1) attracted our attention for several reasons. Since **1** is believed to be formed as a coproduct of the intramolecular insertion of 2-carbenatricyclo[3.2.1.0^{3,6}]octane (2),[2]

(1) NSF Graduate Trainee, June 1971–Sept 1972.

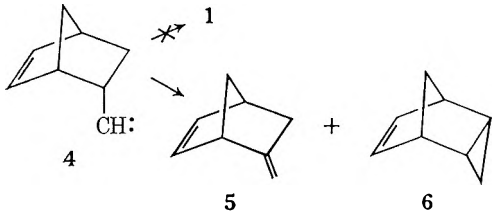
(2) P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965).

an alternative synthesis is desirable to reinforce the spectroscopic and chemical evidence previously reported. In addition, the novelty of this tetracyclic hydrocarbon makes it of considerable interest in our continuing program devoted to the chemistry of small polycyclic ring systems, and the facile hydrogenolysis of **1** provides yet the best route to tricyclo[3.3.0.0^{3,7}]-octane (**3**),[2,3] an unusual molecule (symmetry point

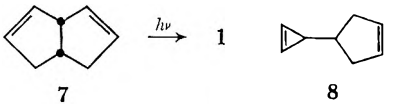


group D_{2d}) whose physical and chemical properties are of continuing interest.[4]

Previous synthetic efforts to prepare tetracyclooctane **1** included generation of bivalent intermediate **4**, the projected intramolecular addition to have yielded **1** directly. Unfortunately, only products arising from hydrogen migration (**5**) and endo C-3 C–H insertion (**6**) were observed.[5]

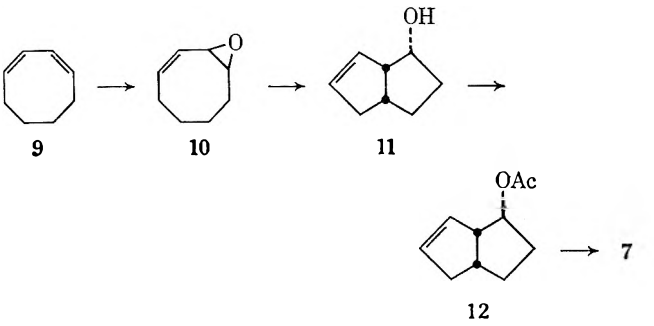


The photochemical synthesis we wish to describe relies on the intramolecular [$_\pi 2_s + {}_\pi 2_s$] cycloaddition[6] of diene **7**. This method was chosen for formation of **1** because of the success of similar reactions,[7,8] the proximity of the two olefinic functions in **7**,[9] and the lack of a reasonable synthesis of alternative photolytic precursor **8**.



Synthesis of key intermediate **7** was accomplished as shown in Scheme I. Monoepoxidation of *cis,cis*-1,3-

SCHEME I



cyclooctadiene (**9**) and subsequent treatment of **10** with lithium diethylamide in ether yields alcohol **11** by transannular carbene or carbenoid insertion.[10-12] Formation of acetate **12** by treatment of **11** at reflux with acetic anhydride, followed by gas-phase pyrolysis, yields required diene **7** in an overall yield of 45%.

The photolytic ring closure of diene **7** to title hydrocarbon **1** was studied in some detail. Photolysis in pentane results in tetracyclic hydrocarbon formation at a rate twice that in ether. However, periodic removal of side products is necessary for completion of the reaction. Furthermore, attempts to obtain a ratio of **1**:**7** greater than 0.5 were unsuccessful. Irradiation in ether, on the other hand, resulted in a corresponding ratio of 1.6, proceeding to this point without filtration, and resulted in a higher yield (35% *vs.* 8%) of desired photoisomer **1**. Irradiation in acetone and in the presence of benzophenone resulted in rapid loss of starting material with no concomitant production of **1**, presumably owing to bimolecular reactions such as oxetane and dimer formation. Attempts to catalyze the reaction by formation of a Cu(I) complex of **7**[13] were unsuccessful.

Overall, the yield of title hydrocarbon **1** based on 1,3-cyclooctadiene is 10%. (The yield can be increased by recycling diene **7** recovered from the photolysis if more than a single photolysis is performed.) This synthetic route has greatly facilitated the investigation of the chemistry of **1** currently in progress in our laboratory.

Experimental Section

All boiling points are uncorrected. Microanalysis was performed by Chemalytics, Inc., Tempe, Ariz. 85282. Infrared spectra were obtained using a Beckman IR-8 spectrophotometer; the nmr spectra were determined on a Varian Associates HA-100 spectrophotometer. Vpc analyses and preparative collections were performed using an Aerograph Model A-90-P gas chromatograph and the columns specified below.

Preparation of *endo*-2-*cis*-Bicyclo[3.3.0]oct-7-enyl Acetate (12).—Heating a solution of 3.0 g (2.42×10^{-2} mol) of alcohol **11**, 3.5 g (3.42×10^{-2} mol) of acetic anhydride, and 0.4 g of sodium acetate at reflux for 2 hr, followed by dilution with ether, extraction with 5% $NaHCO_3$ until no more CO_2 was evolved, and drying

(3) P. K. Freeman, R. B. Kinnel, and T. D. Ziebarth, *Tetrahedron Lett.*, 1059 (1970).

(4) R. R. Sauers and K. W. Kelly, *J. Org. Chem.*, **35**, 3286 (1970); W. T. Borden, V. V. M. Cabell, and T. Ravindranathan, *J. Amer. Chem. Soc.*, **93**, 3800 (1971); R. R. Sauers, K. W. Kelly, and B. R. Sickles, *J. Org. Chem.*, **37**, 537 (1972).

(5) P. K. Freeman and K. B. Desai, *J. Org. Chem.*, **36**, 1554 (1971).

(6) R. B. Woodward and R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(7) W. Eberbach and H. Prinzbach, *Helv. Chim. Acta*, **50**, 2490 (1967); J. Meinwald and B. E. Kaplan, *J. Amer. Chem. Soc.*, **89**, 2611 (1967); J. Meinwald and G. W. Smith, *ibid.*, **89**, 4923 (1967); R. Srinivasan and K. H. Carlough, *ibid.*, **89**, 4932 (1967); S. Moon and C. R. Ganz, *Tetrahedron Lett.*, 6275 (1968).

(8) Subsequent to the initiation of our study, G. Kaupp and K. Krieger, *Angew. Chem., Int. Ed. Engl.*, 719 (1972), have reported the observation of an analogous photoisomerization of the 3,7-diphenyl derivative of **7**.

(9) Dreiding models indicate a C_7–C_8 internuclear distance of 2.56 Å.

(10) A. C. Cope, H. H. Lee, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2849 (1958); A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *ibid.*, **82**, 6370 (1960).

(11) J. K. Crandall and L. H. Chang, *J. Org. Chem.*, **32**,532 (1967).

(12) J. K. Crandall and L.-H. Chang, *J. Org. Chem.*, **32**, 435 (1967).

(13) No 1:1 adduct of CuCl–**7** could be obtained by the method reported for the formation of CuCl–1,5-cyclooctadiene complex.[14]

(14) J. H. van de Hende and W. C. Baird, *J. Amer. Chem. Soc.*, **85**, 1009 (1963).

over sodium sulfate–potassium carbonate, yielded 3.80 g (95%) of crude acetate upon removal of solvent at reduced pressure. This acetate was of sufficient purity (>99% by vpc analysis on a Carbowax 20M on 70/80 Anakron ABS column and nmr analysis) to be used in subsequent reactions without further purification: ir (neat) ν 3080, 2980, 2860, 2885, 1728, 1615, 1375, 1240, 1052, 714 cm^{-1}; nmr (100 MHz, CCl_4) δ 5.68 (doublet of doublets J = 6, 2 Hz, 1 H), 5.38 (doublet of doublets, J = 6, 2 Hz, 1 H), 5.01 (doublet of triplets, J = 6, 6 Hz, 1 H), 3.35 (m, 1 H), 2.66 (m, 2 H), 1.96 (s, 3 H), 2.2–1.3 (m, 5 H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.78.

Preparation of *cis*-2,7-Bicyclo[3.3.0]octadiene (7).—Acetate **12** (2.2 g, 0.0132 mol) was pyrolyzed by dropwise addition onto a 40-cm Pyrex column packed with Pyrex glass beads heated to 475° in a slow nitrogen flow. The product was trapped directly into a receiver cooled to −78°, diluted with pentane, washed once with water, once with 5% $NaHCO_3$, and once with saturated NaCl, and dried over anhydrous Na_2SO_4. Subsequent removal of solvent by distillation through a 10-cm Vigreux column, followed by distillation of the residue, yielded 1.12 g (0.0106 mol, 80% based on acetate lost) of diene **7** and 0.30 g of recovered acetate **12**. The product was pale yellow; a colorless sample having an identical ir spectrum was obtained by chromatography on alumina with pentane elution. The ir spectrum of **7** was identical with that previously reported;[15] nmr (100 MHz, CCl_4) δ 5.54 (m, 4 H), 3.66 (doublet of multiplets, J = 7.5 Hz, 1 H), 3.1–2.5 (complex multiplet, 2 H), 2.55 (doublet of multiplets, J = 7.5 Hz, 1 H), 2.04 (doublet of multiplets, J = 15 Hz, 2 H).

Preparation of Tetracyclo[3.3.0.$0^{2,4}$.$0^{3,7}$]octane (1). A. Photolysis in Pentane.—A stirred solution of 2.45 g (2.29 × 10^{-2} mol) of diene **7** in 250 ml of olefin-free pentane was purged with nitrogen for 30 min, then irradiated under nitrogen with an unfiltered 450-W Hanovia high-pressure mercury lamp using a water-cooled quartz probe. Monitoring the reaction by vpc on a β,β'-oxydipropionitrile on 30/60 Chromosorb P (AW) column indicated a buildup of a new volatile component at the rate of about 1% per hour. At the end of 16 hr, however, conversion stopped. The solution, somewhat yellow and containing a solid material, was passed through a short alumina column, and the resulting clear solution was repurged and irradiated again as above. The new volatile component again grew at the rate of 1% per hour until it was 35% of the starting diene after 40 hr total irradiation. Further manipulation of the solution as above produced no further increase in the ratio of product to starting diene **7**. The yield of **1** as indicated by an internal vpc reference was 8%.

The product was isolated by removal of *ca.* 99% of the pentane by distillation through a 40-cm spinning band column, followed by extraction of the residue with an equal volume of saturated $AgNO_3$. Vpc analysis of this procedure indicated no loss of product relative to an internal norbornane standard, whereas diene **7** was completely removed. The resulting pentane solution was subjected to preparative gas chromatography on a β,β'-oxydipropionitrile on 30/60 Chromosorb P (AW) column, the single product being identified as desired hydrocarbon **1**. Unreacted diene **7** was recovered by dilution of the $AgNO_3$ solution with a tenfold volume of water and extraction by pentane.

B. Photolysis in Ether.—A solution of 2.50 g (2.43 × 10^{-2} mol) of diene **7** was taken up in 250 ml of commercial anhydrous ether, purged with nitrogen, and irradiated as described above. Monitoring the reaction indicated conversion of **7** to **1** at a rate of 0.5% per hour until the ratio of **7**:**1** was **38**:62 as measured by vpc integration. The resulting yellow solution was concentrated by distillation of the ether through a 40-cm Vigreux column, the residue yielding pure **1**. The yield as determined by an internal norbornane vpc reference was 35%.

Acknowledgment.—The authors gratefully acknowledge the support of this work by a grant from the National Science Foundation.

Registry No.—**1**, 4582-22-3; **7**, 41164-14-1; **11**, 41164-15-2; **12**, 40132-71-6.

(15) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

The Synthesis of Cyclic 2-Enones from Cyclic 1,3 Diketones[1a]

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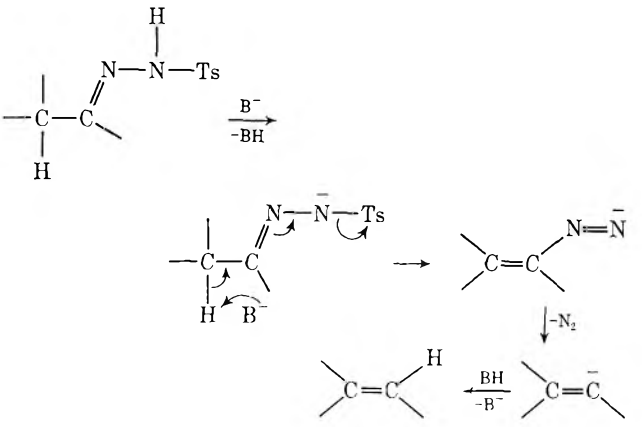
Received April 18, 1973

It has previously been shown that tosylhydrazones are converted into alkenes upon treatment with a strong base such as lithium aluminum hydride,[2] lithium hydride,[3] sodium amide,[4] or alkyllithium.[5] We have found that cyclic 1,3 diketones can be converted into cyclic 2-enones through treatment of their monotosylhydrazones with weak base. This new synthetic method is a simple, safe procedure for preparation of substituted cyclic 2-enones.

The mechanism for strong base conversion of tosylhydrazones into alkenes suggested by Shapiro[6] is outlined in Scheme I. Since the acidic sulfonamide proton (pK_a = 8.5)[7] is presumably removed first, removal of the α proton with concomitant loss of *p*-toluenesulfinate anion requires a strong base.

SCHEME I



If the α proton were more acidic than the sulfonamide proton, however, the reaction should proceed in the presence of a weak base. Since cyclic 1,3 diketones have sufficiently acidic α protons, they would be expected to undergo such a reaction.

5,5-Dimethylcyclohexane-1,3-dione (**1**, pK_a = 5.2)[8] was converted into 5,5-dimethyl-2-cyclohexen-1-one (**3**) in 52% yield on heating the crude monotosylhydrazone (**2**) in aqueous potassium carbonate solution. Enone **3** was also obtained in 53% yield from purified

(1) (a) This work was supported in part by grants from the California State University, Fullerton Foundation; (b) NSF Undergraduate Research Participant.

(2) L. Caglioti and M. Magi, *Tetrahedron Lett.*, 1261 (1962); L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).

(3) L. Caglioti, P. Grasselli, and G. Maina, *Chim. Ind. (Milan)*, **45**, 559 (1963); L. Caglioti, P. Grasselli, and A. Selva, *Gazz. Chim. Ital.*, **94**, 537 (1964).

(4) W. Kirmse, B.-G. von Bülow, and H. Schepp, *Justus Liebigs Ann. Chem.*, **691**, 41 (1966).

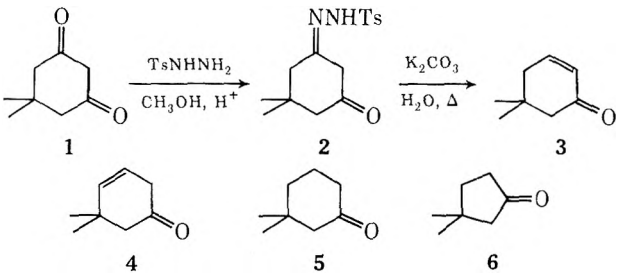
(5) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); G. Kaufman, F. Cook, H. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89**, 5736 (1967).

(6) R. H. Shapiro, *Tetrahedron Lett.*, 345 (1968).

(7) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

(8) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 453.

2. In addition to **3**, a small amount of the 3,4 isomer (**4**), 3,3-dimethylcyclohexanone (**5**), and 3,3-dimethylcyclopentanone (**6**) were identified in the product mixture.



1 2 3 4 5 6

2-Methyl-2-cyclohexen-1-one (**7**) was synthesized in 41% yield from 2-methylcyclohexane-1,3-dione (**8**). Also, small amounts of 2-methylcyclohexanone (**9**) and 2-methyl-2-cyclohexen-1-ol (**10**) were formed. 2-Cyclohexen-1-one (**11**) was prepared in 15% yield from cyclohexane-1,3-dione (**12**). In addition to **11**, a lower yield of the 3,4 isomer (**13**), cyclohexanone (**14**), cyclopentanone (**15**), and 2-methylcyclopentanone (**16**) were formed in the reaction.[9]

In preliminary experiments carried out in a similar fashion with methyl 2-cyclohexanonecarboxylate and ethyl acetoacetate, cyclohexanone and acetone were formed through decarboxylation.

Experimental Section[10]

5,5-Dimethyl-2-cyclohexen-1-one (3).—The following procedure for the preparation of **3** is typical for the conversion of cyclic 1,3 diketones into cyclic 2-enones.

A.—In a round-bottom flask were placed 2.80 g (20.0 mmol) of **1**, 3.83 g (20.6 mmol) of tosylhydrazide, 50 ml of anhydrous methanol, and three drops of concentrated H_2SO_4. After standing overnight at room temperature, the methanol was removed *in vacuo*, 22.1 g (160 mmol) of potassium carbonate and 250 ml of water were added, and the solution was heated to steam distil the product. The largely aqueous distillate was saturated with NaCl and extracted with ether (3 × 30 ml), and the ether was washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, 1.41 g, which gc analysis (FFAP) showed to be a mixture: 90% **3** (52% yield based on **1**),[11] 2% **4**, nmr (CCl_4) δ 1.10 (s, 6, 2 CH_3), 2.33 (s, 2, CCH_2CO), 2.80 (s, 2, $CH{=}CHCH_2CO$), 5.78 (s, 2, $CH{=}CH$), ir (CCl_4) 5.83 μ, 5% **5**,[12] 2% **6**,[13] and 0.5% solvent. Components in the reaction mixture were separated for spectral analysis using preparative gc (SF-96 and FFAP).

B.—Enone was also prepared from purified **2**. A solution of 2.05 g (14.6 mmol) of **1**, 2.84 g (15.2 mmol) of tosylhydrazide, 50 ml of methanol, and two drops of concentrated HCl was allowed to stand overnight at room temperature. Solvent was removed *in vacuo*, and the residue was recrystallized from methanol–benzene to give **2**: crop 1, 3.30 g (71.2%), mp 208.5–209.0° dec; crop 2, 0.39 g (8.0%), mp 205.0–206.5° dec [ir (mull) 6.23, 6.31, 6.45, 7.58 (SO_2), and 8.70 μ (SO_2); nmr [$(CD_3)_2SO$] δ 0.90 [s, 6, $C(CH_3)_2$], 1.92 (s, 2, CH_2), 2.08 (s, 2, CH_2), 2.38 (s, 3, $ArCH_3$), 5.10 (s, 1, CH), 7.40 (d, 2, J = 8.5 Hz, ArH), 7.71 (d, 2, J = 8.5 Hz, ArH), 8.61 (s, 1, NH), and 9.71 (s, 1, NH); analytical sample from methanol, mp 213.5–214.0° dec[14]].

Anal. Calcd for $C_{15}H_{20}N_2SO_3$: C, 58.41; H, 6.54; N, 9.09. Found: C, 58.15; H, 6.53; N, 8.99.

Using a procedure similar to that in part A, 6.17 g (20.0 mmol, mp 209.0–209.7° dec) of **2** with 22.0 g (159 mmol) of K_2CO_3 gave 1.42 g of an oil which was shown by gc analysis (SF-96) to consist of 93% **3** (53% yield based on **2**), 3% **4**, less than 1% **5**, 3% **6**, and 1% solvent.

3,3-Dimethylcyclopentanone (6).—3-Methyl-2-cyclopenten-1-one, which was prepared from 2,5-hexanedione,[15] was converted into **6** through 1,4 addition of methylmagnesium iodide.[16]

A solution of methylmagnesium iodide in ether prepared from 10.1 g (71.3 mmol) of methyl iodide and 1.76 g (72.5 mmol) of magnesium was combined with 0.10 g (0.5 mmol) of anhydrous cuprous chloride, and the mixture was cooled in an ice–salt bath. 3-Methyl-2-cyclopenten-1-one, 5.03 g (52.4 mmol), in 10 ml of dry ether was added dropwise over 9 min while stirring and cooling. Saturated NH_4Cl solution and diluted HCl were added, and the ether layer was separated. The aqueous phase was extracted once with ether, and the combined ether extracts were washed with water and saturated Na_2CO_3 and NaCl solutions and dried ($MgSO_4$). After filtration and removal of the solvent *in vacuo*, the residue was distilled in a short-path still at a bath temperature of 140° (24 Torr) to give 0.75 g of distillate. The nmr spectrum indicated that the distillate was impure. A pure sample of **6** was obtained through preparative gc (FFAP): nmr (CCl_4) δ 1.11 (s, 6, 2 CH_3), 1.95 (s, 2, CH_2), 1.55–2.40 (AA'BB' multiplet, 4, CH_2CH_2); ir (CCl_4) 5.74 μ; semicarbazone mp 177.4–179.2° (lit.[17] mp 178°).

2-Methyl-2-cyclohexen-1-one (7).—Enone **7** was prepared following the typical procedure. Diketone **8**, 0.631 g (5.00 mmol), mp 206.0–206.8°,[18] and 0.940 g (5.04 mmol) of tosylhydrazide were combined to give crude tosylhydrazone. Steam distillation of a solution of tosylhydrazone with 5.50 g (39.8 mmol) of K_2CO_3 gave an oil, 0.247 g, which gc analysis (FFAP) demonstrated to be a mixture: 91% **7** (41% yield based on **8**), nmr (CCl_4) δ 1.72 (broad, 3, CH_3), 1.76–2.55 (m, 6, CH_2CH_2-CH_2), 6.67 (broad, 1, CH), ir (CCl_4) 5.94 μ, semicarbazone mp 207.5–209.1° (lit.[19] mp 207–208°), 1% **9**,[20] 7% **10**,[21] and less than 1% solvent. Components were separated for spectral analysis using preparative gc (FFAP).

An analytical sample of the monotosylhydrazone of **8** was recrystallized from methanol, mp 192.7–193.1° dec.

Anal. Calcd for $C_{14}H_{18}N_2SO_3$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.08; H, 6.21; N, 9.40.

2-Cyclohexen-1-one (11).—Using the typical procedure, 2.24 g (20.0 mmol), mp 104.5–105.1°,[22] of **12** and 3.72 g (20.0 mmol) of tosylhydrazide were converted to the crude tosylhydrazone. Steam distillation of a solution of the tosylhydrazone with 22.14 g (160 mmol) of K_2CO_3 gave 0.361 g of an oil. The oil was analyzed by gc (FFAP) and shown to be a mixture: 81% **11** (15% yield based on **12**), nmr (CCl_4) δ 1.73–2.55 (m, 6, CH_2CH_2-CH_2), 5.87 (pair of t, 1, J = 1.5 and 10 Hz, CH), 6.95 (pair of t, 1, J = 4 and 10 Hz, CH), ir (CCl_4) 5.95 μ,[23] 2% **13**, 4% **14**,[13] 12% of what appeared to be a mixture of **15** and **16** on the basis of nmr and ir spectra, and 1% solvent. Components were separated by preparative gc (FFAP) for spectral analysis. When a sample of the mixture of **15** and **16** from preparative gc was

(9) Ring contractions have also been observed in the Clemmensen reduction of 1,3 diketones; *cf.* A. N. Dey and R. P. Linstead, *J. Chem. Soc.*, 1063 (1935).

(10) Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 spectrometer. Nmr spectra were obtained using a Varian A-60A spectrometer with tetramethylsilane as an internal standard. Gas chromatography was carried out using a Varian Aerograph Model 90-P3 gas chromatograph with a 5 ft × 0.25 in. 10% FFAP or 10% SF-96 on 60–80 Chromosorb W column except where indicated. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(11) Identified by spectroscopic comparison with an authentic sample prepared from **1**: W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960).

(12) Identical with the product of catalytic hydrogenation of **3** in ethanol over 5% Pd/C.

(13) Identified by spectroscopic comparison with an authentic sample.

(14) Cyclic 1,3 diketones and their derivatives exist primarily in the enol form: A. J. Fatiadi, *J. Org. Chem.*, **35**, 831 (1970).

(15) R. M. Acheson and R. Robinson, *J. Chem. Soc.*, 1127 (1952).

(16) The procedure of G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948), was followed.

(17) T. Henshall, *J. Soc. Chem. Ind.*, **62**, 127 (1943).

(18) A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, *Org. Syn.*, **41**, 56 (1961).

(19) F. C. Whitmore and G. W. Pedlow, Jr., *J. Amer. Chem. Soc.*, **63**, 758 (1941).

(20) Identical with the product of catalytic hydrogenation of **7** in methanol over 5% Pd/C, and the infrared spectrum agrees with the published spectrum of **9**: C. J. Pauchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Milwaukee, Wis., 1970, p 198.

(21) Identical with the product of lithium aluminum hydride reduction of **7** at low temperature.

(22) J. C. Sircar and A. I. Meyers, *J. Org. Chem.*, **30**, 3206 (1965).

(23) The infrared spectrum agrees with the published spectrum; see ref 20, p 204.

analyzed on a diisodecyl phthalate column, two components in about equal amounts with retention times identical with those of 15 and 16 were found. Nmr and ir spectra of a mixture of authentic 15 and 16[24] in the same ratio agreed with the spectra obtained from the preparative gc sample. Compound 13 could not be isolated free of 14, but the nmr of the mixture had the characteristic absorption of a 3,4-unsaturated ketone: nmr (CCl_4) δ 2.43 ($CCH_2C{=}O$), 2.78 ($CH{=}CHCH_2C{=}O$), 5.79 ($CH{=}CH$), the remaining CH_2 was obscured by 14.

An analytical sample of the monotosylhydrazone of 12 was recrystallized from methanol, mp 208.3–209.0° dec.

Anal. Calcd for $C_{13}H_{16}N_2SO_3$: C, 55.69; H, 5.75; N, 9.99. Found: C, 55.75; H, 5.62; N, 10.25.

Registry No.—1, 126-81-8; 2, 41189-09-7; 3, 4694-17-1; 4, 41189-10-0; 6, 20500-49-6; 7, 1121-18-2; 8, 1193-55-1; 8 monotosylhydrazone, 41189-12-2; 11, 930-68-7; 12, 504-02-9; 12 monotosylhydrazone, 41189-13-3; 13, 4096-34-8; tosylhydrazide, 1576-35-8; 3-methyl-2-cyclopenten-1-one, 2758-18-1; methyl iodide, 74-88-4.

(24) Compound 16 was synthesized from 2-carbethoxycyclopentanone: F. C. Case and E. E. Reid, *J. Amer. Chem. Soc.*, **50**, 3062 (1928).

Sterol Metabolism. XXV. Cholesterol Oxidation by Singlet Molecular Oxygen[1]

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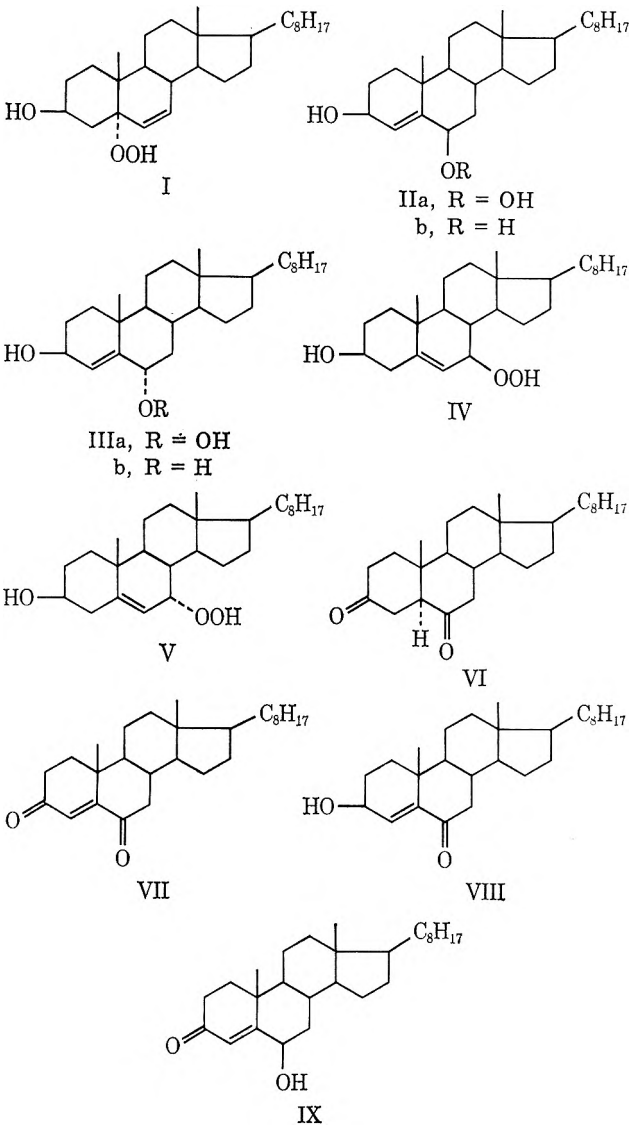
In seeking improved access to cholesterol 20α-hydroperoxide[3] implicated in the biosynthesis of pregnenolone from cholesterol[4] we examined a variety of oxidation reactions of cholesterol, among which was the well-known photosensitized oxidation in solution by excited-state (singlet) molecular oxygen. This reaction is considered to proceed by a cyclic ene mechanism with little ionic character[5] to yield 3β-hydroxy-5α-cholest-6-ene 5-hydroperoxide (I)[6] as major product. We establish herein that the epimeric 3β-hydroxycholest-4-ene 6-hydroperoxides IIa and IIIa are also formed in low yield (1–2%) but that the epimeric cholesterol 7-hydroperoxides IV and V are not formed.

The structures of the new 6-hydroperoxides IIa and IIIa were established by sodium borohydride reduction to the respective diols IIb and IIIb in the usual manner.[3] A B-ring chair conformation for IIa in which the 6β-hydroperoxide bond has quasiaxial character was supported by proton spectra in which the 6α proton appeared as a doublet of doublets coupled moderately and weakly ($J_{6\alpha,7\alpha}$ = 4.5, $J_{6\alpha,7\beta}$ = 2 Hz) to the vicinal 7α and 7β protons. Absence of strong 1,2-diaxial coupling between the 6α proton and either 7 proton together with the strong 1,3-diaxial effects of the



6β-hydroperoxide group on the chemical shift of the C-19 angular methyl group protons (shifted paramagnetically $\Delta\delta$ 0.15 ppm from their position in cholest-4-en-3β-ol[7]) additionally support this conformational assignment for IIa. Quasiaxial character for the 6β-hydroperoxide bond of IIa is thus analogous to the previously demonstrated quasiaxial character of the 6β bond of 6β-hydroperoxycholest-4-en-3-one[8] and of the 3β,6β-diol IIb.[9] The epimeric 6α-hydroperoxide IIa is accordingly the quasiequatorial epimer, a constant B-ring chair conformation being assumed for IIa and IIIa.

The quasiaxial IIa was not epimerized under reac-

(1) Paper XXIV: J. I. Teng and L. L. Smith, *J. Amer. Chem. Soc.*, **95**, 4060 (1973). Financial support of this work by the Robert A. Welch Foundation, Houston, Texas, and the U. S. Public Health Service (research grants AM13520, HE-10160, and NS-08106) is gratefully acknowledged. A preliminary account of this work has been made; *cf.* M. J. Kulig and L. L. Smith, Abstracts of Papers, 165th National Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1973, No. ORGN-078.

(2) Robert A. Welch Foundation Postdoctoral Fellow, 1971–1973.

(3) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **35**, 2627 (1970).

(4) (a) J. E. van Lier and L. L. Smith, *Biochim. Biophys. Acta*, **210**, 153 (1970); **218**, 320 (1970); (b) J. E. van Lier and L. L. Smith, *Biochem. Biophys. Res. Commun.*, **40**, 510 (1970).

(5) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1959); **83**, 1498 (1961).

(6) (a) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); (b) G. O. Schenck, K. Gollnick, and O.-A. Neumüller, *Justus Liebigs Ann. Chem.*, **603**, 46 (1957); (c) G. O. Schenck and O.-A. Neumüller, *ibid.*, **618**, 194 (1958); (d) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *ibid.*, **618**, 202 (1958).

(7) Published proton spectra for cholest-4-en-3β-ol were used for comparison; see (a) I. McClenaghan and P. J. Sykes, *Chem. Commun.*, 800 (1968). (b) C. R. Narayanan and K. N. Iyer, *Tetrahedron Lett.*, 3741 (1965).

(8) J. I. Teng, M. J. Kulig, L. L. Smith, G. Kan, and J. E. van Lier, *J. Org. Chem.*, **38**, 119 (1973).

(9) The quasiaxial conformation for IIb is supported by its more mobile nature in comparison with IIIb on partition chromatographic systems in which axial alcohols generally migrate more rapidly than do equatorial alcohols. The diol IIb is more mobile than IIIb on both paper[10a] and gas–liquid (3% OV-1,[10b] 2% OV-210, and 3% SP-2401 reported herein) partition chromatographic systems.

(10) (a) L. L. Smith, *J. Amer. Chem. Soc.*, **76**, 3232 (1954); (b) J. E. van Lier and L. L. Smith, *Anal. Biochem.*, **24**, 419 (1968).

tion conditions, in solutions, or on storage as a solid, thereby differing in behavior from the analogous quasi-axial cholesterol 7α-hydroperoxide (V) which was epimerized to the quasiequatorial 7β-hydroperoxide IV under a variety of conditions.[8] The 6α-hydroperoxide IIa was also stable to conditions which epimerized the 7α-hydroperoxide V. We conclude that the allylic 6-hydroperoxides IIa and IIIa are not interconverted under the conditions of their formation and, therefore, that both IIa and IIIa are primary products formed under the experimental conditions.

Thermal decomposition of the 6-hydroperoxides IIa and IIIa on gas chromatography afforded similar but distinct patterns of pyrolysis products. Both IIa and IIIa formed their respective 6-alcohols IIb and IIIb on pyrolysis, the IIb component derived from IIa being a prominent peak on the gas chromatographic elution curve, the IIIb component derived from IIIa being in much diminished amount. The diminished yield of IIIb from IIIa reflects the relative stability of the epimeric Δ^4-3β,6-diols IIb and IIIb. The 3β,6β-diol IIb survived gas chromatography in large part whereas the 3β,6α-diol IIIb was less stable. Both Δ^4-3β,6-diols IIb and IIIb decompose on gas chromatography[10b] to two rapidly eluted minor components, one of which (t_R 0.4) may be the common dehydration product cholesta-2,4,6-triene formed pyrolytically from the epimeric cholest-5-ene-3β,7-diols, from 5α-cholest-6-ene-3β,5-diol and from I, IV, and V.[11]

Both 6β-hydroperoxides IIa and IIIa gave as major pyrolysis products 5α-cholestane-3,6-dione (VI) and cholest-4-ene-3,6-dione (VII), formed most probably by initial dehydration of the 6-hydroperoxide group to 3β-hydroxycholest-4-en-6-one (VIII), which does not survive gas chromatography. Pyrolysis of the 6 ketone VIII gave as major products the 3,6 diketones VI and VII in the same proportions as derived from pyrolysis of the 6-hydroperoxides IIa and IIIa, formation of the 5α-3,6 diketone VI and of the Δ^4-3,6 diketone VII, respectively, representing thermal isomerization and dehydrogenation reactions of VIII.

In analogy with the pyrolysis behavior of the other B-ring hydroperoxides I, IV, and V,[11] pyrolysis of the 6-hydroperoxides IIa and IIIa accordingly is rationalized in terms of formal reduction to the respective alcohols IIb and IIIb and dehydration to the common 6 ketone VIII, followed by dehydration of the product alcohols IIb and IIIb (to cholesta-2,4,6-triene) and isomerization and dehydrogenation of the 6 ketone VIII (to VI and VII, respectively). Although we have not examined the pyrolysis behavior of the related epimeric 6-hydroperoxycholest-4-en-3-ones, their close association in isolation procedures with the Δ^4-3,6 diketone VII[12] suggests that dehydration is a prominent mode of their thermal decomposition also.

The 6β-hydroxy Δ^4-3 ketone IX isomeric with VIII also formed both 3,6 diketones VI and VII as major products on pyrolysis. The two Δ^4 hydroxy ketones VIII and IX accordingly behave on pyrolysis exactly the same. Their common isomerization to the 5α-3,6 diketone VI under other thermal conditions is well known,[13] and the thermal dehydrogenations of each to the Δ^4-3,6 diketone VII find analogy in similar thermal dehydrogenations of the epimeric cholest-5-ene-3β-7-diols on pyrolysis.[11]

We have previously established that radiation-induced autoxidations of cholesterol involving radical processes lead to cholesterol 7β-hydroperoxide (IV) as major product, with the 7α-hydroperoxide V as secondary product but with no demonstrable 5α-hydroperoxide.[14] Furthermore, careful examination of these radical autoxidation product mixtures from cholesterol did not afford evidence for the presence of either 6-hydroperoxide IIa or IIIa. Moreover, neither 7-hydroperoxide IV nor V was formed in photosensitized oxygenations of cholesterol.[15] Thus, an absolute distinction between the two reaction processes obtains on the basis of different reaction products, the hydroperoxides I, IIa, and IIIa deriving from photosensitized oxygenations, the 7-hydroperoxides IV and V from radical oxidations.

The mechanism by which the 6-hydroperoxides IIa and IIIa are formed from cholesterol is of interest, the issue being whether they derive *via* attack of excited-state (singlet) molecular oxygen, *via* radical oxidation by ground-state (triplet) molecular oxygen, or *via* both pathways. Even though the 6-hydroperoxides IIa and IIIa are generated in photosensitized oxygenations in which singlet molecular oxygen is implicated, the alternative radical process could be involved, with radiation-induced homolysis of the peroxide bond of the predominant singlet molecular oxygen product 5α-hydroperoxide I leading to radical oxidation of cholesterol and formation of the 6-hydroperoxides IIa and IIIa. However, photolysis of oxygenated solutions of cholesterol in cyclohexane to which the 5α-hydroperoxide I had been added as putative radical initiator did not afford the 6-hydroperoxides IIa and IIIa as products. Rather, only traces of the radical product 7-hydroperoxides IV and V were detected. We reason that radical processes in effect in cyclohexane which formed only traces of the 7-hydroperoxides IV and V and none of the 6-hydroperoxides IIa and IIIa should also lead to formation of the 7-hydroperoxides IV and V in pyridine solution and not to the 6-hydroperoxides IIa and IIIa actually formed. Additionally we would expect of radical processes formation of equal amounts of the 6-hydroperoxides IIa and IIIa or preferential formation of the putatively more stable quasiequatorial 6α-hydroperoxide IIIa but not selective formation of the quasi-axial 6β-hydroperoxide IIa invariably formed in twice the yield of its 6α epimer IIIa. Preferential forma-

(11) J. I. Teng, M. J. Kulig, and L. L. Smith, *J. Chromatogr.*, **75**, 108 (1973).

(12) (a) A. J. Cox, *J. Org. Chem.*, **30**, 2052 (1965); (b) A. Nickon and W. L. Mendelson, *ibid.*, **30**, 2087 (1965); (c) R. Gardi and A. Lusignani, *ibid.*, **32**, 2647 (1967).

(13) (a) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937); (b) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4377 (1953).

(14) L. L. Smith, M. J. Kulig, J. I. Teng, and F. L. Hill, *J. Org. Chem.*, **38**, 1763 (1973).

(15) Our chromatographic methods developed for the purpose readily detect sterol hydroperoxides at levels less than 1% among nonperoxidic sterols; *cf.* (a) L. L. Smith and F. L. Hill, *J. Chromatogr.*, **66**, 101 (1972); (b) ref 11. Traces (much less than 1%) of IV, V, and their thermal decomposition products 3β-hydroxycholest-5-en-7-one, cholesta-3,5-dien-7-one, cholest-5-ene-3β,7α-diol, and cholest-5-ene-3β,7β-diol may be regularly detected in mother liquor fractions after recovery of unreacted cholesterol and of the hydroperoxide products I, IIa, and IIIa. Detection of these sterols in processed mother liquors cannot be taken as evidence for their formation during the oxygenation reactions, since trace amounts of these sterols can be detected in mother liquors from recrystallizations of highly purified cholesterol even though recrystallization was performed under nitrogen and in the dark.[14]

tion of the quasiaxial 6β-hydroperoxide IIa more properly resembles that outcome favored by the cyclic ene mechanism associated with attack of singlet molecular oxygen on steroidal olefins.

In oxygenated pyridine solutions of cholesterol from which both light and photosensitizer were omitted, cholesterol was recovered quantitatively without demonstrable oxidation. Inclusion of light but without added photosensitizer gave the hydroperoxides I, IIa, and IIIa in the same relative proportions but in only about 3% of the conversion yield obtained in the full, photosensitized system. Formation of I, IIa, and IIIa in the same proportions without regard to the presence of added photosensitizer suggests their formation by a common mechanism, and, in that the 5α-hydroperoxide I is an acknowledged singlet molecular oxygen product, we reason that the 6-hydroperoxides IIa and IIIa are also. The diminished level of oxidation of cholesterol to I, IIa, and IIIa in the unsensitized irradiated system may be viewed as arising from an excitation of oxygen by a process of low efficiency in which solvent pyridine act as sensitizer. In support of this view irradiated oxygenated solutions of cholesterol in cyclohexane (a solvent unlikely to act as sensitizer) without added photosensitizer afforded but traces (less than 1%) of the 7-hydroperoxides IV and V and their thermal decomposition products with no detectable 5α-hydroperoxide I or 6-hydroperoxides IIa or IIIa.

Although these arguments do not establish without reservation that the 6-hydroperoxides IIa and IIIa are products of singlet molecular oxygen attack on cholesterol, we regard them as such, and a radical origin for IIa and IIIa is clearly not supported. Formation of I, IIa, and IIIa as distinct products of singlet molecular oxygen attack on cholesterol (with I predominant) in contrast to formation of the 7-hydroperoxides IV and V as radical oxidation products (with IV predominant) suggests use of cholesterol as a suitable substrate for examination of other oxidation systems, both chemical and enzymic,[16] where participation of singlet molecular oxygen or of radical autoxidation processes involving ground-state molecular oxygen is at issue.[17]

Experimental Section[18]

Photosensitized Oxidation of Cholesterol.—A solution of 1.923 g of cholesterol and 32.5 mg of hematoporphyrin in 600 ml of dry pyridine was irradiated with a Hanovia 200-W lamp (using a Pyrex glass filter) for 24 hr with a slow stream of oxygen bubbled through the irradiated solution. The volume of the reaction solution was reduced under vacuum to 50 ml and 50 ml of diethyl ether and 75 mg of decolorizing charcoal (Darco G-60) were added. The mixture was stirred for 30 min, filtered, and evaporated under vacuum at temperatures below 40°. The yellow oil thus obtained was dissolved in 50 ml of benzene, which on standing deposited 1.5520 g (74.5%) of the 5α-hydroperoxide I, mp 148–150° (lit. mp 142° dec,[5b] 148–149° dec,[5c] 145–148° dec,[5d] 149.5–150.5°,[6b] 149–151° dec[3]), identified by thin layer chromatographic and infrared spectral comparisons with an authentic sample. The yellow-colored benzene mother liquor was chromatographed on 1 mm thick Chromatoplates with chloroform–acetone (23:2) using triple ascending irrigations. The more mobile zone was eluted and identified as the 5α-hydroperoxide I. The more polar zone was eluted from the chromatoplate with acetone and rechromatographed on a 1 mm thick chromatoplate with ethyl acetate–benzene (1:1) using triple ascending irrigation thereby resolving the original polar hydroperoxide zone into two distinct hydroperoxide zones, at R_f 0.71 and 0.65.

3β-Hydroxycholest-4-ene 6β-Hydroperoxide (IIa).—Elution with acetone of the R_f 0.65 zone from the preparative thin layer chromatogram of the IIa and IIIa mixture gave 45.1 mg (2.2%) of chromatographically pure IIa. Recrystallization from benzene gave the analytical sample of IIa: mp 162–163°; $\tilde{\nu}_{max}^{KBr}$ 3350, 3125, 1600 cm^{-1}; nmr δ 0.68 (3 H, s, C-18 methyl), 0.88 (6 H, d, J = 6 Hz, C-26, C-27 methyls), 0.90 (3 H, d, J = 5 Hz, C-21 methyl), 1.20 (3 H, s, C-19 methyl), 4.21 (1 H, m, $W_{1/2}$ = 18 Hz, 3α proton), 4.34 (1 H, q, $J_{6\alpha,7\alpha}$ = 4.5, $J_{6\alpha,7\beta}$ = 2 Hz, 6α proton), 5.66 ppm (1 H, s, C-4 vinyl proton); R_f 0.65 using triple ascending irrigation with ethyl acetate–benzene (1:1); brown color with 50% aqueous sulfuric acid spray; positive Wurster red color response to *N,N*-dimethyl-*p*-phenylenediamine; pyrolysis pattern on 2% OV-210 t_R 0.40, 0.78, 1.55, 2.07 (IIb), 7.17 (VI), and 7.81 (VII); on 3% SP-2401 t_R 0.43, 0.80, 1.53, 1.99 (IIb), 6.65 (VI), and 7.13 (VIII).

Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.39; H, 10.98.

Cholest-4-ene-3β,6β-diol (IIb).—A solution of 13.1 mg of IIa in methanol was reduced with an excess of sodium borohydride. After 2 hr the solution was neutralized and the product was recovered in the usual manner, yielding 9.0 mg of IIb: mp 253–256° (lit.[20] mp 254–258°); $\tilde{\nu}_{max}^{KBr}$ 3250, 1540 cm^{-1}; R_f 0.36 in ethyl acetate–benzene (1:1); blue-gray color with 50% aqueous sulfuric acid; pyrolysis pattern on 2% OV-210 t_R 0.40, 0.78, 2.07 (IIb); on 3% SP-2401 t_R 0.43, 0.80, 1.99 (IIb); identical in these properties with an authentic sample of IIb.

Material collected from preparative gas chromatography of IIa and of IIb was chromatographed on thin layer chromatoplates with ethyl acetate–benzene (1:1), and the zone with mobility of that of reference sterol IIb was eluted with acetone, recrystallized from and identified as IIb by comparison of physical properties with those of an authentic sample of IIb.

3β-Hydroxycholest-4-ene-6α-Hydroperoxide (IIIa).—Elution of the R_f 0.71 zone from the chromatogram from which IIa had initially been recovered gave 27.3 mg (1.3%) of chromatographically pure IIIa. Recrystallization from benzene gave the analytical sample of IIIa: mp 152–156°; $\tilde{\nu}_{max}^{KBr}$ 3325, 1600 cm^{-1}; R_f 0.71 in triple ascending irrigation with ethyl acetate–benzene (1:1); brown color with 50% aqueous sulfuric acid; positive Wurster red color response to *N,N*-dimethyl-*p*-phenylenediamine; pyrolysis pattern on 2% OV-210 t_R 0.40, 0.78, 1.56, 2.10 (IIIb), 7.18 (VI), 7.80 (VII); on 3% SP-2401 t_R 0.42, 0.79, 1.53, 2.03 (IIIb), 6.65 (VI), 7.13 (VII).

Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.26; H, 10.97.

Cholest-4-ene-3β,6α-diol (IIIb).—A solution of 8.2 mg of IIIa in methanol was reduced with an excess of sodium borohydride, yielding after preparative thin layer chromatography 5.0 mg of IIIb: mp 174–177° (lit.[20] mp 175–179°); $\tilde{\nu}_{max}^{KBr}$ 3350, 1600 cm^{-1}; R_f 0.38 in triple ascending irrigation with ethyl acetate–benzene (1:1); yellow-tan color with 50% aqueous sulfuric acid; pyrolysis pattern on 2% OV-210 t_R 0.41, 0.78, 2.09 (IIIb); on 3% SP-2401 t_R 0.42, 0.79, 2.03 (IIb); identical in these properties with an authentic sample of IIIb.

(16) We have utilized this approach in examining the actions of soybean lipoxygenase and horseradish peroxidase on cholesterol.[1]

(17) The prior case of cholest-5-en-3-one involved competing singlet molecular oxygen attack to give 5-hydroxy-5α-cholest-6-en-3-one (as its dehydration product cholesta-4,6-dien-3-one) and radical oxidation to the epimeric 6-hydroperoxycholest-4-en-3-ones.[12b]

(18) Experimental procedures used in this study have been previously described in detail,[3] with the exceptions that proton nmr spectra were obtained using a Varian Instruments Model HR-300 spectometer operated at 60 and at 300 MHz and gas chromatography was conducted using 2% OV-210 and 3% SP-2401 columns.[11] Relative retention times (t_R) were measured *vs.* cholesterol as unit time. Preparative gas chromatography was conducted using methods previously described in detail.[19] Thin layer chromatography was conducted on silica gel HF_{254} chromatoplates irrigated with ethyl acetate–benzene (1:1). Sterol hydroperoxides were visualized with *N,N*-dimethyl-*p*-phenylenediamine;[15a] sterols were visualized afterwards with 50% sulfuric acid spray.

(19) (a) J. E. van Lier and L. L. Smith, *Biochemistry*, **6**, 3279 (1967); (b) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **36**, 7 (1968).

(20) Physical data from J. Jacques, H. Kagan, and G. Ourisson, "Selected Constants, Optical Rotatory Power, Ia. Steroids," Volume 14 of "Tables of Constants and Numerical Data," S. Allard, Ed., Pergamon Press, Oxford, 1965, pp 438, 457, 475.

Control Oxidations.—An experiment identical with that described for photosensitized oxidation of cholesterol was run except that no photosensitizer was added. From 2.005 g of cholesterol 1.635 g of unaltered cholesterol was recovered, together with 48.4 mg of I, 1.6 mg of IIa, and 1.0 mg of IIIa, all isolated by the same means previously described. Chromatographic examination of mother liquors following recovery of I, IIa, and IIIa indicated that traces of IV, V, 3β-hydroxycholest-5-en-7-one, cholesta-3,5-dien-7-one, cholest-5-ene-3β,7α-diol, and cholest-5-ene-3β,7β-diol were present, all at much less than 1% levels. A control oxidation including photosensitizer but carried out completely in the dark gave a quantitative recovery of unaltered cholesterol.

Control oxidations carried out in cyclohexane instead of in pyridine were run similarly. A cyclohexane solution of 1.9835 g of cholesterol was irradiated for 22 hr and then processed as previously described. Crystalline cholesterol free of other demonstrable sterols was obtained in four crops (total 1.8035 g) and mother liquors after preparative thin layer chromatography gave 23.5 mg of amorphous sterols which contained IV and V in approximately 1:1 proportions but which did not contain any demonstrable IIa or IIIa. A similar control irradiation (23 hr) of 1.9753 g of cholesterol and 32.4 mg of added I was worked up in the same manner to give 1.8042 g of pure crystalline cholesterol free of other demonstrable sterols. Preparative thin layer chromatography of the mother liquors afforded 47.3 mg of sterol hydroperoxides as amorphous solids containing I, IV, and V in approximately equal proportions but which did not contain any demonstrable amounts of IIa or IIIa.

Pyrolysis Experiments.—Saturated solutions containing 2 mg of IIa, IIIa, VIII, or IX in acetone were injected onto a preparative 2% OV-210 column and material eluted from the column up to 30 min (containing minor components with t_R 0.40, 0.78, and 1.55 and IIb and IIIb if present) was collected in a capillary; material eluted between 30 and 120 min (containing VI and VII) was collected in a second capillary. Sterols were rinsed with acetone from the collecting capillaries and chromatographed on thin layer chromatoplates irrigated several times with ethyl acetate–benzene (1:1) to resolve major components. In no case did VIII or IX survive gas chromatography, both being completely converted to VI and VII.

5α-Cholestane-3,6-dione (VI).—Material eluted between 30 and 120 min from injections of IIa, IIIa, VIII, or IX was resolved by thin layer chromatography into two ultraviolet light absorbing zones at R_f 0.70 and 0.76. Material from the less mobile zone (R_f 0.70) was eluted with acetone and recrystallized from acetone, yielding pure VI: mp 169° (lit.[20] mp 168–172°); $\bar{\nu}_{max}^{KBr}$ 1715 cm^{-1}; R_f 0.70 in ethyl acetate–benzene (1:1); yellow color with 50% aqueous sulfuric acid; t_R 7.14 on 2% OV-210, 6.65 on 3% SP-2401; identical in these properties with authentic samples of VI prepared from VIII[13a] and by alkaline isomerization of IX.[13b]

Cholest-4-ene-3,6-dione (VII).—The more mobile zone (R_f 0.76) containing ultraviolet light absorbing material obtained on thin layer chromatograms from which VI had been isolated (from pyrolysis of IIa, IIIa, VIII, or IX) was eluted with acetone and recrystallized from methanol, yielding pure VII: mp 120–123° (lit.[20] mp 122–125°); $\bar{\nu}_{max}^{KBr}$ 1685, 1600 cm^{-1}; $\lambda_{max}^{CHCl_3}$ 253 nm (lit.[21] $\lambda_{max}^{CHCl_3}$ 252 nm); R_f 0.76 in ethyl acetate–benzene (1:1); yellow color with 50% aqueous sulfuric acid; t_R 7.80 on 2% OV-210, 7.13 on 3% SP-2401; identical in these properties with an authentic sample of VII.

Isomerization of 6β-Hydroxycholest-4-en-3-one (IX).—A solution of 6.3 mg of IX in 10 ml of 10% methanolic KOH was heated at 75° for 99 min. The cooled solution was neutralized and extracted into diethyl ether, the ether extract was evaporated under vacuum, and the residue was chromatographed on a chromatoplate irrigated twice with ethyl acetate–benzene (1:1). The more mobile zone (R_f 0.76) was eluted with acetone and recrystallized from methanol, yielding pure VII, mp 121–124°. The more polar zone (R_f 0.70) eluted with and recrystallized from acetone yielded pure VI, mp 166–170°, identical in physical properties with a sample of VI prepared from VIII.[13a]

Registry No.—IIa, 41209-87-4; IIb, 570-88-7; IIIa, 41209-89-6; IIIb, 15013-60-2; VI, 2243-09-6; VII, 984-84-9; IX, 570-89-8; cholesterol, 57-88-5.

(21) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

A Ring Enlargement Reaction of Phenylmethoxycyclopropenone. A Regiospecific Mass Spectrometric CO Extrusion in Phenylmethoxycyclobutenedione

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Isonitriles have been reported to react with small ring unsaturated ketones to give ring enlarged derivatives. Thus, 2,6-dimethylphenylisonitrile reacts with diphenylcyclopropenone (**1**) to give 4,5-bis(2,6-dimethylphenylimino)-2,3-diphenylcyclopenten-1-one (**2**), which can be hydrolyzed to diphenylcyclopentenetrione.[1] In the presence of triphenylphosphine, **1** is converted into diphenylcyclobutenedione by way of 4-(2,6-dimethylphenylimino)-2,3-diphenylcyclobuten-1-one (**3**).[2] We would like to report the results of similar experiments with phenylmethoxycyclopropenone (**4**)[3] including the structure of the intermediate 4-(2,6-dimethylphenylimino)-3-methoxy-2-phenylcyclobuten-1-one (**5**) and two interesting processes which were discovered during the course of elucidating the structure of **5**: a regiospecific loss of CO from phenylmethoxycyclobutenedione (**6**) upon electron impact and a regioselective incorporation of ^{18}O in phenylhydroxycyclobutenedione (**7**) involving the enolate ion (**7b**).

Treatment of **4** with an excess of 2,6-dimethylphenylisonitrile in refluxing benzene overnight under a nitrogen atmosphere afforded a dark solution which, after removal of the solvent and isonitrile under vacuum, slowly crystallized. Recrystallization from hexane afforded 4-(2,6-dimethylphenylimino)-3-methoxy-2-phenylcyclobuten-1-one (**5**) as yellow crystals. The gross structural features of **5** were established by hydrolysis to phenylmethoxycyclobutenedione[4] (**6**) and 2,6-dimethylaniline, isolated as the hydrochloride, in 80% yield. Compound **6** was identified by comparison to a sample prepared from squaric acid.[5] The nuclear magnetic resonance spectrum of **5** was in agreement with the proposed structure, exhibiting resonances congruous with aromatic protons (8 H), methoxyl protons (3 H), and aromatic methyls (6 H). The mass spectrum of **5**, although consistent with the proposed structure, did not give any additional structural information.

In contrast to **1**, phenylmethoxycyclopropenone (**4**) does not yield cyclopentenetrione derivatives when treated with 2,5-dimethylphenylisonitrile.[1] Carrying out the reaction at room temperature for 20 hr in the presence of trace amounts of triphenylphosphine, conditions which convert **1** into **3**,[2] afforded a mixture of

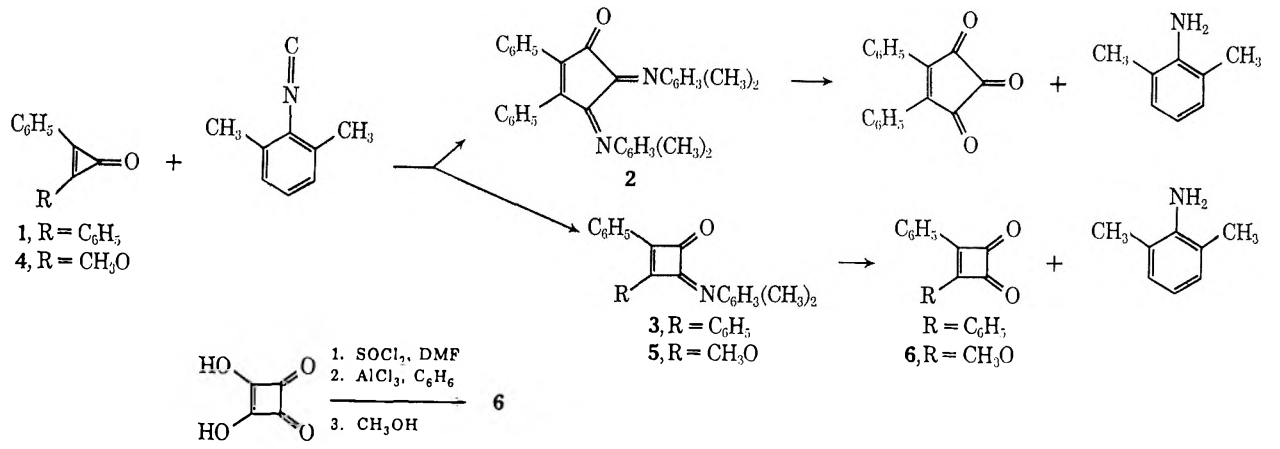
(1) T. Takizawa, N. Obata, Y. Suzuki, and T. Yanagida, *Tetrahedron Lett.*, 3403 (1969).

(2) N. Obata and T. Takizawa, *Tetrahedron Lett.*, 2231 (1970).

(3) (a) D. G. Farnum, J. S. Chickos, and P. Thurston, *J. Amer. Chem. Soc.*, **88**, 3075 (1966); (b) R. West, J. S. Chickos, and S. Osawa, *ibid.*, **90**, 3885 (1968); J. S. Chickos, L. Patton, and R. West, manuscript in preparation.

(4) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 1793 (1960).

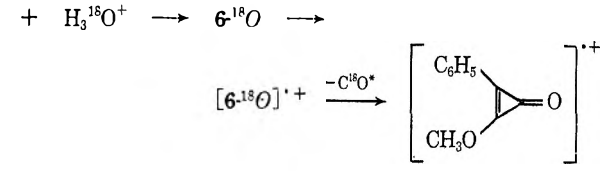
(5) R. C. De Selms, C. J. Fox, and R. C. Riordan, *Tetrahedron Lett.*, 781 (1970).



starting materials and **5**. Heating the reaction mixture increased the conversion into **5**, which could be isolated by column chromatography. The fate of the triphenylphosphine was not determined.

The structure of **5** was completed by mass spectroscopic ^{18}O-labeling experiments performed on **6**. The 70-eV mass spectrum and major fragmentation pattern of **6** are shown in Figure 1 and Scheme I, respectively.[6,7] The fragmentation pathway is based on the labeling experiments and the observation of appropriate metastable ions (*).

Acid-catalyzed hydrolysis of **5** in ^{18}O-enriched water led to the incorporation of only one ^{18}O-labeled oxygen. The single label was identified by the presence of a P + 2 parent molecular ion (29% of the molecular ion intensity) in the mass spectrum of **6**. It was further observed that 99 ± 5% of this label was absent in the P − CO^+ molecular ion, and that metastables corresponding to the loss of $C^{16}O$ and $C^{18}O$ from the parent molecular ion were observable.



To establish which of the three oxygens was specifically being lost, the following experiments were performed. First, to determine whether ^{18}O could be incorporated into **6** by exchange, phenylhydroxycyclobutenedione (**7**, pK_a[4] 0.37), dioxane, and enriched $H_2{}^{18}O$ (38 mol %) were heated for 15 min at 70°. Following methylation with diazomethane, the isotopic distribution associated with the parent P − CO^+ and P − $2CO^+$ ions was found to be consistent with a statistical ^{18}O distribution (29% enrichment; see Experimental Section). As a control experiment, **6**, statistically labeled with ^{18}O, was dissolved in H_2O–dioxane and allowed to stand 30 min at room temperature. Mass spectral analysis revealed that the ^{18}O content of the P^+, P − CO^+, and P − $2CO^+$ ions was approximately the same. Furthermore, unlabeled **6**, dissolved in dioxane–$H_2{}^{18}O$–HCl, for 30 min did not

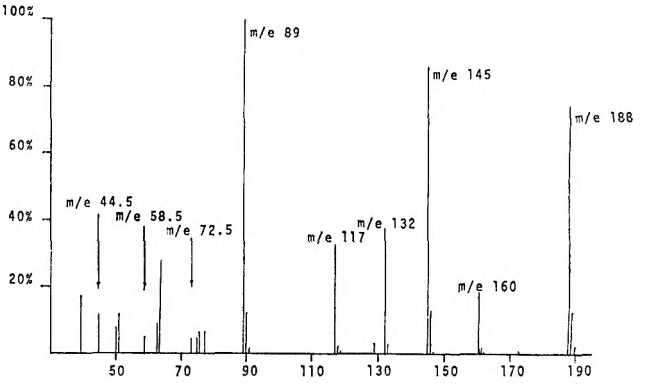
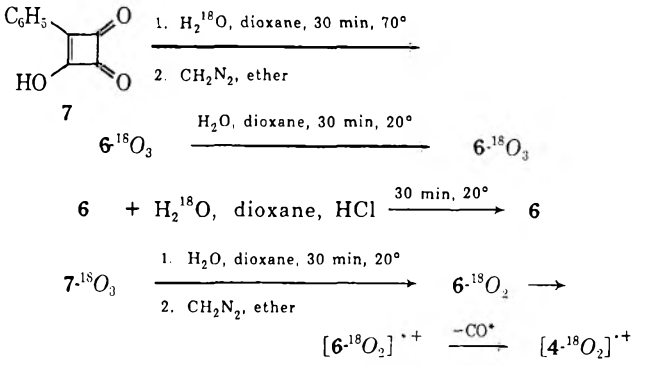


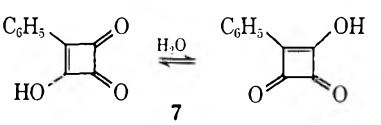
Figure 1.—The mass spectrum of phenylmethoxycyclobutenone (**6**).

incorporate any significant amount of ^{18}O, demonstrating the identity of the position of attachment of the label obtained from hydrolysis of **5** in $H_2{}^{18}O$ and the position of attachment of the imino group in **5**.

Treatment of **7** with $H_2{}^{18}O$–dioxane for 30 min at room temperature followed by methylation, led to incorporation of only one ^{18}O in the parent molecular



ion, 90 ± 5% of which was lost in the P − CO^+ ion. Alternatively, statistically labeled **7**, dissolved in H_2O–dioxane, for 30 min at room temperature followed by methylation afforded **5** in which the parent and P − CO^+ ions contained approximately the same amount of ^{18}O.

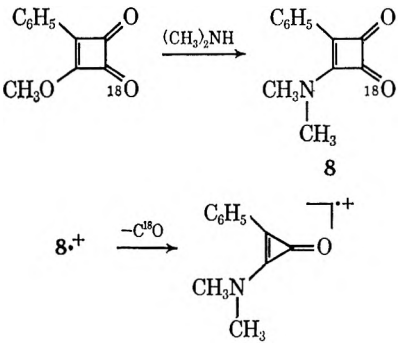


The equivalency of positions 1 and 3 on the time scale employed due to tautomerism in **7** would require loss of

(6) The mass spectrum of **3** was practically superimposable on the spectrum of **5** below *m/e* 160, suggesting common ions and fragmentation pathways.

(7) A similar sequential loss of carbon monoxide has also been observed in the oxocarbons, rhodizonic, croconic, and squaric acids: S. Skujins, J. Delderfield, and G. A. Webb, *Tetrahedron*, **24**, 4805 (1968).

only 50% of the ^{18}O label in the P − CO^+ ion if the oxygen at these positions was lost. On the basis of these experiments therefore, it can be concluded that the 2,6-dimethylphenylimino grouping in **5** is attached at position 4 of the ring as shown.

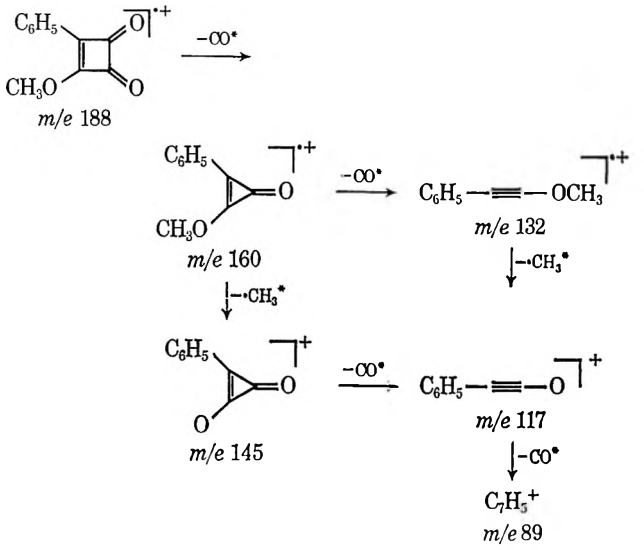


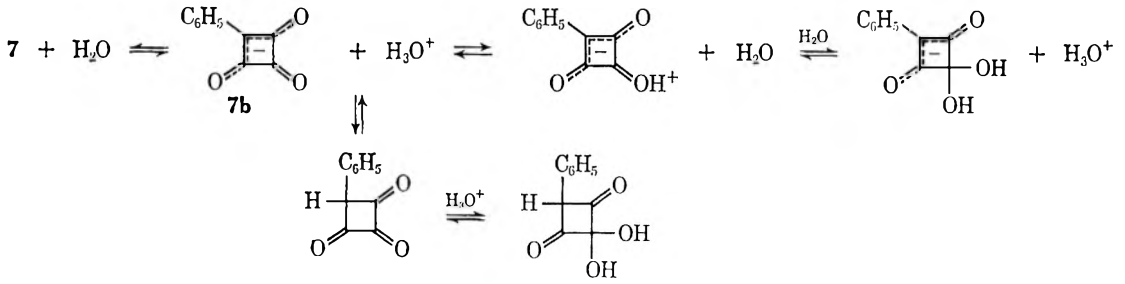
To test the generality of the regiospecific CO extrusion observed in the mass spectrum of **6**, phenyl-*N*,*N*-dimethylaminocyclobutenedione (**8**), labeled with ^{18}O in the 4 position, was prepared as shown. A similar specificity in extruding CO was also observed here. Methylhydroxycyclobutenedione[8] showed a similar selectivity in incorporating ^{18}O by exchange and specificity in extrusion of CO.

The failure to observe ^{18}O exchange in **6** with rates comparable to those in which one label is introduced in **7** suggests that acid-catalyzed ^{18}O exchange of the carbonyl group is occurring *via* the enolate anion as shown. Consistent with this interpretation was the failure to observe any significant change in the rate of ^{18}O incorporation into **7** with added mineral acid. Two possible pathways, protonation at carbon to yield phenylcyclobutanetrione or at oxygen to give a dipolar ion, appear likely. A distinction between these two tautomeric possibilities is not presently possible.

Scheme I

The Major Mass Spectrometric Fragmentation Pathways of Phenylmethoxycyclobutenedione





Similar results involving only the enolate ion and not the neutral enol have recently been reported in a study of the keto–enol tautomerism of 3-hydroxy-2,4-dimethylcyclobutenone.[9] It appears that those factors which promote the strong acid character of these compounds also destabilize protonation of the neutral enols to an extent that prototropic tautomerism by way of the enolate becomes the energetically preferred pathway.

Experimental Section

Melting points were taken on a Hoover Thomas melting point apparatus and are uncorrected. Microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer Infracord, Model 137; nmr spectra were recorded on a Varian T-60 spectrometer and Perkin-Elmer R-20 60MHz spectrometer equipped with a variable temperature probe. Mass spectra were recorded on an AEI MS 12 spectrometer. ^{18}O analyses were obtained by measurement of line intensities at 70 eV and are normalized to 100%. The error associated with measurement of each molecular ion approximates ±1% of the recorded value. The $H_2{}^{18}O$ (38% ^{18}O enrichment) was obtained from Diaprep, Inc., Atlanta, Ga.

Preparation of 4-(2,6-Dimethylphenylimino)-3-methoxy-2-phenylcyclobuten-1-one (5).—Phenylmethoxycyclopropenone, prepared as reported[3] (1.4 g, 8.75 mmol), mp 44–47° (lit.[3a] 54–57), was refluxed in benzene under nitrogen with an excess of 2,6-dimethylphenylisonitrile[10] (3.44 g, 26.3 mmol) for several hours. The solution slowly darkened. Evaporation of the solvent followed by fractional sublimation afforded unreacted isonitrile (2.0 g). The residue, which slowly crystallized, was purified by recrystallization from hexane to afford yellow crystals of **5** (2.05 g, 80%): mp 97–99°; ν_{max} (Nujol) 1780, 1695, and 1590 cm^{-1}; nmr (30°, $CDCl_3$, TMS) τ 7.83 (s, 6 H), 5.28 (broad s, $w_{1/2}$ = 4 Hz, 2.9 H), 3.0 (broad s, 3 H), 2.64 (m, 3 H), 2.15 (m, 2 H); a sharp absorption ($w_{1/2}$ = 1 Hz) for the resonance at 5.28 was observed at −10 and 68°.

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84, O, 10.99; mol wt, 291. Found: C, 77.98; H, 5.68; O, 10.65; *m/e*, 291.

Hydrolysis of 4-(2,6-Dimethylphenylimino)-3-methoxy-2-phenylcyclobuten-1-one (5).—A solution containing **5** (1.87 g, 6.42 mmol), acetone (30 ml), and hydrochloric acid (2.5 *N*, 25 ml) was warmed to 40° briefly, and then a stream of nitrogen was used to remove the solvent. The residue (2.37 g) was extracted with methylene chloride leaving a white crystalline solid behind (1.01 g, 82%) identified as 2,6-dimethylaniline hydrochloride by comparison with an authentic sample. The methylene chloride was evaporated, affording crude **6** (1.11 g, 92%): mp 140–150°; recrystallized (CH_3OH, 640 mg), mp 150–151° (lit.[4] 151–152°). Compound **6** was identical with a sample of material isolated from methanolysis of phenylchlorocyclobutenedione, prepared by the

(8) J. S. Chickos, *J. Amer. Chem. Soc.*, **92**, 5749 (1970).

(9) J. S. Chickos and R. E. K. Winter, *J. Amer. Chem. Soc.*, **95**, 506 (1973).

(10) I. Ugi, U. Fetzer, U. Eholzer, H. Krupfer, and K. Offermann, *Angew. Chem.*, **77**, 492 (1965); *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965); R. Meyer, *Chem. Ber.*, **93**, 239 (1960).

reaction of dichlorocyclobutenedione with benzene and aluminum chloride.[5] Hydrolysis of **6** (640 mg, 3.4 mmol) afforded **7** (400 mg, 68%), mp 206–208° (lit.[4] 208–211°).

Reaction of Phenylmethoxycyclopropenone (4) with 2,6-Dimethylphenylisonitrile in the Presence of Triphenylphosphine.—Phenylmethoxycyclopropenone (200 mg, 1.25 mmol), 2,6-dimethylphenylisonitrile (164 mg, 1.25 mmol), and triphenylphosphine (16 mg) were dissolved in benzene and allowed to stand overnight under an atmosphere of nitrogen. Analysis of the reaction mixture by nmr indicated the presence of approximately 15% **5** and the remainder unreacted **4**. Heating the mixture for several hours afforded mainly **5** (according to nmr analysis). Chromatography of the residue on silica gel (CH_2Cl_2) after removal of the solvent afforded **5** (154 mg, 42%). The fate of the triphenylphosphine was not determined.

Hydrolysis of 4-(2,6-Dimethylphenylimino)-3-methoxy-2-phenylcyclobuten-1-one (5) with $H_2{}^{18}O$.—A solution prepared by dissolving **5** (52 mg, 0.18 mmol), $H_2{}^{18}O$ (47 mg, 2.53 mmol of 38% ^{18}O content), dioxane (787 mg), and concentrated hydrochloric acid (23 mg, 0.205 mmol) was allowed to stand at room temperature. After 30 min the solution was evaporated *in vacuo* and the residue partitioned between methylene chloride–water. Next the organic phase was dried over $MgSO_4$ and evaporated. Sublimation of the residue afforded ^{18}O-labeled **6** (mp 140–150°, 31 mg): recrystallized from methanol, mp 150–151° (18 mg). It was observed that no label was lost during the recrystallization process.

^{18}O Analysis. Found: P, *m/e* 188, 70.2%; P + 2, 29.1%; P + 4, 0.6%; P − CO, *m/e* 160, 98.8%; P + 2, 1.2%. Calcd for P (based on 29% ^{18}O enrichment, 1 ^{18}O incorporated): *m/e* 188, 71%; P + 2, 29%; P − CO (based on natural isotopic abundance), *m/e* 160, 99.1%; P + 2, 0.9%.

Stereoselective ^{18}O Incorporation into Phenylhydroxycyclobutenedione (7).—Compound **7** (31 mg, 0.178 mmol) was dissolved in dioxane (54 mg) containing $H_2{}^{18}O$ (40 mg, 2.1 mmol) and allowed to stand 30 min at room temperature. The solvent was removed *in vacuo* and the residue dissolved in ether, treated with excess anhydrous diazomethane,[11] and then evacuated. Recrystallization of the residue from heptane followed by sublimation afforded **6** (28 mg, 84%), mp 149–151°.

^{18}O Analysis. Found: P, *m/e* 188, 73%; P + 2, 25.9%; P + 4, 1.1%; P − CO, *m/e* 160, 95%; P + 2, 5%. Calcd for stereospecific incorporation of ^{18}O and stereospecific loss of $C^{18}O$: P − CO, *m/e* 160, 99%; P + 2, 1%. Calcd for a 10% statistical incorporation of ^{18}O: P, *m/e* 188, 72.9%; P + 2, 24.3%; P + 4, 2.7%; P + 6, 0.1%; P − CO, *m/e* 160, 81%; P + 2, 18%; P + 4, 1%.

Statistical ^{18}O Incorporation into Phenylhydroxycyclobutenedione (7).—Compound **7** (30 mg, 0.16 mmol), dioxane (30 mg), and $H_2{}^{18}O$ (58 mg, 3.1 mmol) were heated to 70° for 15 min. Evaporation of the solution followed by reaction with diazomethane, recrystallization (heptane), and sublimation gave **6** (25 mg), mp 149–152°. Theoretical equilibrium ^{18}O incorporation calcd, 32.7%; found, 29%.

^{18}O Analysis. Found: P, *m/e* 188, 36%; P + 2, 43.2%; P + 4, 18%; P + 6, 2.7%; P − CO, *m/e* 160, 53.8%; P + 2, 37.3%; P + 4, 8.9%; P − 2CO, *m/e* 132, 73.2%; P + 2, 26.8%. Calcd for 29% ^{18}O statistically distributed: P, *m/e* 188, 35.8%; P + 2, 43.6%; P + 4, 17.9%; P + 6, 2.4%; P − CO, *m/e* 160, 50.4%; P + 2, 41.2%; P + 4, 8.4%; P − 2CO, *m/e* 132, 71%; P + 2, 29%.

Stereoselective ^{18}O Hydrolysis from Statistically Labeled Phenylhydroxycyclobutenedione-$^{18}O_3$ (7).—Compound **7** (12 mg, 0.069 mmol), dioxane (48 mg), and $H_2{}^{18}O$ (23 mg, 1.22 mmol) were heated to 70° for 15 min. The solvent was evaporated *in vacuo*. The residue was dissolved in dioxane (55 mg) and H_2O (53 mg, 2.95 mmol) and kept at room temperature for 30 min. Evaporation of the solvent, reaction with diazomethane, recrystallization, and sublimation afforded **6** (6 mg), mp 148–150°. The ^{18}O distribution could best be accounted for by ^{18}O substitution at positions 1 and 3 and ^{16}O at position 4, assuming a regiospecific loss of CO from position 4.

^{18}O Analysis. Found: P, *m/e* 188, 63.2%; P + 2, 31.6%; P + 4, 5.3%; P − CO, *m/e* 160, 66.3%; P + 2, 29.8%; P + 4, 3.9%; P − 2CO, *m/e* 132, 82%; P + 2, 18%. Calcd assuming a 14% statistical distribution of ^{18}O: P, *m/e* 188, 63.5%; P + 2, 31.1%; P + 4, 5%; P + 6, 0.3%; P − CO, *m/e* 160, 74%; P + 2, 24%; P + 4, 2%; P − 2CO, *m/e* 132, 86%; P + 2, 14%. Calcd assuming a 19% ^{18}O content at positions 1 and 3 and 100% ^{16}O content at position 4 and a regiospecific loss of CO from position 4: P, *m/e* 188, 65.6%; P + 2, 30.8%; P + 4, 3.6%; P − CO, *m/e* 160, 65.6%; P + 2, 30.8%; P + 4, 3.6%; P − 2CO, *m/e* 132, 81%; P + 2, 19%.

Attempted ^{16}O Exchange in Statistically Labeled Phenylmethoxycyclobutenedione-$^{18}O_3$ (6).—Statistically labeled **6**, from **7** (14 mg, 0.08 mmol) and $H_2{}^{18}O$ (21 mg, 1.12 mmol) in dioxane (29 mg), was prepared as previously described. Next, 2.5 *N* HCl (32 mg) and dioxane (438 mg) were added; the solution was allowed to stand for 30 min and then evacuated. The residue was recrystallized (heptane) and sublimed giving **6** (10 mg): mp 140–150°; recrystallized (CH_3OH), mp 148–150°. The ^{18}O content remained the same (within experimental error) after recrystallization from methanol. Less than 10% of the ^{18}O in the carbonyl group at position 4 was lost as indicated by mass spectroscopy.

Anal. Found: P, *m/e* 188, 37.5%; P + 2, 43%; P + 4, 17%; P + 6, 2.5%; P − CO, *m/e* 160, 50.5%; P + 2, 40%; P + 4, 9.3%; P − 2CO, *m/e* 132, 70.7%; P + 2, 29.4%.

Attempted ^{18}O Exchange in Unlabeled Phenylmethoxycyclobutenedione (6).—A solution containing **6** (7 mg, 0.021 mmol), dilute HCl (2.5 *N*, 10 mg), $H_2{}^{18}O$ (38% ^{18}O, 10 mg), and dioxane (138 mg) was allowed to stand 30 min at room temperature. Evaporation of the solvent followed by sublimation of residue afforded **6** (4 mg), mp 140–148°; recrystallized (methanol), mp 148–150°.

Anal. Found: P, *m/e* 188, 87%; P + 1, 10.8%; P + 2, 2.2%; P − CO, *m/e* 160, 89.2%; P + 1, 10%; P + 2, 2.5%. Calcd for natural isotopic abundance: P, *m/e* 188, 88.2%; P + 1, 10.8%; P + 2, 1.12%; P − CO, *m/e* 160, 89.2; P + 1, 10%; P + 2, 0.8%. Calcd for incorporation of 1 ^{18}O (theoretical): P, *m/e* 188, 73.2%; P + 1, 8.1%; P + 2, 16.7%; P + 3, 1.8%.

Preparation of Phenyl-*N*,*N*-dimethylaminocyclobutenedione (8).—To a solution of **6** (100 mg, 0.532 mmol) in ether was added an excess of dimethylamine gas. A yellow crystalline solid (**8**) was isolated by filtration (100 mg, 93%): mp 132–134° (heptane); ν max (Nujol) 1785, 1730, and 1610 cm^{-1}; nmr ($CDCl_3$, TMS, 30°) τ 6.83, 6.53 (broad s, 6 H, coalescence temp 39°), 2.6 (m, 5.1 H).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96; mol wt, 201.21. Found: C, 71.84; H, 5.61; N, 6.82; *m/e*, 201.

Preparation of ^{18}O-Labeled Phenyl-*N*,*N*-dimethylaminocyclobutenedione (8).—Compound **6** (10 mg, 0.053 mmol) specifically labeled at the 4 position with ^{18}O (26% ^{18}O enrichment) was treated with anhydrous dimethylamine in anhydrous ether affording **8** (10 mg, 93%), mp 130–132°.

^{18}O Analysis. Found: P, *m/e* 201, 75%; P + 2, 25%; P − CO, *m/e* 173, 86.2%; P + 1, 12%; P + 2, 1.8%. Calcd for P − CO (natural isotopic abundance): *m/e* 173, 88%; P + 1, 11%; P + 2, 0.8%.

Incorporation of ^{18}O in Methylhydroxycyclobutenedione (9).—Compound **9**[8] (25 mg, 0.223 mmol) was dissolved in $H_2{}^{18}O$ (36 mg, 1.8 mmol) and heated to 70°. Evaporation of the solvent followed by sublimation afforded **9** (24 mg), mp 160–163° (lit.[8] 162–164).

^{18}O Analysis. Found: P, *m/e* 112, 34.1%; P + 2, 43.2%; P + 4, 18.9%; P + 6, 2.7%; P − CO, *m/e* 84, 50.7%; P + 2, 42%; P + 4, 7.2%. Calcd (statistical distribution, 30% ^{18}O enrichment): P, *m/e* 112, 34.3%; P + 2, 44.2%; P + 4, 18.9%; P + 6, 2.7%; P − CO, *m/e* 84, 49%; P + 2, 42%; P + 4, 9%.

Compound **9** (11 mg, 0.1 mmol, 30% ^{18}O enrichment, statistical distribution), dissolved in $H_2{}^{16}O$ (27 mg, 1.4 mmol) for 30 min at room temperature followed by evaporation of the solvent *in vacuo* and sublimation afforded **9** (8 mg), mp 160–163°.

^{18}O Analysis. Found: P, *m/e* 112, 51.2%; P + 2, 40%; P + 4, 9%; P − CO, *m/e* 84, 51.5%; P + 2, 40%; P + 4, 8.6%. Calcd for 28.5% ^{18}O enrichment at positions 1 and 3 and stereospecific loss of CO at position 4: P, P − CO; P, 51.2%; P + 2, 40.6%; P + 4, 8.1%.

Acknowledgment.—I would like to thank the Research Corporation for support, and Mr. William Garrison for running the mass spectra.

(11) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

Registry No.—4, 6460-83-9; 5, 41328-60-3; 6, 711-78-4; 6-^{18}O, 41328-63-6; 6-$^{18}O_2$, 41391-12-2; 6-$^{18}O_3$, 41328-64-7; 7, 708-10-1; 7-$^{18}O_3$, 41328-66-9; 8, 22118-96-4; 8-^{18}O, 41328-68-1; 9, 29769-75-3; 9-$^{18}O_2$, 41328-70-5; 2,6-dimethylphenylisonitrile, 2769-71-3.

Abnormal Michael Reaction. The Reaction between 2-Cyclohexenone and Diethyl Methylmalonate

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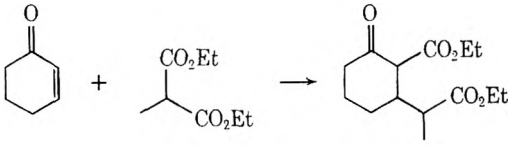
Although the abnormal Michael reaction has been investigated for a number of years, the synthetic aspects of this reaction have not been studied.[1-7] Recently, we have been interested in developing new syntheses of the sesquiterpene series, and thought that the reaction between 2-cyclohexenone and diethyl methylmalonate under these conditions would afford, if successful, the β-keto ester **1**, which could be a potential precursor for the synthesis of the cadalene family.



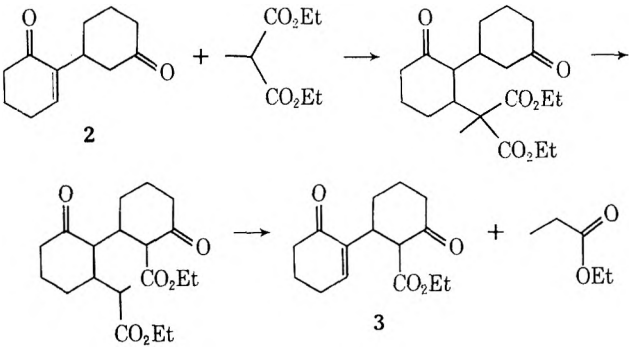
1

On investigating this reaction, we found that the reaction failed under the usual abnormal Michael conditions.[2] Distillation of the reaction mixture afforded only starting materials. Extending the reaction time did not affect the reaction course; however, when the concentrations of both reactants were increased, a reaction did occur. Under these modified conditions, the reaction mixture gave a positive ferric chloride test, and distillation of this mixture afforded ethyl propionate, diethyl methylmalonate, and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**). We were unable to distill any substance which displayed a positive ferric chloride test from the mixture.

Thick layer chromatographic analysis of the remaining oil afforded a band which gave the enol test. Extraction of this band with methanol and subsequent 2,4-dinitrophenylhydrazone formation yielded a crystalline compound which analyzed for $C_{21}H_{24}N_4O_7$. Based upon nmr analysis, the hydrazone appears to be a derivative of 2-(2-ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone (**3**). In addition to the characteristic signals due to the protons of the 2,4-dinitrophenyl nucleus, the derivative has a complex series of signals at δ 1.5–2.5, a quartet centered at δ 4.05, and a complex multiplet at δ 7.42. The upfield portion of the spectrum and the signal in the vinyl region are very similar to the signals in the spectrum of 2-(3-oxocyclohexyl)-2-cyclohexenone.

(1) A. Michael, *J. Prakt. Chem.*, **35**, 349 (1887).
(2) A. Michael and J. Ross, *J. Amer. Chem. Soc.*, **55**, 1632 (1932).
(3) N. E. Holden and A. Lapworth, *J. Chem. Soc.*, 2368 (1931).
(4) A. Michael, *J. Org. Chem.*, **2**, 303 (1937).
(5) E. D. Bergmann, D. Ginsberg, and R. Pappo, *Org. React.*, **10**, 191 (1959).
(6) G. E. Risinger and H. Dupont Durst, *Chem. Ind. (London)*, 1647 (1967).
(7) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

The isolation of **2** and **3** suggests the following conversion.



2 **3**

In order to test this reaction scheme, we prepared 2-(3-oxocyclohexyl)-2-cyclohexenone[8] and subjected it to abnormal Michael conditions. Analysis of this mixture revealed the presence of the same reaction products as in the 2-cyclohexenone reaction. Distillation afforded ethyl propionate, diethyl methylmalonate, and **2**; thick layer chromatography of the residue yielded a single positive ferric chloride band which gave a 2,4-dinitrophenylhydrazone identical with the one produced from the 2-cyclohexenone sequence.

Thus, it appears that the facile conversion of 2-cyclohexenone into **2** precludes the employment of the abnormal Michael reaction in the synthesis of cyclic terpenoid systems.

Experimental Section

Reaction of Diethyl Methylmalonate with 2-Cyclohexenone with a Minimum of Solvent.—Diethyl methylmalonate (8.7 g, 0.05 mol) and 2-cyclohexenone (4.8 g, 0.05 mol) were refluxed in a solution of sodium (1.15 g, 0.05 mol) in absolute ethanol (25 ml) for 24 hr under nitrogen. The reaction mixture was neutralized, taken up in ether (100 ml), and washed with water (2 × 50 ml). The ether was dried and concentrated to give a crude oil (10.0 g). Distillation of this oil gave ethyl propionate (0.2 g, 22%), diethyl methylmalonate (2.8 g, 32%), and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**): 1.1 g (23%); bp 132–134° (4 mm); ir (CCl_4) 5.82 (C=O), 5.95 μ (α,β-unsaturated C=O); uv max (95% EtOH) 233 mμ; nmr ($DCCl_3$) δ 6.74 (t, 1). Chromatography of the crude oil (silica; elution with 3% ethyl acetate in heptane) followed by extraction of the enolic band with methanol gave a yellow oil (0.050 g): 2,4-dinitrophenylhydrazone mp 182–184°; nmr ($DCCl_3$) δ 9.11 (d, 1), 8.30 (d, 1), 7.94 (d, 1), 7.42 (m, 1), 4.05 (m, 2).

Anal. Calcd for $C_{21}H_{24}N_4O7$: C, 56.76; H, 5.41; N, 12.61. Found: C, 56.58; H, 5.55; N, 12.97.

Preparation of 2-(3-Oxocyclohexyl)-2-cyclohexenone.—2-Cyclohexenone (9.6 g, 0.1 mol) was treated with a solution of sodium (0.23 g, 0.01 mol, in 100 ml of ethanol) at 0° for 72 hr. Neutralization and concentration gave a crude mixture, which was taken up in diethyl ether (100 ml) and washed with water (2 × 50 ml). The ether layer was dried (Na_2SO_4) and concentrated. The resulting oil afforded 3-ethoxycyclohexanone (0.8 g, 6%) and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**) (3.2 g, 33%) which was identical with the compound produced in the reaction between diethyl methylmalonate and 2-cyclohexenone.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.18; H, 7.99.

Reaction between 2-(3-Oxocyclohexyl)-3-cyclohexenone and Diethyl Methylmalonate.—2-(3-Oxocyclohexyl)-2-cyclohexenone (7.7 g, 0.08 mol) and diethyl methylmalonate (13.9 g. 0.08 mol) in absolute ethanol (20 ml) were refluxed in the presence of sodium (1.8 g, 0.08 mol) for 24 hr under nitrogen. The reaction mixture was neutralized, taken up in ether, and washed with water. The ethereal solution was dried (Na_2SO_4) and concentrated. Subsequent distillation of the oil yielded ethyl propionate, diethyl methylmalonate, and 2-(3-oxocyclohexyl)-2-cyclohexenone. Chromatography of the pot residue and subsequent treatment of the enol component with 2,4-dinitrophenyl-

(8) J. E. Englehart and J. R. McDivitt, *J. Org. Chem.*, **36**, 367 (1971).

hydrazine yielded a 2,4-dinitrophenylhydrazone which was identical with the $C_{21}H_2N_4O_7$ derivative isolated from the 2-cyclohexenone reaction.

Registry No.—2, 5216-84-2; 3 dinitrophenylhydrazone, 41008-55-3; diethyl methylmalonate, 609-08-5; 2-cyclohexenone, 930-68-7.

Photochemistry of Diazonium Salts. III. A New and Facile Synthesis of 4-Fluoroimidazoles

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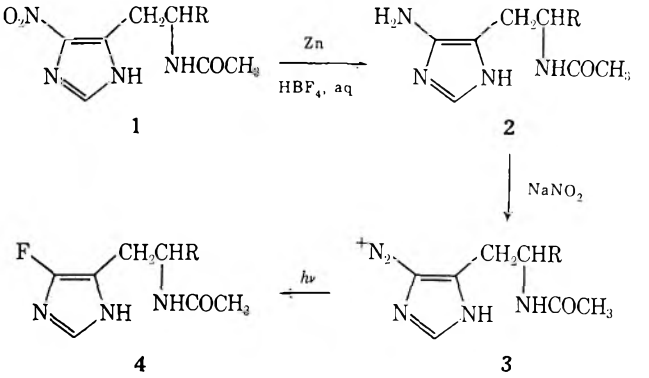
In paper I of this series,[1] we described the synthesis of a variety of 4-fluoroimidazoles, based on the irradiation of 4-diazonium imidazoles in aqueous tetrafluoroboric acid. Since the immediate precursors of the diazonium salts, 4-aminoimidazoles, are often too unstable for isolation, indirect and tedious synthetic routes were found necessary. Thus, 4-aminoimidazole itself was generated, *in situ*, by acid cleavage of its *tert*-butoxycarbonyl derivative; the latter compound was derived from ethyl imidazole-4-carboxylate by a three-step procedure. Other 4-fluoroimidazoles (*e.g.*, 4-fluoro-L-histidine, **4a**) were obtained by converting the stable 4-aminoimidazole-5-carboxylic esters to 4-fluoro analogs, followed by synthetic elaboration of the side chain, as necessary. Thus, the synthesis of 4-fluorohistamine required a sequence of nine steps from the commerically available 4-aminoimidazole-5-carboxamide. Subsequent to our announcement of these compounds,[1,2] extensive interest developed in the synthesis of polypeptide analogs containing 4-fluoro-L-histidine,[3] as well as in the pharmacological and enzymatic properties of the amino acid and the amine. This interest emphasized to us the fact that considerably larger quantities of these compounds would be required than could be obtained practically by our published procedures.

Initial attempts to exploit the readily available 4-nitroimidazoles as precursors were thwarted, repeatedly, by the instability of the amines. For example, catalytic hydrogenation of 4-nitroimidazole, followed by rapid work-up of the product under nitrogen and either in the presence or absence of tetrafluoroboric acid, resulted in extensive decomposition, as evidenced by insoluble dye formation. Diazotization and irradiation of the crude reduction products in tetrafluoroboric acid solution resulted in recoveries of only trace amounts of 4-fluoroimidazole. Catalytic reductions in other solvents, including 50% tetrafluoroboric acid itself, were similarly fruitless; however, the nitroimidazole was rapidly reduced with zinc dust in the same fluoroboric acid system and with little evidence of decomposition of the product. The aminoimidazole so formed can be diazotized and irradiated *in situ*. Thus, 4-nitroimidazole was rapidly reduced to 4-aminoimidazole at −10 to 0° (nitrogen atmosphere), progress of the reduction being monitored by disappearance of the chromophore at 298 nm. When reduction was complete, 1 equiv of sodium nitrite was added, generating a diazonium ion chromophore at 270 nm. The solution was subjected to irradiation at 0°, progress of the reaction being monitored by loss of the diazonium ion chromophore. From the reaction mixture, 4-fluoroimidazole was obtained in 17% yield. Considering the ready availability of 4-nitroimidazole and the fact that no intermediates were isolated, this overall yield is quite acceptable, and compares favorably with that reported previously.[1] With 4-nitro-5-methylimidazole, a 37% yield of the fluoro derivative was obtained by use of the same procedure.

In our earlier synthesis of 4-fluoro-L-histidine, an overall yield of 1.5% was obtained after eight steps, beginning with 4-aminoimidazole-5-carboxamide. 4-Fluorohistamine was obtained in 0.7% yield after nine steps from the same starting point. Recent development of the direct nitration of histidine and histamine (and their derivatives)[4,5] widened the range of accessible nitroimidazoles, and led us to explore the simplified synthetic approach with the more complex compounds. Indeed, α-*N*-acetyl-4-nitro-L-histidine methyl ester (**1a**) was converted into its fluoro analog **4a** in 10% yield, and α-*N*-acetyl-4-nitrohistamine (**1b**) was converted into its fluoro analog **4b** in 18% yield.



a, R = $COOCH_3$
b, R = H

Removal of the blocking groups from these derivatives incurs no losses.

This considerable facilitation of the syntheses of the histidine and histamine analogs removes the principal obstacle to expansion of a wide variety of biochemical and pharmacological studies, either already under way or being planned. A relatively broad spectrum of functional groups can be introduced into the imidazole ring (both at C-2 and at C-4) by photochemical decomposition of the respective diazonium ions.[6] These syntheses are also made more inviting and practical by the

(1) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 4619 (1973).

(2) A preliminary report was presented at the Symposium on Fluorine in Medicinal Chemistry, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971; see also K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3060 (1971).

(3) See, *e.g.*, B. M. Dunn, C. DiBello, and I. M. Chaiken, *Fed. Proc.*, **32**, 541 (1973). Reports of other studies are in preparation.

(4) W. Tautz, S. Teitel, and A. Brossi, *J. Med. Chem.*, **16**, 705 (1973). We are indebted to these investigators for providing us with experimental details of the nitration procedure prior to publication.

(5) (a) Racemic 4-nitrohistidine has been obtained by synthetic elaboration of the side chain in 4-chloromethyl-5-nitroimidazole: G. E. Trout, *J. Med. Chem.*, **15**, 1259 (1972). (b) Nitration of α-*N*-acetyl-L-histidine, under more vigorous conditions, has been reported to yield a racemic, dinitrated product of unknown structure: N. P. Buu-Hoi and C. Lepoivre, *C. R. Acad. Sci.*, **257**, 3618 (1963).

(6) These studies are in progress and will be reported separately.

possibility of utilizing nitroimidazoles as precursors, at least in the 4-nitro case.

Experimental Section[7]

α-*N*-Acetyl-4-nitro-L-histidine Methyl Ester (1a).—α-*N*-Acetyl-4-nitro-L-histidine[4] (43 g, 0.18 mol) was added to 600 ml of methanol to which had previously been added 7 ml of thionyl chloride.[8] The solution was stirred at ambient temperature for 8 hr, after which time tlc showed almost complete esterification. The solvent was removed *in vacuo* (below 40°), 500 ml of cold water was added to the residue, and the aqueous solution was neutralized (pH 4) with solid sodium bicarbonate. The solution was chilled overnight and the colorless solid was collected by filtration. The product was recrystallized from water and then from ethanol to yield 29 g (63%) of **1a**, mp 202–205°.

Anal. Calcd for $C_9H_{12}N_4O_5$: C, 42.19; H, 4.72; N, 21.87. Found: C, 42.03; H, 4.92; N, 21.64.

The same compound was obtained in lower yield by introduction of hydrogen chloride gas into a cold, methanolic solution of the acid. Even at low temperature, N-deacylation occurred to a significant extent. Direct nitration of α-*N*-acetylhistidine methyl ester could not be effected without demethylation. Use of the free carboxylic acid in the irradiation step proved unsatisfactory.

α-*N*-Acetyl-4-nitrohistamine (1b).—This compound was prepared by nitration of α-*N*-acetylhistamine, following the published procedure for α-*N*-acetylhistidine.[4] The product was obtained in 44% yield following crystallization from water and ethanol–ethyl acetate, mp 225–229° dec (with gas evolution).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 41.90; H, 5.17; G, 28.42.

General Fluorination Procedure.—A solution of 20 mmol of the nitromidazole in 100 ml of 50% tetrafluoroboric acid was cooled to −10°. While the solution was stirred rapidly and was aerated with nitrogen, zinc dust was added in portions of *ca.* 25 mg, until a total of 4.25 g (65 mmol) had been added. Each addition was made only after the prior portion had dissolved and the temperature had fallen to at least −5°; the interval between additions ranged from 1 to 3 min, increasing toward the end of the reduction. Small aliquots were removed periodically and diluted with water, and the solutions were assayed at 298 nm. Total loss of the chromophore was taken to indicate complete reduction.[9] A solution of sodium nitrite (1.52 g, 22 mmol) in the minimum volume of water was then added dropwise over 15 min. The resulting solution was diluted to 185 ml with cold 50% tetrafluoroboric acid and was irradiated (Corex filter) as described previously.[10] Small aliquots were withdrawn periodically, diluted with water, and asayed at 270 nm; again, completion of the reaction was indicated by total loss of absorption at this wavelength. The solution was neutralized with cold, concentrated sodium hydroxide (the precipitate of zinc hydroxide was not removed), and the mixture was extracted continuously for 24 hr with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated, and the residual solution was filtered through a short silica gel column to remove inorganic salts. The products were then purified by crystallization or sublimation, or both.

4-Fluoroimidazole was obtained in 17% yield, mp 101.5–104°; this material was identical with the product described previously.[1]

4-Fluoro-5-methylimidazole was obtained in 37% yield from 4-nitro-5-methylimidazole.[11] The product was purified by sublimation: mp 66–69°; nmr ($CDCl_3$) δ 2.20 (d, J = 1.5 Hz, 3 H, 5-CH_3)[12] and 7.11 ppm (d, J = 2 Hz, 1 H, 2-H).

Anal. Calcd for $C_4H_5N_2F$: C, 48.00; H, 5.03; N, 27.99. Found: C, 47.93; H, 5.03; N, 27.82.

α-*N*-Acetyl-4-fluoro-L-histidine Methyl Ester (4a).—The amino acid derivative was obtained in 10% yield from **1a**, mp 153.5–154.5° (ethanol–ethyl acetate).[13]

Anal. Calcd for $C_9H_{12}N_3O_3F$: C, 47.16; H, 5.28; N, 18.34. Found: C, 46.92; H, 5.42; N, 18.53.

Acid hydrolysis of **4a** gave a quantitative recovery of 4-fluoro-L-histidine, identical with the earlier product[1] with respect to spectral, chromatographic, and optical rotatory properties.

α-*N*-Acetyl-4-fluorohistamine (4b).—This compound was obtained in 18% yield from **1b**, mp 172–173° (ethanol–ethyl acetate).

Anal. Calcd for $C_7H_{10}N_3OF$: C, 49.12; H, 5.89; N, 24.55. Found: C, 48.72; H, 5.94; N, 25.15.

Acid hydrolysis of **4b** gave 4-fluorohistamine, characterized as its picrate, mp 202–204° dec.[1]

Registry No.—**1a**, 41429-88-3; **1b**, 41366-97-6; **4a**, 41366-98-7; **4b**, 41366-99-8; α-*N*-acetyl-4-nitro-L-histidine, 41367-00-4; tetrafluoroboric acid, 16872-11-0; 4-fluorimidazole, 30086-17-0; 4-nitroimidazole, 3034-38-6; 4-fluoro-5-methylimidazole, 41367-01-5; 4-nitro-5-methylimidazole, 14003-66-8.

(7) Analytical and spectral data were supplied by the Analytical Services and Instrumentation section of this laboratory, under the direction of Dr. D. F. Johnson. Melting points are uncorrected. Identity and homogeneity were confirmed, wherever feasible, by tlc and mass spectrum.

(8) E. Taschner and C. Wasielewski, *Justus Liebigs Ann. Chem.*, **640**, 136 (1961).

(9) Since a stoichiometry could be demonstrated between the per cent loss of absorption and the amount of zinc added, it was evident that intermediate stages were undergoing reduction at least as fast as the nitro group. The calculation is based on three atoms of zinc per mole of nitro compound.

(10) K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Amer. Chem. Soc.*, in press.

(11) W. E. Allsebrook, J. M. Gulland, and L. F. Strong, *J. Chem. Soc.*, 232 (1942).

(12) Both the C-4 methyl group and the C-2 hydrogen are coupled to the fluorine atom.

(13) Undoubtedly, the low yield reflects some ester hydrolysis in the 50% tetrafluoroboric acid solvent.

Detection of Protonated Aldimine Group by Proton Magnetic Resonance Spectroscopy

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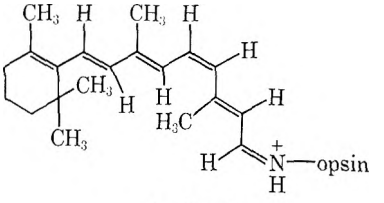
Rhodopsin, the visual pigment of the eye, is a Schiff base formed by the condensation of the aldehyde group of 11-*cis*-retinal with the ε-amino group of a lysine residue in the protein opsin.[1] Several models to explain the anomalous spectroscopic properties of rhodop-



rhodopsin

sin propose that the Schiff base linkage of this molecule is protonated.[2] However, except for the observation that the *N*-retinylidene moiety of rhodopsin shows λ_{max} in the same region where *N*-retinylidene-*n*-butylammonium ion (**8**) absorbs,[3] no direct experimental evidence for the presence of a protonated aldimine group (–HC=$^+$NH–) in the visual pigment has yet been obtained.

It occurred to us that the presence of a protonated aldimine group in rhodopsin may be directly observed by nmr spectroscopy. In principle, the resonance of the azomethine proton, H_a, of a protonated Schiff base

(1) D. Bownds, *Nature*, **216**, 1178 (1967).

(2) C. D. B. Bridges, "Comprehensive Biochemistry," Vol. 27, M. Florkin and E. H. Stolz, Ed., Elsevier, New York, N. Y., 1967, pp 31–78; J. Heller, *Biochemistry*, **7**, 2914 (1968); J. Toth and B. Rosenberg, *Vision Res.*, **8**, 1471 (1968).

(3) P. E. Blatz and J. H. Mohler, *Biochemistry*, **11**, 3240 (1972).

TABLE I
THE NMR DATA FOR THE COMPOUNDS 1–4 IN $CDCl_3$, TFA, AND $CDCl_3$ + TFA AT −55°

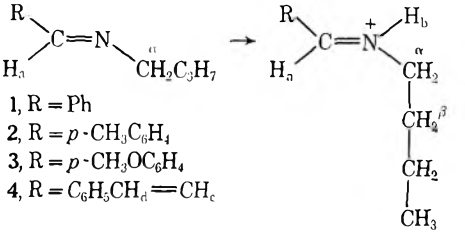
Schiff base	(Multiplicity, J in Hz) In $CDCl_3$ H_a	In $CDCl_3$ α-CH_2	In TFA H_a	In TFA α-CH_2	In $CDCl_3$ + TFA[a] H_a	In $CDCl_3$ + TFA[a] α-CH_2	Coalescence temp, °C
1	8.25 (t, $J_{a,\alpha}$ = 1.3)	3.6 (td, $J_{a,\alpha}$ = 1.3, $J_{\alpha,\beta}$ = 7.1)	8.81 (d, $J_{a,b}$ = 18)	4.06 (q, $J_{\alpha,b}$ = 7, $J_{\alpha,\beta}$ = 7)	8.72 (d, $J_{a,b}$ = 14)	3.96 (q, br)	−45
2	8.23 (s)	3.61 (t, $J_{\alpha,\beta}$ = 7.0)	8.68 (d, $J_{a,b}$ = 17.5)	4.00 (q, $J_{\alpha,b}$ = 7, $J_{\alpha,\beta}$ = 7)	8.63 (d, $J_{a,b}$ = 15.7)	3.9 (q, $J_{\alpha,b}$ = 5.5, $J_{\alpha,\beta}$ = 5.5)	−40
3	8.18 (t)	3.55 (td, $J_{a,\alpha}$ = 1.2, $J_{\alpha,\beta}$ = 6.6)	8.52 (d, $J_{a,b}$ = 17.6)	3.93 (q, $J_{\alpha,b}$ = 7, $J_{\alpha,\beta}$ = 7)	8.45 (d, $J_{a,b}$ = 16)	3.85 (q, $J_{\alpha,b}$ = 5, $J_{\alpha,\beta}$ = 5)	−33
4	8.02 (tt, $J_{a,\alpha}$ = 1.5, $J_{a,b}$ = 4.3, $J_{a,d}$ = 4)	3.51 (td, $J_{a,\alpha}$ = 1.5, $J_{\alpha,\beta}$ = 7)	8.45 (dd, $J_{a,b}$ = 16.7, $J_{a,c}$ = 10.5)	3.87 (q, $J_{\alpha,b}$ = 7, $J_{\alpha,\beta}$ = 7)	8.45 (m, $J_{a,b}$ = 14, $J_{a,c}$ = 4.5, $J_{a,d}$ = 4.5)	3.77 (q, $J_{\alpha,b}$ = 6.5, $J_{\alpha,\beta}$ = 6.5)	−40

[a] At −55°.

should exhibit additional splitting because of coupling to the proton, H_b, present on the imine nitrogen. The numerical value of the coupling constant $J_{a,b}$ should be 15–18 Hz if the protonated Schiff base has the *trans* configuration at the carbon–nitrogen double bond. On the other hand, if the stereochemistry at the carbon–nitrogen double bond is cis, then $J_{a,b}$ should be in the range of 8–12 Hz. Thus, the presence of a protonated aldimine group in a molecule may be inferred from the multiplicity of the azomethine proton resonance. However, it was realized at the outset that the above results would be obtained only if the proton exchange in protonated Schiff bases is slow on the nmr time scale. In addition, there should be no free rotation about the carbon–nitrogen bond of these positively charged species. The free rotation about the protonated Schiff base linkage of rhodopsin may be expected if there is a substantial delocalization of the positive charge over the polyene chain of the *N*-retinylidene moiety of this molecule. Furthermore, the nmr spectroscopy will be most effective in detecting the presence of a protonated aldimine group in rhodopsin if the resonance of the azomethine proton occurs in the region below 9 ppm. This region is normally free from absorption by other protons and the resonance due to an azomethine proton should be easily detectable. To gain information on these points we have studied the nmr spectra of *all-trans-N*-retinylidene-*n*-butylamine (**7**) and of the Schiff bases **1**–**4** in trifluoroacetic acid (TFA) and in $CDCl_3$ acidified with equimolar amounts of TFA. The results of these investigations are reported in this note.

The imines **1**–**4** and **7** were prepared according to the procedures reported in the literature.[4,5] All spectra were recorded on a Varian HR-220 MHz nmr spectrometer. The discussion is restricted in the main to the nmr parameters of azomethine protons (H_a) and α-methylene protons (α-CH_2). The other spectral features were much as expected and showed no abnormalities.

In the nmr spectra of the trifluoroacetic acid (TFA) solutions of **1**, **2**, and **3**, the resonances of H_a and α-CH_2 appear as doublets and quartets, respectively. When deuteriotrifluoroacetic acid is used as the solvent, the azomethine protons give singlets and the α-methylenes appear as triplets. These results show that the Schiff bases **1**–**3** are protonated in trifluoroacetic acid. The splitting of H_a resonances into doublets ($J_{a,b}$ = 16–18 Hz) and of α-CH_2 resonances into quartets ($J_{\alpha,b}$ = $J_{\alpha,\beta}$ = 7 Hz) is due to coupling with the proton H_b present on the imine nitrogen. The resonance of the azomethine proton of the protonated species **5** (R = $C_6H_5CH_d{=}CH_c$) (produced by dissolving **4** in TFA) was a doublet of doublets ($J_{a,b}$ = 16.7 and $J_{a,c}$ = 10.5 Hz) because of coupling to H_b and H_c.



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The nmr data collated in Table I suggest that the resonances of H_a and α-CH_2 shift downfield when the Schiff bases **1**–**4** are protonated. The numerical values of the coupling constants $J_{a,b}$ = 16–18 Hz indicate that the protonated Schiff bases have trans configuration **5** at the carbon–nitrogen double bond. These coupling constants further suggest that there is no rotation about the CN bond of protonated Schiff bases.

The Schiff bases **1**–**3** dissolve readily in $CDCl_3$ acidified with equimolar amounts of TFA. In the nmr spectra of these solutions determined at −55°, the azomethine protons and the α-methylenes exhibit the same multiplicities as observed in trifluoroacetic acid (Table I). As the temperature is raised, the doublets due to H_a and the quartets due to α-CH_2 broaden and finally coalesce to give singlets and triplets, respectively. The coalescence temperatures are given in Table I. These spectral data suggest that the Schiff bases **1**–**3** are protonated in $CDCl_3$ by equimolar amounts of TFA, and at −55° the protonated species exhibit extremely slow exchange rates allowing the observation of well-resolved nmr spectra.

The Schiff base **4** is also protonated in $CDCl_3$ acidified with equimolar amounts of TFA. The azomethine

(4) C. S. Irving and P. A. Leermakers, *Photochem. Photobiol.*, **7**, 665 (1968).

(5) K. A. W. Perry, P. J. Robinson, P. J. Sainsbury, and M. J. Waller, *J. Chem. Soc. B*, 700 (1970).

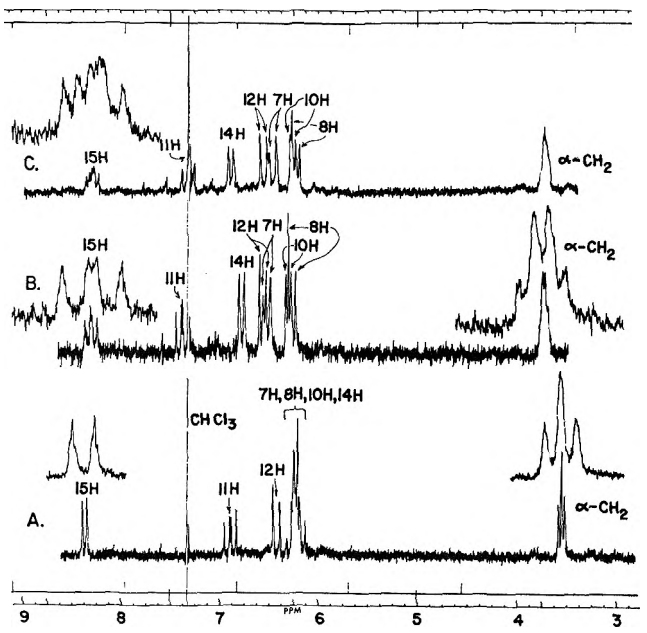
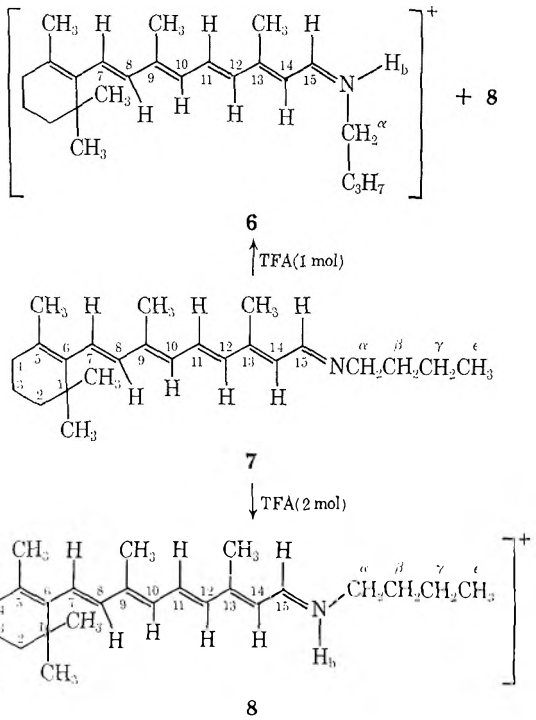


Figure 1.—The 3-9-ppm regions of the nmr spectra of *N*-retinylidene-*n*-butylamine (**7**) in $CDCl_3$ at −5° (trace A), in $CDCl_3$ + 2 mol equiv of TFA at −5° (trace B), and in $CDCl_3$ + equimolar amounts of TFA at −50° (trace C).

proton of the protonated species gives a sextet ($J_{a,b}$ = 14 and $J_{a,c}$ = $J_{a,d}$ = 4.5 Hz) in the nmr spectrum determined at −55°.

The *N*-retinylidene-*n*-butylammonium ion (**8**) was obtained by treating the deuteriochloroform solution of **7** at −60° with 2 mol equiv of TFA (Scheme I).

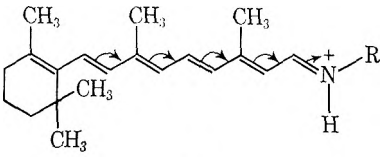
SCHEME I



The formation of **8** was recognized by the presence of a doublet of doublets at δ 8.3 (1 H, $J_{15,b}$ = 15.5, $J_{14,15}$ = 11.5 Hz, 15-H) and a quartet at 3.7 (2 H, $J_{\alpha,b}$ = $J_{\alpha,\beta}$ = 7 Hz, α-CH_2) in the nmr spectrum of the acidified solution, determined at −5°. The other protons of **8** showed bands at δ 7.38 (dd, 1 H, $J_{11,12}$ = 15 and $J_{10,11}$ = 12 Hz, 11-H), 6.73 (d, 1 H, $J_{14,15}$ = 11.5 Hz, 14-H), 6.52 (d, 1 H, $J_{11,12}$ = 15 Hz, 12-H), 6.47 (d, 1 H, $J_{7,8}$ = 16 Hz, 7-H), 6.27 (d, 1 H, $J_{10,11}$ = 12 Hz, 10-H), 6.22 (d, 1 H, $J_{8,7}$ = 16 Hz, 8-H), 2.3 (s, 3 H, 13-CH_3), 2.07 (s over m, 5 H, 4-CH_2 and 9-CH_3), 1.72 (s over m, 5 H, 3-CH_2 and 5-CH_3), 1.62 (m, 2 H, β-CH_2), 1.48 (m, 2 H, 2-CH_2), 1.34 (m, 2 H, γ-CH_2), 1.04 (s, 6 H, 1-CH_3), and 0.95 (t, 3 H, ε-CH_3). The signals of 15-H and α-CH_2 did not coalesce as the temperature was raised to 17°. The coupling constant $J_{15,b}$ = 15.5 Hz again suggests that the ion **8** has trans configuration at the aldimine linkage.

The 3-9-ppm regions of the nmr spectra of **7** and **8** are compared in Figure 1 (trace A and trace B). The comparison reveals that the resonances of 7-H, 11-H, and 14-H suffer a large downfield shift (0.3, 0.52, and 0.6 ppm, respectively) when the imine nitrogen of **7** is protonated. The protonation, however, does not affect the chemical shift of the azomethine proton, 15-H.

The deshielding of 7-H and 11-H upon protonation of *N*-retinylidene-*n*-butylamine indicates that there is a delocalization of the positive charge over the polyene chain of *N*-retinylidene-*n*-butylammonium ion owing to the resonance interaction of the type[6-8] shown in **8a**.



8a

The resonance of 15-H is not affected by protonation because the deshielding induced by the residual positive charge on the imine nitrogen is balanced by the decrease in the double-bond character and hence by the decrease in the anisotropy of the C–N bond. The large deshielding of the resonance of 14-H upon protonation of **7** is anomalous and cannot be explained on the basis of charge delocalization.

Addition of equimolar amounts of TFA to the deuteriochloroform solution of **7** at −60° appears to produce two products. Thus, in the nmr spectrum of the acidified solution at −50°, the azomethine proton, 15-H, gave seven lines and α-CH_2 appeared as a broad band (Figure 1, trace C). Above −16° (coalescence temperature) the resonances of 15-H and α-CH_2 were doublets ($J_{14,15}$ = 10.5 Hz) and triplets, respectively. These results indicate the formation of isomeric (cis and trans) monoprotonated species **8** and **6**. The doublet of doublets due to 15-H of **8** ($J_{15,b}$ = 15.5 and $J_{14,15}$ = 11.5 Hz) and the doublet of doublets due to 15-H of **6** ($J_{15,b} \simeq 11$ and $J_{14,15} \simeq 9$ Hz) would partially overlap to give seven lines in the nmr spectrum.

In conclusion it may be remarked that, in the low temperature nmr spectra of the protonated Schiff bases, the azomethine protons and the α-methylenes exhibit additional fine structure because of coupling to the proton present on the imine nitrogen. This observation is of diagnostic value and may be used to detect the presence of a protonated aldimine group in simple organic molecules. It may be noticed that the azo-

(6) D. J. Patel, *Nature*, **221**, 825 (1969).
(7) D. J. Patel, *Nature*, **224**, 700 (1969).
(8) D. J. Patel and R. G. Schulman, *Proc. Nat. Acad. Sci.*, **65**, 31 (1970).

methine proton of *N*-retinylidene-*n*-butylammonium ion (**8**) resonates at 8.3 ppm. If in the nmr spectrum of rhodopsin the region around 8.3 ppm is not masked by bands from the aromatic protons of the protein moiety (opsin) and the resonance due to the azomethine proton is easily detectable, then this technique (nmr spectroscopy) may reveal whether the Schiff base linkage of the visual pigment is protonated or not. We would have been more confident if the resonance of the azomethine proton had occurred in the region below 9 ppm.

Acknowledgments.—This work was supported in part by NSF Grant No. GB-29946 and Grants from the Research Corporation and Sloan Foundation to a consortium at the Rockefeller University for 220-MHz nmr facilities. We wish to thank Peter Ziegler for assistance in obtaining the nmr spectra.

Registry No.—*1*, 1077-18-5; *2*, 7020-93-1; *3*, 3910-55-2; *4*, 15286-55-2; 7, 36076-04-7; 8, 32798-55-3.

The Methyl Signals in the Proton Magnetic Resonance Spectra of Some 2-Methylnorbornanes. A Cautionary Tale

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Received May 8, 1973

Proton magnetic resonance spectroscopy is frequently used for distinguishing between a methyl group bonded to a quaternary carbon atom and a methyl group bonded to an sp^3 carbon atom bearing a hydrogen atom. Although in the latter case the signal may deviate from a simple AX_3 doublet owing to strong or virtual coupling, it is usually readily distinguishable from the singlet signal in the former case, because the chemical shift differences between the methyl and methine protons is normally appreciable. If, however, there were accidental chemical equivalence between the methyl and methine protons because of special structural features in the molecule, the methyl signal could appear as a singlet, superimposed on the methine signal. We have observed examples of this circumstance in the spectra of the norbornanes **1a–c**.

Compounds **1a–c** were prepared from the acid **1d**.[1] Although the methyl group of **1d** gives rise to a conventional CH_3CH doublet (Table I), the methyl groups of **1a–c** give rise to singlets. By contrast, the methyl groups of **2a–c** give rise to doublets; these compounds were prepared from the acid **2d**,[1] whose spectrum also showed a methyl doublet. It is known that the endo proton signal in norbornane occurs at unusually high field,[2,3] and we conclude that this effect, combined with a further upfield shift resulting from shielding by the endo C–CH_2X bond in **1a–c**,[4] results in accidental chemical equivalence of the methyl protons and the endo methine proton.[5] As expected for this interpretation, the methyl singlets are superimposed on multiplets, the total peak area corresponding to four protons. The absence of this effect in the spectrum of **1d** is attributable to deshielding of the endo methine proton by the carboxylic acid group and in the spectra of **2a–d** to the fact that exo protons are not shielded by the norbornane system.[2,3]

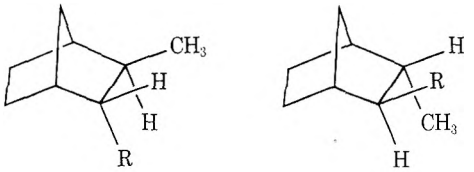
TABLE I

METHYL PROTON SIGNALS[a]

Compd	δ	Compd	δ
1a	0.93 (s)	**2a**	0.97 (d)
1b	0.98 (s)	**2b**	1.01 (d)
1c	0.95 (s)	**2c**	0.97 (d)
1d	0.97 (d)	**2d**	1.06 (d)
3a	1.10 (d)	**4a**	0.84 (d)
3b	0.79 (d), 1.03 (d)	**4c**	0.93 (d)
3c	1.18 (d)		

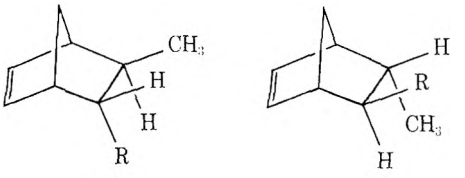
[a] For all doublets, J = 6–7 Hz.

Related observations have been made in the norbornene series. Compounds **3a** and **3b** give rise to methyl doublets in which the higher field component is considerably more intense than the lower field component,[6] whereas compounds **3c**, **4a**, and **4c** give rise to conventional CH_3CH doublets.[7] It is known that signals arising from endo protons in norbornene occur at yet higher field than those in norbornane.[2] Thus, the spectra of **3a** and **3b** can be interpreted in terms of a shift of the endo methine signals to higher field than those of the exo methyl protons; indeed, such signals are observed as multiplets as $\delta \sim 0.90$ and 0.80, respectively.



1 2

a, R = CH_2OH
b, R = CH_2Cl
c, R = CH_2OAc
d, R = CO_2H



3 4

a, R = CH_2OH
b, R = CH_3
c, R = CO_2H

(1) S. Beckmann, A. Dürkop, R. Bamberger, and R. Mezger, *Justus Liebigs Ann. Chem.*, **594**, 199 (1955).

(2) A. P. Marchand and N. W. Marchand, *Tetrahedron Lett.*, 1365 (1971).

(3) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963); P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

(4) R. G. Foster and M. C. McIvor, *Chem. Commun.*, 280 (1967).

(5) Broadening of the methyl singlets indicates that the chemical equivalence is not exact.

(6) In the case of **3b**, this refers to the lower field doublet, assigned to the exo methyl group; the endo methyl group gives rise to a conventional CH_3CH doublet.

(7) The pmr spectra of **3a** and **4a** have been discussed earlier,[8] but no reference was made to the methyl signal of **3a**.

(8) H. Christol, J. Coste, and F. Plénat, *Ann. Chim. (Paris)*, **4**, 93, 105 (1969).

It is clear from these results that caution must be exercised in the interpretation of singlet methyl proton signals and that other evidence should be adduced, *e.g.*, from solvent or lanthanide shift studies, in order to exclude the possibility of accidental chemical equivalence of the methyl and vicinal methine protons.

Experimental Section

Materials.—Compounds **3c** and **4c** were prepared from cyclopentadiene and crotonic acid, and hydrogenated to give **1d** and **2d**.[9] These were reduced with lithium aluminum hydride to give **1a** and **2a**,[1] which were converted to **1b** and **2b** by treatment with triphenylphospine and carbon tetrachloride,[10] and to **1c** and **2c** by acetylation with acetic anhydride and sulfuric acid. Compounds **3a** and **4a** were prepared by reduction of **3c** and **4c** with lithium aluminum hydride.[8]

Spectra.—Pmr spectra were recorded in carbon tetrachloride solution at 100 MHz. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane.

Acknowledgments.—We thank Dr. R. A. Blattel for the spectrum of **3b** and the National Research Council of Canada for support of this work.

Registry No.—**1a**, 18377-07-6; **1b**, 41476-85-1; **1c**, 41476-86-2; **1d**, 41476-87-3; **2a**, 18377-06-5; **2b**, 41476-89-5; **2c**, 41476-90-8; **2d**, 41476-91-9; **3a**, 24557-29-7; **3b**, 695-80-7; **3c**, 4397-23-3; **4a**, 24557-37-7; **4**, 4397-24-4.

(9) G. Komppa and S. Beckmann, *Justus Liebigs Ann. Chem.*, **523**, 68 (1936); K. Alder, W. Günzl, and K. Wolff, *Chem. Ber.*, **93**, 809 (1960).

(10) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966); J. B. Lee, *J. Amer. Chem. Soc.*, **88**, 3440 (1966).

Synthesis of Spiro Ketals from Japanese Hops

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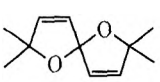
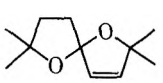
Received May 22, 1973

Among the volatile components of the pistillate cones of "Shinshu-wase," a variety of hop plant (*Humulus lupulus*, L.) cultivated in Japan, are two C_{11} unsaturated spiro ketals having a pleasant, apple-like odor.[1] On the basis of spectral properties and hydrogenation to the known[2] saturated spiro ketal **3**, structures **1** and **2** have been assigned[3] to these two compounds. Here we describe a simple confirmatory synthesis of **1** and **2** together with an alternative route to **3**.



1



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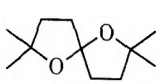


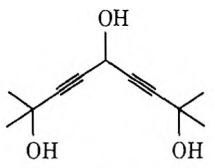
3

Addition of 2 mol of the dimagnesium salt of 2-methyl-3-butyn-2-ol to ethyl formate afforded the desired product, 2,8-dimethyl-3,6-nonadiyne-2,5,8-triol (**4**), in 33% yield as a solid which crystallized readily from chloroform. Reaction of the same salt with 4-hydroxy-4-methyl-2-pentynal gave material with spectral evidence for the presence of **4**; however, no crystalline product could be isolated.

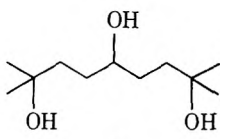
(1) Y. Naya and M. Kotake, *Nippon Kagaku Zasshi*, **88**, 1302 (1967); *Chem. Abstr.*, **69**, 44038 (1968).

(2) T. Strom, *J. Prakt. Chem.*, **48**, 209 (1893).

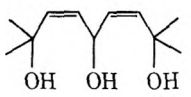
(3) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 1715 (1967).



4



5



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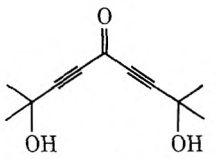

7

Hydrogenation of **4** to the saturated triol **5** proceeded smoothly over 5% palladium on charcoal. Partial hydrogenation of **4** was unsuccessful over a Lindlar catalyst[4] of demonstrated activity but was satisfactory over quinoline-poisoned, 5% palladium on barium sulfate, giving the crystalline dicisoid dienetriol **6** in 95% yield. Upon oxidation with active manganese dioxide,[5] crude **6** was converted in fair yield directly into the dienic spiro ketal **1**, the spectral properties of which correspond to those recorded[3] for the natural compound.

By partial hydrogenation, **1** gave a mixture containing the monounsaturated ketal **2** and the saturated ketal **3**, separable by gas chromatography. An alternative route to **3** was achieved by oxidation with accompanying cyclodehydration of the saturated triol **5** with Jones reagent[6] and also by similar oxidation of **4** to the dihydroxydiynone **7**, followed by hydrogenation and spontaneous ketal formation.

Experimental Section[7]

2,8-Dimethyl-3,6-nonadiyne-2,5,8-triol (4).—2-Methyl-3-butyn-2-ol (84 g, 1 mol) was added, with stirring, over a period of 1 hr at 20° to 2 mol of ethylmagnesium bromide in 1.2 l. of dry tetrahydrofuran (THF). To the resulting dimagnesium salt, 37 g (0.5 mol) of ethyl formate in 50 ml of dry THF was added slowly, with stirring, and the mixture was heated at reflux for 36 hr. With cooling, 500 ml of saturated ammonium chloride solution was added, and the mixture was extracted with four 500-ml portions of ether. The combined organic extracts were dried over powdered 4-A molecular sieves and then concentrated under reduced pressure to remove the ether, THF, and unreacted 2-methyl-3-butyn-2-ol. The residue was placed on a column of 80–100 mesh Alcoa alumina (3.5 × 50 cm) and washed with ether. A brown, foul-smelling oil was eluted and discarded. Further elution with ether and then methanol gave a nearly odorless brown syrup which when dissolved in chloroform crystallized in several crops, yielding a total of 32.8 g (33%) of triol **4**, mp 92–97°. Recrystallization from chloroform gave product with mp 95–98°; ir (KBr) 2.95 (b), 4.45 μ (w); nmr (DMSO-d_6) δ 1.33 (12 H, s, $-CH_3$), 5.10 (1 H, d, J = 6.5 Hz, HCOH), 5.28 (2 H, s, –OH), 5.94 (1 H, d, J = 6.5 Hz, –OH); mass spectrum m/e 181 ($M^+ - CH_3$), 163, 145, 91, 43 (base). The nmr absorptions at δ 5.28 and 5.94 disappeared upon addition of D_2O.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 8.50.

(4) H. Lindlar and R. Dubuis, *Org. Syn.*, **46**, 89 (1966).

(5) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(7) Melting points and boiling points are uncorrected. Microanalyses were performed by K. Widiger, University of Kansas Medicinal Chemistry microanalyst. Infrared spectra were recorded on a Perkin-Elmer Infracord 137B spectrophotometer; nmr spectra were taken on a Varian A-60 instrument; mass spectra were obtained on a Varian CH-5 spectrometer.

4-Hydroxy-4-methyl-2-pentynal.—This compound was prepared for use in place of ethyl formate in the foregoing reaction. A solution of 2.0 g (17.5 mmol) of 4-methyl-2-pentyne-1,4-diol[8] in 100 ml of methylene chloride was stirred for 0.5 hr with 20 g of active manganese dioxide.[5] After filtration and concentration, distillation afforded 0.5 g (25%) of 4-hydroxy-4-methyl-2-pentynal: bp 58–60° (0.6 mm); ir ($CHCl_3$) 2.75, 2.95 (b), 3.35, 3.50, 3.65 (w), 4.5 (s), 6.0 (s), 8.6, 9.55, 10.5 μ; nmr ($CDCl_3$) δ 1.43 (6 H, s, $-CH_3$), 3.93 (1 H, s, –OH), 9.10 (1 H, s, –CHO); mass spectrum *m/e* 112 (M^+), 97, 43, 32, 28 (base); 2,4-DNP (from ethanol–water) mp 103–105°.

Anal. (2,4-DNP). Calcd for $C_{12}H_{12}N_4O_5$: C, 49.32; H, 4.14; N, 19.17. Found: C, 49.11; H, 3.99; N, 18.96.

Although spectral analysis indicated the formation of **4** from the addition of this aldehyde to the dimagnesium salt of 2-methyl-3-butyn-2-ol, no crystalline product was obtained.

2,8-Dimethyl-2,5,8-nonatriol (5).—A solution of 235 mg (1.2 mmol) of **4** in 40 ml of ethyl acetate was stirred with 6 mg of 5% palladium on charcoal under 1 atm of hydrogen at 25°. After 1 hr, uptake of hydrogen (4.8 mmol) was complete. After removal of the catalyst and solvent, **5** was recovered as an analytically pure, clear, viscous oil (228 mg, 93%): ir ($CHCl_3$) 2.7, 2.9 (b), 7.2, 7.3, 8.65, 11.0 μ; nmr (DMSO-d_6) δ 1.05 (12 H, s, $-CH_3$), 0.73–2.20 (8 H, m, $-CH_2CH_2-$), 3.35 (1 H, m, HCOH), 4.07 (2 H, b, –OH), 5.43 (1 H, m, –OH).

Anal. Calcd for $C_{11}H_{24}O_3$: C, 64.67; H, 11.84. Found: C, 64.80; H, 12.00.

2,8-Dimethyl-3-*cis*,6-*cis*-nonadiene-2,5,8-triol (6).—To a mixture of 186 mg of synthetic quinoline and 157 mg of hydrogen-equilibrated 5% palladium on barium sulfate in 100 ml of ethyl acetate was added 2.94 g (15 mmol) of diynetriol **4** in 50 ml of the same solvent. After the mixture was stirred for 45 min at 25°, 30 mmol of hydrogen was absorbed. Filtration and evaporation afforded 3.18 g of a pale yellow oil which slowly solidified. The nmr spectrum indicated 95% conversion of **4** to **6**. Chromatography of 107 mg of the crude product on 10 g of silica gel (Grace, neutral) gave 18 mg of analytically pure **6**: mp 75.5–77.5°; ir (KBr) 2.65, 3.0 (b), 3.3, 7.25, 7.3, 8.55, 10.05, 10.4, 11.15, 12.70 μ; nmr ($CDCl_3$) δ 1.37 (12 H, s, $-CH_3$), 4.80 (3 H, b, –OH), 5.50 (4 H, s, =CH–), 5.85 (1 H, m, HCOH); mass spectrum *m/e* 185 ($M^+ - CH_3$), 149, 43, 28 (base).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.28; H, 9.99.

Attempts to hydrogenate **4** in the presence of an active Lindlar catalyst[4] capable of reducing diphenylacetylene to *cis*-stilbene were unsuccessful.

2,2,7,7-Tetramethyl-1,6-dioxaspiro[4.4]nona-3,8-diene (1).—Crude **6** (3.06 g, 15.3 mmol) in 100 ml of methylene chloride was added to a suspension of 60 g of active manganese dioxide[5] in 240 ml of the same solvent. The mixture was stirred for 2 hr at 25° and filtered and the solvent was removed, leaving 2.19 g of a clear, fragrant oil containing 1.43 g of **1** by nmr spectral analysis. Distillation afforded 1.26 g (46%) of **1**: bp 74–76° (11 mm) [lit.[3] bp 82° (12 mm)]; ir ($CHCl_3$) 3.3, 6.1, 7.35, 7.4, 9.2, 10.0, 11.3, 11.9 μ; nmr ($CDCl_3$) δ 1.30 (6 H, s, $-CH_3$), 1.38 (6 H, s, $-CH_3$), 5.55 (2 H, d, J = 5.5 Hz, =CH–), 6.05 (2 H, d, J = 5.5 Hz, =CH–), [lit.[3] nmr (solvent not given) δ 1.33 (6 H, s), 1.36 (6 H, s), 5.40 (2 H, d, J = 5 Hz), 5.89 (2 H, d, J = 5 Hz)]; mass spectrum *m/e* 180 (M^+), 165, 43, 32, 28 (base).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.50; H, 8.99.

2,2,7,7-Tetramethyl-1,6-oxaspiro[4.4]non-3-ene (2).—To a suspension of prereduced platinum oxide (25 mg) in 30 ml of ether, 541 mg (3.0 mmol) of **1** was added under hydrogen. After the solution was stirred for 0.5 hr, 1.5 mmol of hydrogen was absorbed. Filtration and evaporation afforded an oil which was resolved into three components by glc on a 6-ft column of 15% Carbowax 20M on Chromosorb W at 100° with a flow rate of 40 ml/min. The first fraction (6.75 min) was 2,2,7,7-tetramethyl-1,6-oxaspiro[4.4]nonane (**3**) (see below); the third fraction (12.25 min) was starting material (**1**). The middle fraction (9.5 min) was identified as **2**[9] by the nmr spectrum ($CDCl_3$): δ 1.09 (3 H, s, $-CH_3$), 1.17 (3 H, s, $-CH_3$), 1.25 (3 H, s, $-CH_3$), 1.27 (3 H, s, $-CH_3$), 1.87–2.03 (4 H, m, $-CH_2CH_2-$), 5.38 (1 H, d, J = 5.5 Hz, C=CH), 5.83 (1 H, d, J = 5.5 Hz, =CH–) [lit.[3] nmr (solvent not given) δ 1.11 (3 H, s), 1.20 (3 H, s), 1.27 (3 H, s), 1.30 (3 H, s), 1.86–2.0 (4 H, m), 5.39 (1 H, d, J = 5 Hz), 5.84 (1 H, d, J = 5 Hz)].

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.54; H, 10.27.

The ratio of **2** to **3** was *ca.* 55:45.

2,2,7,7-Tetramethyl-1,6-oxaspiro[4.4]nonane (3). A. From 2,8-Dimethyl-2,8-dihydroxy-3,6-nonadiyn-5-one (7).—Treatment of 197 mg (1.0 mmol) of **4** with a slight excess of Jones reagent in 2 ml of acetone for 1 hr gave 181 mg (93%) of product which slowly solidified. Distillation onto a cold finger condenser at 60° (0.02 mm) afforded an analytical sample of **7**: mp 37–42°; ir ($CHCl_3$) 2.8, 2.95 (b), 3.35, 4.55, 6.15, 8.05 μ; nmr ($CDCl_3$) δ 1.60 (12 H, s, $-CH_3$), 2.98 (2 H, b, –OH); mass spectrum *m/e* 194 (M^+), 161, 59, 58, 43 (base), 28; 2,4-DNP (from ethanol–water) mp 156.5–158°.

Anal. (2,4-DNP). Calcd for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.50; H, 4.71; N, 15.01.

For conversion to **3**, **7** (1.97 g, 10.0 mmol) was added to a suspension of 212 mg of hydrogen-equilibrated 5% palladium on charcoal in 40 ml of methanol. After 45 min 40 mmol of hydrogen was adsorbed. Filtration, evaporation of the solvent, and elution of the yellow residue through acidic alumina with ether gave, after short-path distillation, 0.89 g (48%) of **3** as a colorless oil: bp 70–72° (12 mm) [lit.[2] bp 178.5° (760 mm)]; ir (CCl_4) 3.35, 3.45, 6.85, 7.25, 7.3, 8.8, 9.6, 10.1, 10.35, 11.55 μ; nmr (CCl_4) δ 1.09 (6 H, s, $-CH_3$), 1.27 (6 H, s, $-CH_3$), 1.45–1.95 (8 H, m, $-CH_2CH_2-$) [lit.[3] nmr (solvent not given) δ 1.13 (6 H, s), 1.30 (6 H, s), 1.60–1.93 (8 H, m)]; mass spectrum *m/e* 184 (M^+), 115, 43, 32, 28 (base).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.57; H, 11.11.

B. From 2,8-Dimethyl-2,5,8-nonatriol (5).—Treatment of 133 mg (0.65 mmol) of **5** in 4 ml of acetone with a slight excess of Jones reagent[6] for 15 min gave, after extraction and passage through acidic alumina with ether, 65 mg (54%) of **3**, the spectral properties of which were identical with those of material prepared above in part A.

Registry No.—**1**, 15129-55-2; **2**, 15031-05-7; **3**, 15031-07-9; **4**, 41189-22-4; **5**, 41189-23-5; **6**, 41189-24-6; **7**, 41189-25-7; **7** 2,4-dinitrophenylhydrazone, 41189-26-8; 2-methyl-3-butyn-2-ol, 115-19-5; 4-hydroxy-4-methyl-2-pentynal, 41189-27-9; 4-hydroxy-4-methyl-2-pentynal 2,4-dinitrophenylhydrazone, 18938-43-7; 4-methyl-2-pentyne-1,4-diol, 10605-66-0; quinoline, 91-22-5.

(8) W. Reppe, *et al.*, *Justus Liebigs Ann. Chem.*, **596**, 36 (1955).

(9) Isolated by preparative glc on a 10-ft column of 15% SF-96 on ABS at 110° with a flow rate of 60 ml/min.

A New Approach to α-Keto Esters

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During the past few years several asymmetric syntheses of α-amino acids from their biological precursors (α-keto acids) have been reported.[1]

This paper describes the possibility of preparing α-keto esters from readily available terminal acetylenes by ozonation followed by dehydration, as shown in Scheme I.[2]

This hypothesis is based on the behavior of ozone toward internal acetylenes,[2] and on the formation of α-hydroperoxy-α-methoxyacetophenone by ozonation of phenylacetylene in methanol.[3]

(1) (a) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Amer. Chem. Soc.*, **92**, 2476 (1970), and references cited therein; (b) E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, **92**, 2488 (1970); (c) K. Harada and T. Yoshida, *Bull. Chem. Soc. Jap.*, **43**, 921 (1970).

(2) (a) T. L. Jacobs, *J. Amer. Chem. Soc.*, **58**, 2272 (1936); (b) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958), and references cited therein.

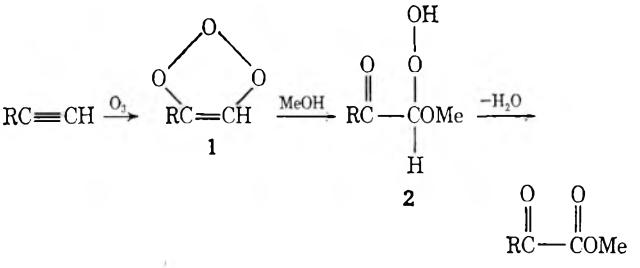
(3) P. S. Bailey, Y.-G. Chang, and W. W. L. Kwie, *J. Org. Chem.*, **27**, 1198 (1962).

TABLE I

Registry no.	Starting material	Registry no.	α-Keto ester obtained[a]	Bp, °C (mm)	Yield, %
1119-64-8	$C_4H_9C{\equiv}CBr$	6395-83-1	$C_4H_9COCOOMe$	48–52 (12)	40
38761-67-0	$C_6H_{13}C{\equiv}CBr$	41172-04-7	$C_6H_{13}COCOOMe$	82–85 (5)	50
932-87-6	$PhC{\equiv}CBr$	15206-55-0	PhCOCOOMe	87–90 (2)	50

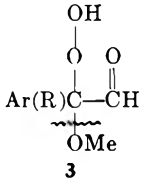
[a] The ir, pmr, and mass spectra are identical with those of authentic specimens.

SCHEME I



1-Hexyne, 1-octyne, and phenylacetylene were used as starting materials. The ozonation reaction was carried out in dry methanol, and $SOCl_2$ was used for the dehydration.

The corresponding α-keto methyl esters were prepared in 10–20% yield. The reason for the low yield is probably because the cleavage of the unstable intermediate **1** is controlled by resonance and inductive effects which promote the formation of α-hydroperoxy-α-methoxy aldehydes such as **3**;[3] dehydration of these compounds does not give α-keto esters.



The above reaction was then modified using 1-bromoacetylenes, which are readily available from terminal acetylenes by treatment with alkaline aqueous solutions of sodium or potassium hypobromite,[4] as starting materials. The bromine atom was introduced assuming that it would facilitate zwitterion formation on the terminal carbon atom, while zwitterion formation on the "internal" carbon atom should give an acylic bromine easily esterified by methanolic acylation.

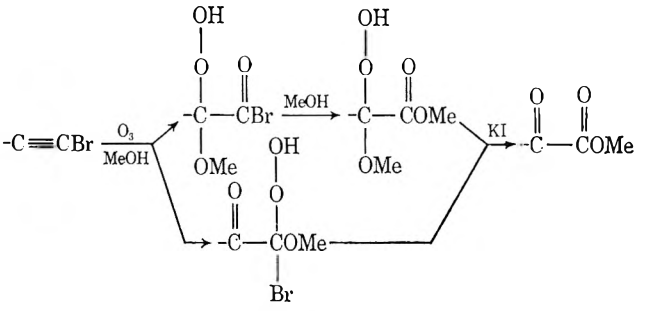
Finally, the ozonolysis of 1-bromoacetylenes in methanol solution should give two peroxides, both of which can be converted to α-keto esters by reduction with potassium iodide (Scheme II).

By this route, 1-bromohexyne,[5] 1-bromooctyne,[6] and bromophenylacetylene[7] were converted to the corresponding α-keto esters in 40–50% yields (Table I).

In both reactions considerable amounts of the carboxylic acid methyl esters were obtained as side products from the decomposition of the intermediate hydroperoxides in methanolic solution.[3,8]

The present work opens a new route to this important class of α-keto esters. Work is in progress on generalization of the method and on improving the yields.

SCHEME II



Experimental Section

α-Keto Methyl Esters from 1-Acetylenes. General Procedure.—An ozone–oxygen stream was passed through a solution of 0.04 mol of the terminal acetylene in 100 ml of dry methanol at −30°, until 90–95% of the starting material had reacted (determined by glc). The solvent was removed at low temperature under reduced pressure. Then 50 ml of cold, dry chloroform was added and a cold mixture of 7.3 ml (0.1 mol) of $SOCl_2$ and 16.1 ml (0.2 mol) of dry pyridine in 9 ml of dry chloroform was added dropwise with stirring at about −10°. The resulting mixture was allowed to warm to room temperature, added to water, and extracted with chloroform. The chloroform extract was neutralized with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Fractional distillation of the yellow-brown oil under reduced pressure gave the α-keto esters.

α-Keto Methyl Esters from 1-Bromoacetylenes. General Procedure.—An ozone–oxygen stream was passed through a solution of 0.04 mol of the 1-bromoacetylene in 100 ml of dry methanol at −30° until 90–95% of the starting material had reacted (determined by glc). Dry nitrogen was passed through the solution to remove excess ozone. Then 33.2 g (0.2 mol) of potassium iodide was added portionwise at about −30° with stirring. The reaction mixture was allowed to stand at room temperature for about 30 min and then 0.1 *N* aqueous sodium thiosulfate was added to neutralize the liberated iodine. The solution was extracted with ether, and the extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Fractional distillation of the yellow-brown oil under reduced pressure gave the α-keto esters.

(4) R. G. Viehe, "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969, p 680.
(5) W. Chodkiewicz, *Ann. Chim.* (*Paris*), **2**, 819 (1957).
(6) G. Eglington and W. McCrae, *J. Chem. Soc.*, 2295 (1963).
(7) S. I. Miller, G. R. Ziegler, and R. Wieleseck, *Org. Syn.*, **45**, 86 (1965).
(8) P. S. Bailey and Y.-G. Chang, *J. Org. Chem.*, **27**, 1192 (1962).

The Preparation of Diacyl Dithiosulfites

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Although esters of sulfurous acid, $(RO)_2SO$, are readily prepared from alcohols and thionyl chloride,[1] thio esters of sulfurous acid, $(RS)_2SO$, have not been reported.

Mercaptans react with thionyl chloride to give the corresponding disulfides and trisulfides instead of the thio esters.[2] On the other hand, Tommasi reported

(1) W. E. Bessinger and F. E. Kung, *J. Amer. Chem. Soc.*, **69**, 2158 (1947).
(2) B. Holmberg, *Justus Liebigs Ann. Chem.*, **359**, 81 (1908); B. Holmberg, *Ber.*, **43**, 226 (1910); S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petrol. Technol.*, **39**, 206 (1953).

TABLE I[a]

RCSSSCR′
‖ ↓ ‖
O O O

Compd	R	R′	Mp, °C	Yield, %	Ir (KBr), cm⁻¹ C=O	Ir (KBr), cm⁻¹ S→O
1a[b]	CH_3	CH_3	76–78	79	1705	1140
1b	CH_2Cl	CH_2Cl	66–67	30	1700	1150
1c	C_6H_5	C_6H_5	108–109	93	1675	1145
1d	*p*-ClC_6H_4	*p*-ClC_6H_4	130–131	94	1680	1145
1e	*p*-$O_2NC_6H_4$	*p*-$O_2NC_6H_4$	152–153	96	1680	1145
1f	*o*-$CH_3OC_6H_4$	*o*-$CH_3OC_6H_4$	95–96	84	1640	1120
3a	C_6H_5	*p*-ClC_6H_4	111–112	86	1675, 1600	1140
3b	C_6H_5	*p*-$O_2NC_6H_4$	130–131	90	1675, 1660	1145
3c	C_6H_5	*o*-$CH_3OC_6H_4$	106–107	85	1675, 1630	1130
3d	*o*-$CH_3OC_6H_4$	*p*-ClC_6H_4	110–111	73	1670, 1630	1135
3e	*o*-$CH_3OC_6H_4$	*p*-$O_2NC_6H_4$	115–116	92	1670, 1640	1130

[a] Satisfactory analytical data (±0.4% for C, H, and S) were reported for all new compounds listed in the table: Ed. [b] This compound was recrystallized from chloroform–petroleum ether (bp 30–70°) and analyzed; however, the melting point was not determined accurately for its instability.

the formation of diacetyl sulfite (acetic sulfurous anhydride) in the reaction of acetyl chloride with lead sulfite.[3] However, no attempt to prepare diacyl dithiosulfites (**1** or **3**), the sulfur analog of diacyl sulfites, has been reported. In this paper, the preparation of **1** and **3** by the reaction of thiocarboxylic acid with thionyl chloride is described.

The reaction of 2 mol of thiocarboxylic acid with 1 mol of thionyl chloride proceeded readily in ether under cooling, and symmetrical diacyl dithiosulfites (**1a–f**) were prepared in good yields (Table I). The

$$2RCOSH + SOCl_2 \longrightarrow \underset{\substack{\| \ \downarrow \ \| \\ O\ O\ O}}{RCSSSCR} + 2HCl$$

1

ir, nmr, and analytical values were in accord with the expected structure for **1a–f**. The ir of **1a–e** showed the carbonyl and sulfinyl absorptions in the region of 1705–1675 and 1150–1140 cm^{-1}, respectively, whereas **1f** showed the both absorptions at 1640 and 1120 cm^{-1} (Table I). **1c–f** were relatively stable and could be stored in a refrigerator for several months.

By the decomposition of **1a** or **1c** at the melting point, carboxylic anhydride and elementary sulfur were formed.

When the reaction mixture of 1 mol of thiocarboxylic acid and 1 mol of thionyl chloride was treated successively with 1 mol of another thiocarboxylic acid, unsymmetrical diacyl dithiosulfites (**3a–e**) were prepared (Table I). The sulfinyl absorption in ir of

$$RCOSH + SOCl_2 \longrightarrow \underset{\substack{\| \ \downarrow \\ O\ O}}{RCSSCl} + HCl$$

2

$$2 + R'COSH \longrightarrow \underset{\substack{\| \ \downarrow \ \| \\ O\ O\ O}}{RCSSSCR'} + HCl$$

3

3c (1130 cm^{-1}) appeared in the region between those of **1c** (1145) and **1f** (1120). Similar results were also observed for **3d** and **3e**. The preparation of **3a–e** suggested the possibility of the formation of acyl thiochlorosulfinates (**2**) as interesting intermediates in the reaction.

(3) D. Tommasi, *Ber.*, **7**, 826 (1874).

Actually, when the reaction of thiobenzoic acid with thionyl chloride was carried out in concentrated solution, benzoyl thiochlorosulfinate (**2a**, R = Ph) was isolated. On standing at room temperature, **2a** decomposed in half a day to benzoic anhydride, benzoyl chloride, and sulfur. When **2a** was immediately allowed to react with *p*-nitrothiobenzoic acid, **3b** was obtained in a good yield.

Experimental Section

Materials.—Thioacetic acid and thiobenzoic acid were obtained commercially. Chlorothioacetic acid[4] and *p*-nitrothiobenzoic acid[5] were prepared by the methods of the literature. *p*-Chlorothiobenzoic acid, mp 70–71°, and *o*-methoxythiobenzoic acid, bp 101–103° (2 mm), were prepared in a way similar to the preparation of *p*-nitrothiobenzoic acid.

Symmetrical Diacyl Dithiosulfites (1a–f).—To a solution of 0.10 mol of thiocarboxylic acid in 150 ml of ether, 0.05 mol of thionyl chloride in 10 ml of ether was added dropwise over 0.5-hr period at −60 to −40°. The stirring was continued for additional 2 hr and then the temperature of the mixture was allowed to rise to −20 to −10°. The precipitated material was collected by filtration, washed with ether, and dried to obtain **1a–f**. The results are shown in Table I.

Decomposition of 1a.—**1a** (20.0 g, 0.11 mol) was heated at 75–80° for 1 hr under nitrogen atmosphere. On standing at room temperature, the mass turned to a yellow liquid mixed with elementary sulfur. Distillation of the liquid gave 6.5 g of acetic anhydride, bp 58–59° (39 mm).

Decomposition of 1c.—**1c** (19.2 g, 0.06 mol) was heated at 110–115° for 1 hr under nitrogen atmosphere. On standing at room temperature, the mass turned to a yellow liquid mixed with elementary sulfur. Distillation of the liquid gave 5.2 g of benzoic anhydride, bp 160–163° (1.5 mm).

Unsymmetrical Diacyl Dithiosulfites (3a–e).—To a solution of 0.02 mol of thionyl chloride in 60 ml of ether, 0.02 mol of thiocarboxylic acid in 20 ml of ether was added dropwise over 0.5-hr period at −40°. After the stirring was continued for additional 0.5 hr at −40°, 0.02 mol of another thiocarboxylic acid in a mixture of 10 ml of ether and 10 ml of THF[6] was added dropwise for 1 hr at −40°. The stirring was continued for additional 2 hr and then the temperature of the mixture was allowed to rise to −5°. The precipitated material was collected by filtration, washed with ether, and dried to obtain **3a–e**. The results are shown in Table I.

Benzoyl Thiochlorosulfinate (2a).—To a solution of 19.0 g (0.16 mol) of thionyl chloride in 30 ml of ether, 11.0 g (0.08 mol) of thiobenzoic acid in 10 ml of ether was added dropwise for 0.5 hr at −40°. The stirring was continued for additional 1 hr and

(4) F. Arndt and N. Bekir, *Ber.*, **63**, 2390 (1930).

(5) A. M. Khaletskii and A. M. Yanovitskaya, *Zh. Obshch. Khim.*, **19**, 1193 (1949).

(6) *o*-Methoxythiobenzoic acid was dissolved in 20 ml of ether.

then the temperature of the mixture was allowed to rise to −20°. The precipitated material was collected by filtration, washed with petroleum ether, and dried to obtain 8.0 g (45%) of **2a** as white solid: mp 39–42°; ir (CS_2) 1665 (C=O), 1215 cm^{-1} (S → O).

Anal. Calcd for $C_7H_5ClO_2S_2$: C, 38.10; H, 2.28. Found: C, 38.68; H, 2.55.

Decomposition of 2a.—When 19.0 g (0.086 mol) of **2a** was allowed to stand at room temperature for 1 day, the mass turned to a yellow liquid mixed with elementary sulfur. Fractional distillation of the liquid gave 3.0 g of benzoyl chloride, bp 55–56° (4 mm), and 5.5 g of benzoic anhydride, bp 160–165° (1.5 mm).

Benzoyl *p*-Nitrobenzoyl Dithiosulfite (3b).—This sulfite was prepared by the reaction of 4.41 g (0.02 mol) of **2a** in 60 ml of ether with 3.66 g (0.02 mol) of *p*-nitrothiobenzoic acid in a mixture of 10 ml of ether and 10 ml of THF at −40°. The precipitated material was collected by filtration to obtain 6.79 g (93%) of **3b**, mp 129–130°.

Registry No.—**1a**, 41118-48-3; **1b**, 41118-49-4; **1c**, 41118-50-7; **1d**, 41118-51-8; **1e**, 41118-52-9; **1f**, 41118-53-0; **2a**, 41118-54-1; **2d**, 41118-55-2; **3a**, 41118-56-3; **3b**, 41118-57-4; **3c**, 41118-58-5; **3d**, 41118-59-6; **3e**, 41118-60-9; RCOSH (R = CH_3), 507-09-5; RCOSH (R = $ClCH_2$), 867-49-2; RCOSH (R = C_6H_5), 98-91-9; RCOSH (R = *p*-ClC_6H_4), 31143-03-0; RCOSH (R = *p*-$O_2NC_6H_4$), 39923-99-4; RCOSH (R = *o*-$CH_3OC_6H_4$), 41118-62-1; thionyl chloride, 7719-09-7; acetic anhydride, 108-24-7; benzoic anhydride, 93-97-0; benzoyl chloride, 98-88-4.

The Reaction of Phenyllithium with Cinnamyl Chloride

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Received January 22, 1973

The reaction of phenyllithium with cinnamyl chloride has been found to form the following mixture of hydrocarbons in the per cent yields indicated based on the cinnamyl chloride used: 3,3-diphenyl-1-propene (**1**) (0.2), *cis*-1,3-diphenylpropene (**2**) (0.2), *trans*-1,3-diphenylpropene (**3**) (23.1), *cis*-1,2-diphenylcyclopropane (**4**) (0.8), *trans*-1,2-diphenylcyclopropane (**5**) (12.8), 1,1-diphenyl-1-propene (**6**) (1.2), 1,6-diphenyl-1,5-hexadiene (**7**) (5.2), 1,6-diphenyl-1,3,5-hexatriene (**8**) (5.6), and benzylacetylene (**9**) (35.7). Identification of the various compounds was made by comparing their retention times and ir and nmr spectra with those of authentic samples.

The first five compounds are similar to those formed in the reaction of phenyllithium with 1-halo-2-butenes[2] and result by either displacement reactions of phenyllithium on cinnamyl chloride (**1**, **2**, **3**)[3] or through an intermediate carbene followed by cyclization to phenylcyclopropene that reacts further with phenyllithium and forms **4** and **5**.[4] The ratio (94.1:5.9) of *trans*-1,2-diphenylcyclopropane (**5**) to *cis*-1,2-diphenylcyclopropane (**4**) found was similar to that (94:6) found for the 1-methyl-2-phenylcyclopropanes[2] and substantiated such a reaction.

The formation of the other products isolated can be rationalized in the following manner. 1,1-Diphenyl-1-propene (**6**) is formed by the isomerization of **1** by phenyllithium or by heat. 1,6-Diphenyl-1,5-hexadiene (**7**) is produced by the chlorine–lithium exchange

$$C_6H_5CH{=}CHCH_2Cl \xrightarrow{C_6H_5Li} C_6H_5CH{=}CHCH_2Li \xrightarrow{C_6H_5CH{=}CHCH_2Cl} \mathbf{7}$$

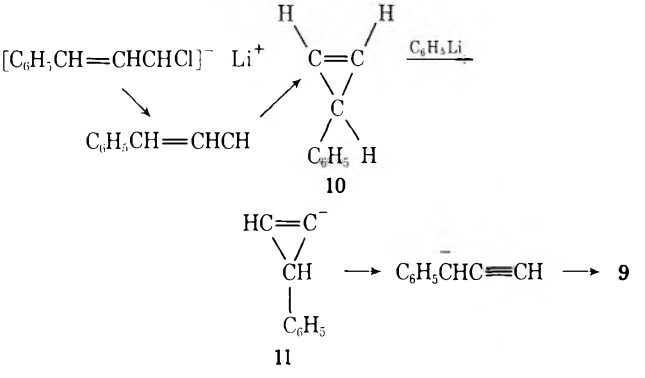
of cinnamyl chloride followed by coupling with another molecule of cinnamyl chloride.

1,6-Diphenyl-1,3,5-hexatriene (**8**) is probably formed by the dimerization of the intermediate carbene. Evidence for its presence in the crude reaction mixture was obtained by ultraviolet spectroscopy; a curve was obtained with three shoulders corresponding to the absorption peaks for the triene at 372, 353, and 336 nm. These peaks were better developed in the uv examination of the fraction boiling at 115–140° obtained by distillation of the mixture at reduced pressure (0.8 mm). This temperature is below that required to isomerize the diolefin **7** to the triene.[5]

Benzylacetylene (**9**) is probably formed by an elimination of hydrogen chloride from cinnamyl chloride with the formation of phenylallene, which would be isomerized by phenyllithium to **9**.

A second possible source of **9** is the intermediate phenylcyclopropene (**10**) formed by the action of phenyllithium on cinnamyl chloride.[4]

The vinyl hydrogens in cyclopropenes are acidic[6] enough to react with phenyllithium and form a carbanion (**11**) which would isomerize to **9**. Such a re-



arrangement of a cyclopropene to an acetylene has thus far been only carried out thermally with cyclopropene and 1-methylcyclopropene.[7]

Attempts to prepare 3-phenylcyclopropene for the verification of this reaction were not successful. The reaction of phenylacetylene with methylene iodide and zinc–copper couple gave methylphenylacetylene. Lead tetraacetate oxidation and electrolytic oxidation of 3-phenylcyclopropane-*cis*-1,2-dicarboxylic acid[8] gave no hydrocarbon products. Thermolysis of 3-phenylcyclopropane-*trans*-1,2-di-*tert*-butyl perester gave acetone, methanol, and polymer.

(1) Abstracted in part from the Ph.D. Thesis of A. R. Z., 1966.
(2) S. Wawzonek, B. J. Studnicka, and A. R. Zigman, *J. Org. Chem.*, **34**, 1316 (1969).
(3) R. M. Magid, E. C. Nish, and R. D. Gandour, *J. Org. Chem.*, **36**, 2099 (1971).
(4) J. G. Welch and R. M. Magid, *J. Amer. Chem. Soc.*, **89**, 5300 (1967).
(5) H. P. Koch, *J. Chem. Soc.*, 1111 (1948).
(6) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **85**, 99 (1963).
(7) R. Srinivasan, *J. Amer. Chem. Soc.*, **91**, 6250 (1969).
(8) S. Wawzonek and R. A. Zigman, *Org. Prep. Proced.*, **1**, 243 (1969).

Experimental Section[9]

Reaction of Phenyllithium with Cinnamyl Chloride.—A solution of phenyllithium (0.5 mol) prepared by treating lithium metal (10 g) with bromobenzene (80 g) in ether (500 ml) and filtering was added dropwise to a solution of cinnamyl chloride[10] (38 g, 0.25 mol) in ether (100 ml) and the resulting mixture was refluxed for 2 hr and then decomposed cautiously with water, since the reaction was very exothermic owing to the presence of phenyllithium. The ether layer after washing with water and drying gave a liquid (48 g) which upon distillation at 16 mm gave a fraction (18 g) boiling at 30–60°. Vpc analysis on a 10 ft × 0.375 in. column packed with 1% Carbowax 20M on Gas-Chrom P 100/200 mesh indicated the presence of bromobenzene (35.8%), benzylacetylene (57.5%), and a third compound (6.7%) which was present in insufficient quantity for identification. The retention times were 18.2, 27.8, and 32.4 min, respectively. The experimental conditions were as follows: column temperature, 200°; detector and injection port temperature, 300°; helium pressure, 30 psi; helium flow rate, 60 ml/min. Preparative vpc gave a sample of benzylacetylene which had an ir and nmr spectra similar to that of an authentic sample:[11] ir (neat) 4.71 μ (C≡C); nmr (neat) 7.19 (s, 5, C_6H_5), 3.40 (d, 2, CH_2), 2.06 (t, 1, ≡CH, J = 2.8 Hz).

The residue from the distillation was chromatographed on silica gel using 60–68° petroleum ether–benzene (75:25) as an eluent and gave 22 g of material which was analyzed by vpc on a 10 ft × 0.375 in. column containing 10% Apiezon L on 100/200 mesh Gas-Chrom P; column temperature, 250°; detector and injection port temperatures, 300°; helium gas flow, 60 ml/min; helium pressure, 30 psi. The compounds indicated and identified with their relative percentages exclusive of biphenyl are 1,1-diphenyl-1-propene (2.7), 3,3-diphenyl-1-propene (0.56), *cis*-1,2-diphenylcyclopropane (1.86), *cis*-1,3-diphenylpropene (0.37), *trans*-1,2-diphenylcyclopropane (28.14), *trans*-1,3-diphenylpropene (51), 1,6-diphenyl-1,5-hexadiene (7), and 1,6-diphenyl-1,3,5-hexatriene (7.4). The retention times were 20.7, 23.2, 26, 33.7, 41.5, 46.5, 66.7, and 86.5 min, respectively. 1,1-Diphenyl-1-propene,[12] 3,3-diphenyl-1-propene,[12] *cis*-1,3-diphenylpropene,[13] 1,6-diphenyl-1,5-hexadiene,[5] and 1,6-diphenyl-1,3,5-hexatriene[14] were identified by comparing their retention time with those of authentic samples. *cis*-1,2-Diphenylcyclopropane, *trans*-1,2-diphenylcyclopropane,[15] and *trans*-1,3-diphenylpropene[12] were separated by preparative vpc and identified by comparison of their ir and nmr spectra with those of authentic samples.

Reaction of Phenylacetylene with Methylene Iodide and Zinc–Copper Couple.—A suspension of zinc–copper couple (10 g)[16] in ether (75 ml) was treated with a solution of methylene iodide (28 g) in ether (75 ml) and the resulting mixture was treated dropwise at reflux with phenylacetylene (10 g) and heated for 30 hr. Treatment with water followed by separation of the ether layer resulted in a liquid (17 g) which consisted of phenylacetylene (62%) and methylphenylacetylene (38%).

3-Phenylcyclopropane-*trans*-1,2-di-*tert*-butyl Perester.—A solution of the acid chloride of 3-phenylcyclopropane-*trans*-1,2-dicarboxylic acid, prepared by treating the acid (6.7 g) with thionyl chloride (9.5 g) in ether (100 ml) containing pyridine (8.1 ml), was treated dropwise at −40° with *tert*-butyl hydroperoxide (20 ml). The resulting solution was stirred for 2 hr at this temperature and for 3 hr at 0°, and then allowed to stand at room temperature for 12 hr. The resultant semisolid solution was treated with water and the resulting ether layer was washed with water, 10% sulfuric acid, sodium bicarbonate, and water. Removal of the ether gave an oil which was chromatographed on silica gel using pentane and 10% ether as eluents. The resulting solid after recrystallization from methanol–water melted at 79–81°, yield 2.1 g. A second recrystallization from the same mixture gave a sample melting at 83–85°: ir (Nujol) 5.65, 5.69 μ (COOC$_4H_9$); nmr ($DCCl_3$) δ 7.20 (s, 5, C_6H_5), 2.4–3.4 (m, 3, 3 H), 1.33 [s, 9, $C(CH_3)_3$ cis to C_6H_5], and 1.13 [s, 9, $C(CH_3)_3$ trans to C_6H_5].

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.43. Found: C, 65.18; H, 7.62.

Thermal gravimetric analysis using a heating rate of 3°/min indicated that the perester started to decompose at 125°; 60% weight loss occurred at 170°.

Registry No.—Phenyllithium, 591-51-5; cinnamyl chloride, 102-92-1; 3-phenylcyclopropane-*trans*-1,2-di-*tert*-butyl perester, 41563-54-6; 3-phenylcyclopropane-*trans*-1,2-dicarboxylic acid chloride, 41563-55-7; *tert*-butyl hydroperoxide, 75-91-2.

(9) Boiling points are not corrected; melting points are corrected. Infrared spectra were obtained using films of undetermined thickness between sodium chloride windows and a Perkin-Elmer 21 double-beam recording spectrophotometer. Nmr spectra were obtained with a Varian A-60 nmr spectrometer. Ultraviolet spectra were determined with a Cary 14 spectrometer using cyclohexane as a solvent. Vapor phase chromatographic analyses were carried out with a F & M 5750 dual column gas chromatograph equipped with a thermal conductivity detector. Peak areas were used in calculating the per cent yields of the hydrocarbons. Preparative vapor phase chromatographic separations were carried out with an F & M Model 500 gas chromatograph outfitted with a Model 720 oven.

(10) H. Gilman and S. A. Harris, *Recl. Trav. Chim. Pays-Bas*, **50**, 1052 (1931). The nmr spectrum indicated that only the trans isomer was present.

(11) J. E. Mulvaney, T. L. Folk, and D. J. Newton, *J. Org. Chem.*, **32**, 1674 (1967).

(12) P. Sabatier and M. Murat, *Ann. Chim. (Paris)*, **4**, 287 (1951).

(13) E. K. Raunio and W. A. Bonner, *J. Org. Chem.*, **31**, 396 (1966).

(14) T. Curtius and R. Jay, *J. Prakt. Chem.*, [2] **39**, 27 (1889).

(15) D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, **83**, 4839 (1961).

(16) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

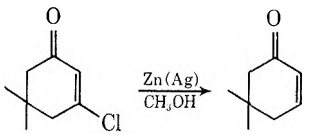
Communications

See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

The Reduction of β-Halo-α,β-Unsaturated Ketones

Summary: β-Chloro-α,β-unsaturated ketones are reduced to α,β-unsaturated ketones by silver-promoted zinc dust in methanol.

Sir: We have found that silver-promoted zinc dust in methanol is an efficient reagent for the reduction of β-halo-α,β-unsaturated ketones to the corresponding α,β-unsaturated ketones; *i.e.*, **1** → **2**. The reducing



1 **2**

agent is prepared by a modification of Conia's procedure.[1] A procedure for the conversion of **1** to **2** follows.

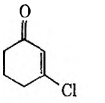
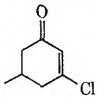
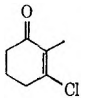
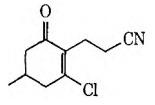
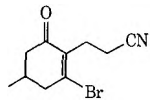
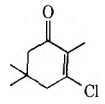
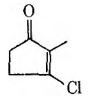
Zinc dust (Mallinckrodt Analytical Reagent, 2.1 g) is stirred for 4 min with 10 ml of 10% aqueous HCl. The supernatant liquid is decanted and the zinc is washed with acetone (2 × 10 ml) and ether (10 ml). A suspension of 60–70 mg of anhydrous silver acetate in 10 ml of boiling acetic acid is then added. After the mixture is stirred for 1 min, the supernatant is again decanted and the black zinc–silver couple is washed with acetic acid (5 ml), ether (4 × 10 ml), and methanol (10 ml). To the moist couple is added a solution of 1 g of chloroenone **1** in 3 ml of methanol. The reduction is exothermic and glpc analysis shows it to be complete after being stirred vigorously at room temperature for 15–30 min. The spent zinc is filtered off and washed with 30 ml of methanol. The methanol is then evaporated under reduced pressure to give a gel which is partitioned between ether and 10% aqueous HCl. The ether layer is dried and evaporated to yield the crude enone **2**. Distillation of the combined product from five similar runs yielded 3.17 g (81%) of enone **2** as a clear liquid. In a large-scale run (21 g of zinc dust, 10 g of chloroenone **1**), the reaction was much slower, requiring about 6 hr for completion.

Other β-haloenones are also reduced by the procedure. When there is an alkyl substituent in the α position, the reduction is much slower but is complete in about 1 day at room temperature. One compound, 3-chloro-2,5,5-trimethylcyclohexenone (**8**), is reduced to the extent of only 58% after 37 hr. Data are collected in Table I.

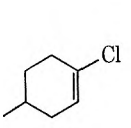
The simple vinyl chloride **10**, the dichlorodiene **11**, *p*-bromoethylbenzene, and α-bromobenzoic acid are not reduced to any noticeable extent after 24 hr.

β-Chloroenones **3**, **4**, **5**, **6**, **8**, and **9** were prepared by treating a suspension of the corresponding 1,3-diketone with oxalyl chloride in benzene or chloroform. β-Bromoenone **7** was prepared from the 1,3-diketone and phosphorus tribromide.

TABLE I
REDUCTION OF β-HALOENONES

Reactant	No.	Reaction time	Yield,[a] %
	3	1.5 hr[b]	75
	4	30 min	75
	5	40 hr	77
	6	24 hr	93
	7	30 min	81
	8	37 hr	*c*
	9	26 hr	65

[a] Isolated yield. [b] Reaction carried out at 0°. At room temperature, the chloroenone reacts with methanol. [c] After 37 hr, glpc analysis shows that the original chloroenone is 58% reduced.



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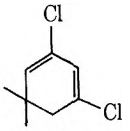

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(1) J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, **5**, 549 (1972).

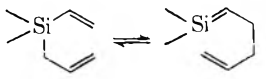
Silicon-Cope Rearrangement. Reversible Formation of a Silicon–Carbon Double Bond

Summary: Evidence has been adduced for a Cope rearrangement in propenylallyldimethylsilanes involving the intermediacy of (what has been regarded as a high energy) double bonded silicon intermediate.

Sir: Currently there is considerable interest in compounds possessing a silicon–carbon double bond. Although no such stable, isolable compounds[1] have been reported, their intermediacy has been implicated in a number of examples. The trapping of $(CH_3)_2Si{=}CH_2$ generated by (1) the pyrolysis of 1,1-dimethyl-1-silacyclobutane[2-4] and (2) the retroene reaction of allyltrimethylsilane[5a] has been reported.[5b-d] The formation of $(Ph)_2Si{=}CH_2$ by photolysis of 1,1-diphenyl-1-silacyclobutane[6] or pentaphenylmethyldisilane[7] has also been reported. Recently the first spectroscopic observation of a silicon–carbon doubly bonded compound was obtained at −196°.[8] Theoretical aspects of the silicon–carbon π bond have been reviewed.[9]

We were interested in whether such silyl olefins could, in general, be generated by concerted, thermal rearrangements. The superior migratory aptitude of silicon in sigmatropic rearrangements has been demonstrated in 5-trimethylsilylcyclopentadiene[10] and 1-trimethylsilylindene[11] and more recently in allylsilanes.[12] The participation of silicon in pericyclic transition states which lead to a doubly bonded silicon has not been reported in the literature.

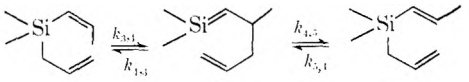
The reaction selected for study was the [3,3] sigmatropic or Cope rearrangement. The possibility of observing **2** (eq 1) by conventional methods in an equi-



(1)

1 2

librium mixture seemed remote because the equilibrium is expected to greatly favor **1** owing to the greater stability of the carbon–carbon double bond. Therefore, an experiment which could detect the intermediacy of **2** was devised. It was expected that, if the reversible Cope rearrangement occurred, the interconversion (eq 2) of *cis*- and *trans*-propenylallyldimethylsilane (**3** and **5**)[13] would be revealed. The analogous inter-



(2)

3 4 5

conversion of *cis*- and *trans*-1,5-heptadiene has already been studied in detail by Frey and Solly.[14]

We have found that *cis*- and *trans*-propenylsilanes, **3** and **5**, were interconvertible upon gas phase thermolysis in a gold reactor flow system[15] at temperatures above 500° and reaction times >1 sec. At 560° the equilibrium mixture consisted of 21% **3** and 79% **5**. Reaction kinetics[16] were studied over the temperature range of 500–580°, and least-squares analysis of the kinetic data yielded the following Arhenius parameters: E_a = 39.2 ± 0.4 kcal/mol and log A = 9.93 ± 0.12. The relatively low preexponential factor is not uncommon for Cope rearrangements.[14,17] Since the calculated activation parameters correlate with the reactions given by $k_{3,4}$ and $k_{5,4}$, it is seen that these reactions require only ~3-kcal/mol greater activation energy than the corresponding all-carbon heptadienes.[14,18] This small activation energy difference may at first glance seem surprising because it does not appear to reflect a much greater energy requirement for the formations of a silicon–carbon double bond. However, coupled with analogous results obtained in these laboratories on the retroene reaction of allyltrimethylsilane (**6**, E_a = 55.9 kcal/mol, log A = 12.55) and 3,4-dimethyl-1-pentene (**7**, E_a = 53.6 kcal/mol, log A = 13.25), an explanation emerges. The ~10-kcal/mol greater E_a for the all-carbon substrate, **7**, compared with certain oxygenated ones[19] is a reflection of the greater endothermicity of the former reaction (*i.e.*, C=C less stable than C=O).[20,21] In the case of silicon, moreover, preliminary results indicating approximately the same E_a for analogous oxygenated[22] and nonoxygenated[22] substrates appear to reflect the smaller difference in endothermicity between these reactions (*i.e.*, Si=C *vs.* approximately Si=O).[23,24] It could, therefore, be the enhanced ability of silicon to participate in pericyclic transition states which partially compensates the greater energy requirement for the formation of the less stable, multiply bonded silicon.[23] The larger 3p orbitals of silicon may be held responsible for the difference in reactivity.

(1) Compounds of the type $R_2Si{=}CH_2$ are "unstable" in the reactivity sense, *i.e.*, tend to dimerize.

(2) L. E. Gusel'nikov and M. C. Flowers, *J. Chem. Soc., Chem. Commun.*, 864 (1967).

(3) M. C. Flowers and L. E. Gusel'nikov, *J. Chem. Soc. B*, 419 (1968).

(4) D. N. Roark and L. H. Sommer, *J. Chem. Soc., Chem. Commun.*, 167 (1973).

(5) (a) W. J. Bailey and M. S. Kaufmann, Abstracts of the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, p Org 55; (b) T. J. Barton and E. Kline, *J. Organometal. Chem.*, **42**, C21 (1972); (c) R. P. Clifford, B. G. Gowenlock, C. A. F. Johnson, and J. Stevenson, *ibid.*, **34**, 53 (1972); (d) I. M. T. Davidson and C. A. Lambert, *J. Chem. Soc. A*, 782 (1971).

(6) P. Boudjouk and L. H. Sommer, *J. Chem. Soc., Chem. Commun.*, 54 (1973).

(7) P. Boudjouk, J. R. Roberts, C. M. Goleno, and L. H. Sommer, *J. Amer. Chem. Soc.*, **94**, 7926 (1972).

(8) T. J. Barton and C. L. McIntosh, *J. Chem. Soc., Chem. Commun.*, 861 (1973).

(9) C. J. Attridge, *Organometal. Chem Rev.*, **5** (A), 323 (1970).

(10) See, for examples, E. W. Abet, M. O. Dunster, and A. Waters, *J. Organometal. Chem.*, **49**, 287 (1973).

(11) A. J. Ashe III, *Tetrahedron Lett.*, 2105 (1970).

(12) H. Kwart and J. Slutsky, *J. Amer. Chem. Soc.*, **94**, 2515 (1972).

(13) *cis*- and *trans*-propenylallyldimethylsilanes and *cis*- and *trans*-propenyltrimethylsilanes were prepared by the reaction of propenylmagnesium bromide (mixture of cis and trans) in tetrahydrofuran with allyldimethylchlorosilane and trimethylchlorosilane, respectively. Pure samples of each isomer were obtained by preparative glc on a 12-ft 10% Apiezon L column.

(14) H. M. Frey and R. K. Solly, *Trans. Faraday Soc.*, 1858 (1968).

(15) H. Kwart, S. F. Sarner, and J. H. Olsen, *J. Phys. Chem.*, **73**, 4056 (1969).

(16) Kinetic analysis was carried out as follows. Since the concentration of **4** is very much smaller than those of **3** and **5**, **4** is treated as a reactive intermediate. The equilibrium then simplified to

$$3 \underset{k_R}{\overset{k_F}{\rightleftharpoons}} 5$$

and the kinetic expression for the simplified equilibrium is

$$\ln [(A_o - A_e)/(A - A_e)] = kt$$

where k is the rate constant for the first-order approach to equilibrium ($k_F + k_R$).

(17) H. M. Frey and D. H. Lister, *J. Chem. Soc. A*, 26 (1967).

(18) M. R. Willicott, R. L. Cargill, and A. B. Sears, *Progr. Phys. Org. Chem.*, **9**, 25 (1972).

(19) Methyl allyl ether (E_a = 41.6 kcal/mol), ethyl vinyl ether (E_a = 44.1 kcal/mol), 3-buten-1-ol (E_a = 41.0 kcal/mol): results of these laboratories.

(20) For example, 1-pentene → propene + ethylene ($\Delta H_R°$ = +2.3 kcal/mol). Calculated by S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968.

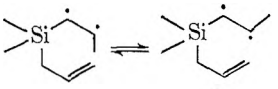
(21) This concept will be elaborated upon in another article which will be submitted for publication in the near future. A referee has questioned the validity of comparing these relative endothermicities. The question of seeing this factor reflected in the activation energy requirements of the respective reactions will be treated in this forthcoming article.

(22) For examples, $R_2HSiOCH_2CH{=}CH_2$ and $R_2HSiCH_2CH_2CH{=}CH_2$.

(23) R. Walsh, *J. Organometal. Chem.*, **38**, 245 (1972).

(24) I. M. T. Davidson and J. M. Thompson, *J. Chem. Soc. D*, 251 (1971).

Alternative mechanisms for the interconversion of **3** and **5** have been considered. It is well known that cis–trans isomerization of olefins[18] occurs upon heating to sufficiently high temperature, presumably *via* a biradical intermediate. To evaluate this possibility, a model compound, *cis,trans*-propenyltrimethylsilane[13] was prepared and thermolyzed. It was found that nearly 100° higher temperatures were required to effect isomerization. This result could have been anticipated if the activation parameters were similar to those of the diradical course of 2-butene thermal isomerization (E_a = 63 kcal/mol, log A = 13.8).[25] It would suggest that a reaction course for isomerization of **3** to **5** passing through the diradical intermediate **8** would have an



8

activation requirement >20 kcal higher than observed. Several other alternative mechanistic possibilities can be regarded as unlikely, and in the interests of brevity will not be discussed.

This work clearly indicates that the enhanced ability of silicon to participate in pericyclic transition states may lead to the reversible or irreversible formation of multiply bonded silicon.

(25) R. B. Cundall and T. F. Palmer, *Trans. Faraday Soc.*, **57**, 1936 (1961).

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RECEIVED JUNE 12, 1973

Selective Reduction of Aromatic Carboxyl Groups to Methyl in the Presence of Ester Functionality. A New Procedure for the Preparation of Ester-Containing Organosilanes

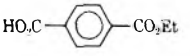
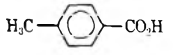
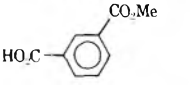
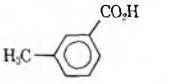
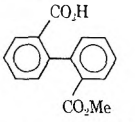
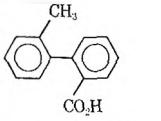
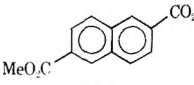
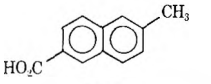
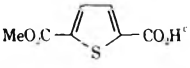
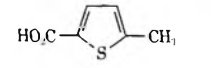
Summary: New synthetic procedures for the selective reduction of the carboxyl group of aromatic half-esters to methyl and for the preparation of benzylic silanes containing ester groups is described.

Sir: It is well documented that ester groups can usually be reduced with relative ease while carboxyl groups are relatively resistant to reduction. Further, reduction of a carboxyl group usually results in the production of aldehydes[1] or alcohols.[2]

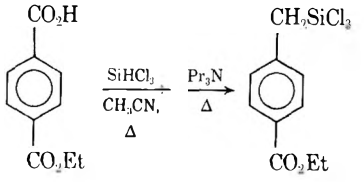
Previously[3] we reported the unprecedented reduction of aromatic carboxyl groups directly to methyl groups by the use of a trichlorosilane–*tert*-amine combination. In an endeavor to extend the scope of this reduction, we attempted to reduce aromatic esters under the same conditions. Surprisingly, esters like ethyl benzoate and phenyl benzoate were totally unreactive and could be recovered virtually unchanged.[4] This immediately raised the possibility that aromatic half-esters might be made to undergo reduction of the carboxyl group to a methyl while the ester group would be left intact. Accordingly the "one-pot" reduction procedure developed earlier[3] was applied to a representative series of aromatic half-esters with the results depicted in Table I. As will be noted from this table the unreduced ester groups were saponified by the base treatment employed to cleave the intermediate benzylic silanes. In the case of ethyl hydrogen terephthalate (entry 1 of table) the intermediate benzylic silane was isolated and characterized in a 79% yield. Benzylic silicon–carbon cleavage of this product was achieved

TABLE I

SELECTIVE REDUCTION OF AROMATIC HALF-ESTERS

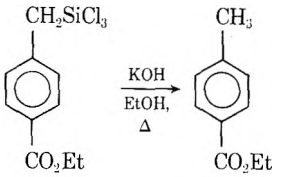
Entry	Half-ester	Product[a]	Yield[b], %
1			64
2			42
3			41
4			37
5			26

[a] Satisfactory agreement with literature melting points and spectral correlations were obtained for all products. [b] Based on weight of starting half-ester. [c] New compound which gave satisfactory analysis and spectral correlation.



(79%)

with a slight excess of base in only 0.5 hr. to give a 75% yield of *p*-ethyl toluate. The ester was not saponified under these conditions.



(75%)

While this investigation is still in its preliminary stages, the results to date suggest that the procedures

(1) S. Ono and T. Yamauchi, *Bull. Chem. Soc. Jap.*, **25**, 404 (1952); H. A. Staab and H. Braunling, *Justus Liebigs Ann. Chem.*, **654**, 119 (1962).

(2) V. Bazant, *et al.*, *Tetrahedron Lett.*, 3303 (1968); H. S. Broadbent, G. C. Campbell, W. J. Bartley, and J. H. Johnson, *J. Org. Chem.*, **24**, 1847 (1959); H. C. Brown and B. C. Subba Rao, *ibid.*, **22**, 1135 (1957); H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **77**, 3164 (1955); R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 2548 (1947).

(3) R. A. Benkeser, K. M. Foley, J. M. Gaul, and G. S. Li, *J. Amer. Chem. Soc.*, **92**, 3232 (1970).

(4) Unpublished studies by Robert T. Roche of our laboratory.

herein described not only provide for a unique reduction of aromatic half-esters, but can be used as a one-step method for preparing benzylic silanes containing ester groups—compounds not readily accessible at the present time.

p-**Carboethoxybenzyltrichlorosilane.**—To 10 g (52 mmol) of ethyl hydrogen terephthalate and 40 ml of acetonitrile was added 32 ml (0.32 mol) of trichlorosilane. The resulting solution was stirred at reflux for 1 hr. It was then cooled to 0° as 30 ml (0.16 mol) of tri-*n*-propylamine was rapidly added. This solution was refluxed for 16 hr, followed by addition of 500 ml of diethyl ether. After storage in a cold room for a few hours, the tri-*n*-propylamine hydrochloride precipitate was removed by filtration. Solvent removal followed by distillation *in vacuo* gave 13.4 g of product, bp 110–115° (0.85 mm), mp 72–73°, which was purified for analysis by vpc (10% SE-30 on Chromosorb A, 10 ft × $^3/_8$ in.).

Anal. Calcd for $C_{10}H_{11}Cl_3SiO_2$: C, 40.35: H, 3.73: Cl, 35.73: Si, 9.44. Found: C, 40.34: H, 3.93: Cl, 35.53: Si, 9.43.

Ethyl *p*-**Toluate.**—A solution of 9.4 g (30 mmol) of *p*-carboethoxybenzyltrichlorosilane in 100 ml of ethanol was refluxed for 1 hr. Potassium hydroxide (2.2 g, 33 mmol) in 50 ml of ethanol was added to the refluxing solution over a 15-min period. The addition was accompanied by the evolution of hydrogen chloride gas and the formation of a flocculent precipitate. An additional 4.1 g (62 mmol) of potassium hydroxide was added to make the solution just basic to Hydrion paper. After 0.5 hr at reflux, the solution was decanted and filtered. The filtrate was diluted with 500 ml of water and then extracted with four small portions of diethyl ether. The usual work-up followed by distillation resulted in 3.7 g (75%) of ethyl *p*-toluate [bp 75° (1.9 mm), lit.[5] bp 111° (13 mm)].

General Procedure for the Reduction of Half-Esters to Methyl-Substituted Carboxylic Acids.—The reduction of ethyl hydrogen terephthalate is described. The other half-esters in Table I were reduced in a similar fashion.

The procedure was the same as above up to the distillation *in vacuo*. Instead, the brown oily residue was combined with 50 ml of methanol and refluxed for 1 hr. To this mixture was added slowly with cooling 29 g (0.5 mol) of potassium hydroxide in 100 ml of methanol and 25 ml of water. The resulting mixture was refluxed for 19 hr, then diluted with 750 ml of water and filtered. The filtrate was treated with dilute hydrochloric acid until precipitation of all of the carboxylic acid was complete. The crude brown product was purified by sublimation to give 4.5 g (64% yield) of *p*-toluic acid.

Acknowledgment.—We are grateful to the National Science Foundation (GP 12049) whose financial assistance made this work possible.

(5) E. W. Timm and C. N. Hinshelwood, *J. Chem. Soc.*, 866 (1938).

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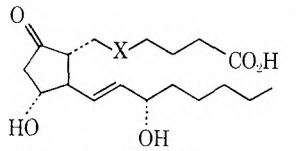
Transition Metal Ion Assisted Chromatography. Separation of Prostaglandins PGA_2 and PGB_2

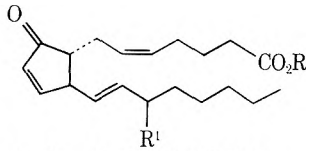
Summary: Using transition metal salts other than silver, chromatographic separations have been made that appear to be based on the metal ion complexing with carbon–oxygen double bonds.

Sir: Organic compounds differing either in number or geometry of carbon–carbon double bonds have traditionally been separated by chromatography on silver nitrate impregnated supports.[1]

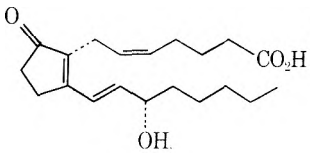
π-Complex formation between silver(I) ions and carbon–carbon double bonds forms the basis of such separations. Prostaglandins of the 2 series can be separated from those of the closely related 1 series, *e.g.*, PGE_1 (1) and PGE_2 (2), on silver nitrate systems.[2] However, this method fails[3] when applied to the difficult separation of prostaglandins PGA_2 (3) and PGB_3 (4).



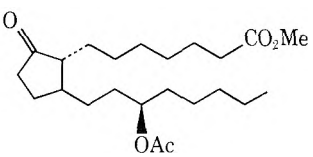
1, X = $-CH_2CH_2-$
2, X = cis-CH=CH-



3, R = H; R^1 = 15(S)-OH
5, R = Me; R^1 = 15(*R*)-OAc



4



6

Prostaglandin PGA_2 is easily isomerized to PGB_2 by both acid and base catalysis as well as by an isomerase in cat blood.[4] Because of this easy isomerization, methods for separating PGA_2 and PGB_2 are of importance to synthetic and metabolic studies. Such methods would also have utility for the purification of PGA_2 isolated from the coral *Plexaura homomalla*.

In the present investigation, an improved method of separation of these two compounds was sought. Precoated Brinkman tlc plates (0.25 mm, silicic acid) were impregnated with various transition metal salts by dipping the plates in a 10% solution of the salt in acetonitrile, ethanol, or a 50:50 mixture of these solvents. Table I contains the R_f values of PGA_2 (3),

TABLE I

R_f VALUE OF PROSTAGLANDINS ON SILICIC ACID PLATES[a] COATED WITH VARIOUS COMPLEXING METALS

Compd	Normal	$AgNO_3$	$NiCl_2$	$CoCl_2$	$FeCl_3$	$CrCl_3$
V[b]	0.36	0.41	0.37		0.34	0.37
VI[b]	0.43	0.55	0.45		0.48	0.45
PGA_2[c]	0.34	0.23	0.25	0.34	0.16	0.41
PGB_2[c]	0.34	0.27	0.25	0.35	0.23	0.41

[a] Brinkman 0.25-mm silicic acid plate. [b] 20% ethyl acetate in hexane as developing solvent. [c] 40% ethyl acetate, 1% HOAC in hexane as developing solvent.

(1) C. B. Barrett, M. S. J. Dallas, and F. B. Padley, *Chem. Ind. (London)*, 1050 (1962).
(2) K. Green and B. J. Samuelsson, *J. Lipid Res.*, **5**, 117 (1964).
(3) J. E. Shaw and P. W. Ramwell, *Methods Biochem. Anal.*, **17**, 325 (1969).
(4) R. L. Jones, *J. Lipid Res.*, **13**, 511 (1972).

PGB_2 (**4**), methyl 15(*R*)-acetoxy-9-oxo-5-*cis*,10,13-*trans*-prostatrienoate (5), and methyl 15(*R*)-acetoxyl-9-oxo-prostanoate (6) on Brinkman silicic acid plates and on plates additionally impregnated with transition metal ions. Complexing was indicated in all systems tried except possibly for chromium(III) chloride. Iron(III)-coated plates were the only ones that were effective for the clear separation of prostaglandins PGA_2 and PGB_2. Two competing factors appear to be influencing R_f values of the compounds. A partial deactivation of the silicic acid plates caused by the coating process gives rise to increased mobility compared to normal plates [similar to that seen for silver(I) ion plates]. Competing with deactivation is complexing between the metal ions and the substrate which retards the substrate's movement on the plate.

It is interesting that **6** which contains no carbon–carbon double bonds is retarded on iron(III) plates compared to silver nitrate plates. This suggested that the separation of PGA_2 and PGB_2 on iron(III) plates might be due to factors other than simple differential complexation of the iron(III) with the carbon–carbon double bonds of PGA_2 and PGB_2.[5]

It was demonstrated that 3,7,12-triketochlolanic acid is strongly retarded on iron(III) tlc plates (R_f 0.22, EtOAc–Bz–HOAc, 49.75:49.75:0.50) relative to uncoated plates (R_f 0.65) and plates coated with silver nitrate.[6] Ergosterol, however, was strongly retarded on silver nitrate plates (R_f 0.20, 17% EtOAc–hexane) relative to uncoated plates (R_f 0.38). Ergosterol (R_f 0.67) was only slightly retarded on iron(III) plates compared to cholesterol using 17% EtOAc–hexane as developing solvent. The $FeCl_3$ plates appear somewhat deactivated toward both sterols relative to uncoated plates.

Several different columns were tested for extending the results obtained from tlc to preparative column chromatography. On a column packed with a support made from 10% $FeCl_3$ coated on silicAR CC-4, elimination of the C-15 acetoxy group was complete during the time necessary for chromatography of the diester of 15-epi-PGA_2 (**5**) (obtained from *Plexaura homomalla*)—obviously iron(III) effects this elimination. Attempted purification of 15 epi-PGA_2 by chromatography over an iron(III)-impregnated column required large amounts of ethyl acetate in the eluting solvent mixture (75:25, hexane–ethyl acetate). This led to the elution of $FeCl_3$ as well as the prostaglandin. Probably this drawback can be overcome by using other solvents or a less soluble iron(III) salt. It was found that 10% $CuCl_2$ on silicic acid was effective for the purification of the sample of prostaglandin 15-epi-PGA_2 from *Plexaura homomalla*. This sample contained several small peaks by glc (as methyl esters) which were not separated by further column chromatography on silicic acid supports.[7] Chromatography on 10% $CuCl_2$ supported on silicAR CC-4 (support to sample ratio of 50:1) using a solvent of 25% ethyl acetate in hexane was sufficient to elute 15-epi-PGA_2 [217 nm (ϵ 10,800)] essentially pure by glc. Indications were any minor impurities could be removed using a higher support to compound ratio.

(5) R. L. Spraggins, *Proc. Food Drugs Sea Conf.*, **3**, in print (1972).

(6) Work done in the laboratory of Professor A. K. Bose (Stevens Institute of Technology) by Robert L. Spraggins and John J. Savarese.

(7) R. L. Spraggins, Doctoral Dissertation, University of Oklahoma, 1970.

(8) Now Research Scientist at Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Castle Point Station, Hoboken, N. J. 07030.

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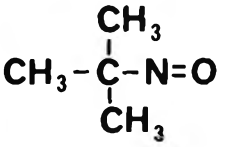

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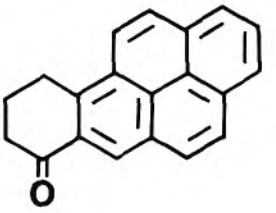
2-Methyl-2-nitrosopropane
"Spin-trap"
Accts. Chem. Res., **4,** 31 (1971).
1g 9.00 5g 38.00



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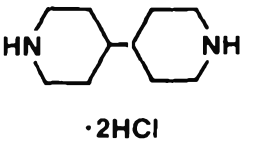
9,10-Dihydrobenzo[a]pyren-7(8H)-one
Precursor of benzo[a]pyrene
1g 9.00 5g 30.00



18,074-2
4,4'-Bipiperidine dihydrochloride
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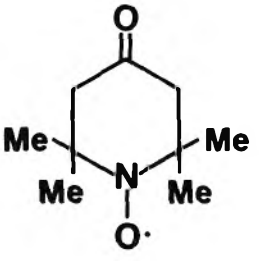

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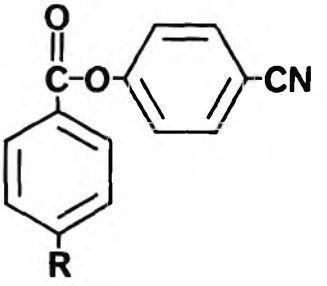
Spin label
1g 6.00 5g 20.00



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Proc. IEEE, **60,** 1002 (1972).
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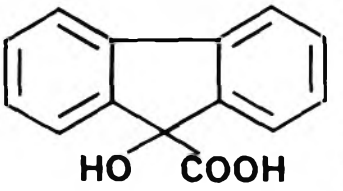
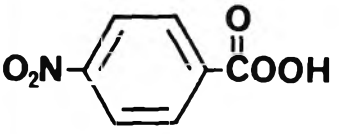
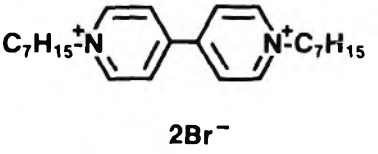
18,032-7 R=butyl 1g 16.00



18,063-7
9-Hydroxy-9-fluorene-carboxylic acid
Basic synthetic building block
25g 7.50 100g 24.00



18,044-0
***p*-Nitroperoxybenzoic acid,** tech. 85%
Oxidizing agent
5g 5.00 25g 16.00



18,085-8
***N,N'*-Diheptyl-4,4'-bipyridinium dibromide**
Viologen for electrochromic memory display
Appl. Phys. Letters, **23,** 64 (1973).
10g 20.00

18,038-6
2,2,2-Trifluoroethylamine hydrochloride
Basic synthetic building block
10g 15.00 50g 44.00

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Craftsmen in Chemistry

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