VOLUME 36 AUGUST 27, 1971 NUMBER 17 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, DEBORAH K. MILLER

Advertising Office: Century Communication Corporation, 142 East Ave., Norwalk, Conn. 06851.

Business and Subscription Information

Correspondence concerning business matters should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue plus time normally required for postal delivery of journal and claim; (2) if loss was due to failure to notify the Subscription Service Department of a change of address; or (3) if the reason for the claim is that a copy is "missing from files."

Change of address: Notify Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Such notification should include both old and new addresses and postal ZIP number, if any. Please send an old address label, if possible. Allow 4 weeks for change.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should issues of the current volume be out of print at the time the subscription order is received, the pro rata value of such issues will be refunded to the subscriber.

Subscriptions should be renewed promptly, to avoid a break in your series. Orders should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Subscription rates for 1971: $20.00 per volume to members of the ACS and $40.00 per volume to all others. Those interested in becoming members should write to the Admissions Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Add $4.50 per subscription for Canada and countries belonging to the Postal Union, and $5.50 for all other countries.

Single copies for current year: $2.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

This publication and the other ACS periodical publications are now available on microfilm. For information write to MICROFILM, Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Notice to Authors last printed in the issue of July 2, 1971

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 17 AUGUST 27, 1971

NOTES

AUTHOR INDEX

In papers with more than one author the name of the author to whom inquiries about the paper should be addressed is marked with an asterisk in the by-line.

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 17

AUGUST 27, 1971

Synthesis and Reactions of 5α,8-Epidioxyandrost-6-enes

WILLIAM F. JOHNS

Division of Chemical Research, G. D. Searle & Company, Chicago, Illinois 60680

Received May 30, 1969

Photooxygenation of 3β-hydroxyandrosta-5,7-dien-17-one (1) yields the 5α,8-epidioxide **2a** accompanied by the 5,8-dien-7-one **6a** and the two unsaturated 5α,6-epoxides **5a** and **9a**. The epidioxide **2a** undergoes a palladium-catalyzed reaction to yield first the triolone **3a** and then androsta-4,6,8(14)-triene-3,17-dione (**4a**). The 3-keto epidioxide **7** rearranges at room temperature in pyridine to the 4α,5-epoxide **8**. This epoxide is transformed to the 3,4-seco acid **12** in acetic acid and to the 4-hydroxytriene **11** in base.

Reports of the physiological potency of the estra-4,9,11- and 4,9,8(14)-trienes[1] led to studies which culminated in the synthesis of several estra-4,6,8(14)-trienes.[2] Accompanying this research were investigations dealing with the preparation of the analogous androstatrienes. The discovery of a high yield transformation of ergosterol epidioxide to ergosta-4,6,8(14)-trien-3-one with a palladium catalyst[3] greatly simplified this undertaking. Although other routes to this conjugated system have been described,[4] none could match the efficacy of this direct approach.

A. Photooxygenation of the 5,7-Dienes.—Oxygenation of an illuminated solution of the 3β-acetoxyandrosta-5,7-diene (1a 3-acetate) in the classical manner[5] (eosin sensitized, in ethanol) gave by direct crystallization the expected 5α,8-epidioxide **2a** (3-acetate). As anticipated, the product contained two additional oxygen atoms, showed no new functionality in the infrared, and exhibited a pair of doublets for the 6 and 7 protons in the nmr spectrum. Configurational assignment is by analogy to the ergosterol and cholesterol work.[6] The observed deshielding of the 18-methyl group in the nmr can be rationalized by noting, in a molecular model, the nearly coplanar relationship of the 18-methyl and the 6,7 double bond caused by the ring B boat conformation. The 19-methyl signal is also shifted downfield, an effect ascribed to the 5α,8-epidioxide bridge.[7] Despite the strained appearance of the model, the compound was relatively stable to a variety of reagents (see below).

The nmr spectrum of the photooxygenation mother liquors contained clear signals for the angular methyl groups and characteristic C-6 protons of three new components. Chromatographic separation of the mixture afforded first an unsaturated ketone (λ_{max} 245 nm) in 15% yield. The unperturbed 3-proton signal and that of a single vinyl proton (368 Hz) suggested the 5,8-dien-7-one structure **6a** (3-acetate).[8,9] A chemical synthesis later supported this postulation.

The second major by-product of the eosin-sensitized photooxygenation (10% yield) was the hydroxy oxide **9a**. The gross structure, suggested by spectral data, was confirmed chemically by oxidation of its 3-monoacetate to the unsaturated ketone **10** and subsequent potassium iodide reduction[10] to the 5,8-dienone **6a**, described above. Since this photooxygenation product **9a** was identical with one of the pyrolysis products of the epidioxide **2a**, the stereochemistry at C-5, -6, and -7 is presumably the same as that assigned to an ergosterol epidioxide pyrolysis product.[10] The position of the double bond was decided by comparison of the cal-

(1) R. Joly, J. Warnant, J. Jolly, and J. Mathieu, *C. R. Acad. Sci.*, **258**, 5669 (1964) and references cited therein; T. B. Windholz, J. H. Fried, H. Schwam, and A. A. Patchett, *J. Amer. Chem. Soc.*, **85**, 1707 (1963).

(2) W. F. Johns, *J. Org. Chem.*, **31**, 3780 (1966).

(3) R. M. Dodson, G. D. Valiaveedan, H. Ogasawara, and H. M. Tsuchiya, the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p I-33; the author is indebted to Professor Dodson, University of Minnesota, for a private communication describing this reaction.

(4) See, *e.g.*, D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 2728 (1951); J. Elks, *ibid.*, 468 (1954); F. Bohlmann, U. Hinz, and B. Diedrich, *Chem. Ber.*, **96**, 1316 (1963); D. M. Sivanandaiah and W. R. Nes, *Steroids*, **5**, 539 (1965); J. D. White, and S. I Taylor, *J. Amer. Chem. Soc.*, **92**, 5812 (1970); J. Lakeman, W. N. Speckamp, and H. O. Huisman, *Tetrahedron*, **24**, 5151 (1968); H. Morimoto, I. Imada, T. Murata, and N. Matsumoto, *Justus Liebigs Ann. Chem.*, **708**, 230 (1967); R. D. Daftary, Y. Pomeranz, R. G. Cooks, and N. L. Wolfe, *Experientia*, **26**, 1056 (1970).

(5) L. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 96.

(6) J Suzuki and K. Tsuda, *Chem. Pharm. Bull.*, **11**, 1028 (1963); S. Iwasaki and K. Tsuda, *ibid.*, **11**, 1034 (1963); F. Dolton and G. D. Meakins, *J. Chem. Soc.*, 1880 (1961).

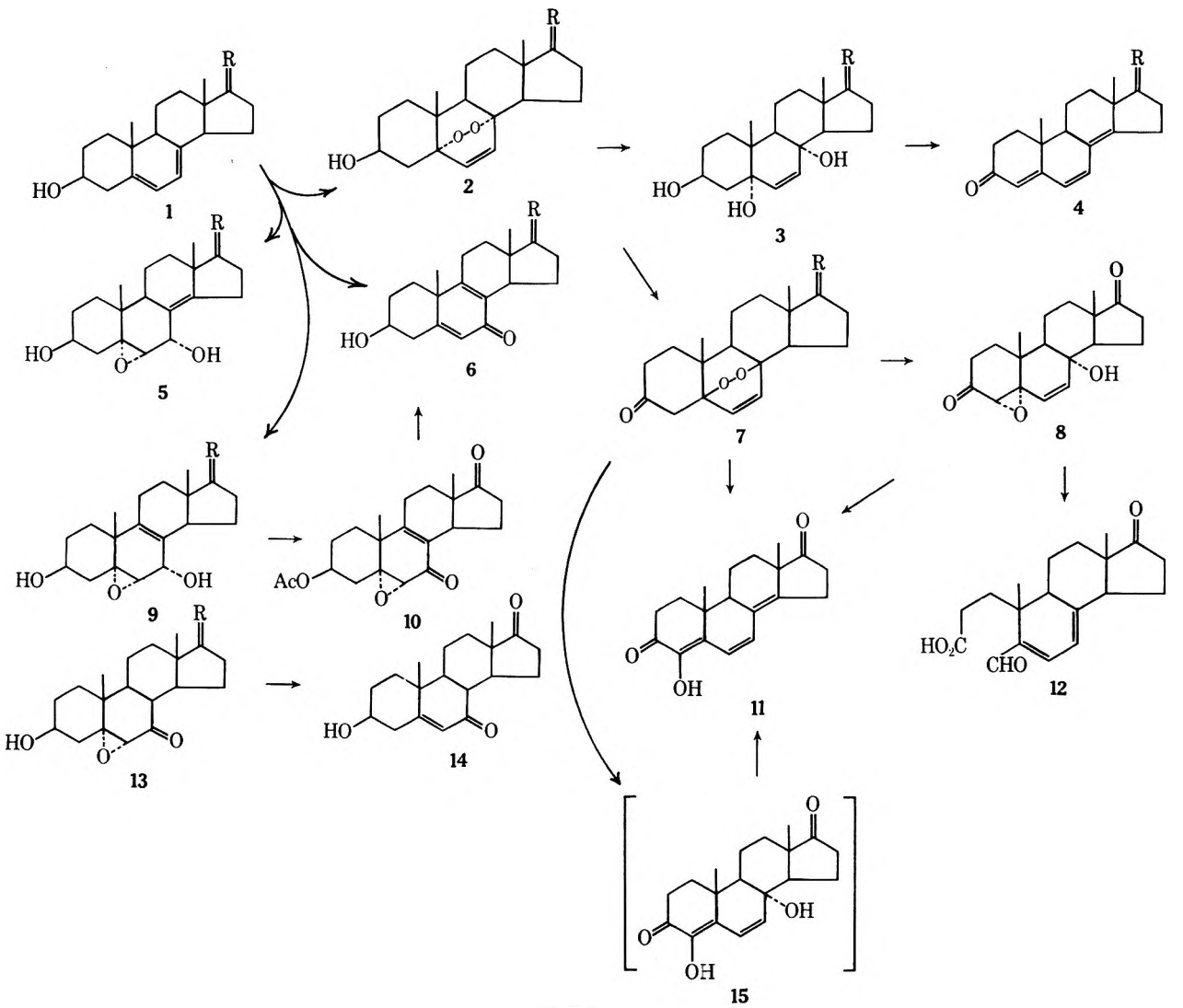
(7) This effect is similar to that recorded for the paramagnetic shift of the 5α,6-epoxides; see R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2071 (1963).

(8) The ergosterol analog of this compound has a similar absorption; see J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas, *J. Chem. Soc.*, 451 (1954).

(9) K. Tsuda, J Suzuki, and S. Iwasaki, *Chem. Pharm. Bull.*, **11**, 405 (1963).

(10) W. Bergmann and M. B. Meyers, *Justus Liebigs Ann. Chem.*, **620**, 46 (1959). An interesting microbiological preparation of analogous oxides from ergosterol peroxide has appeared: K. Petzoldt and K. Kieslich, *ibid.*, **724**, 194 (1969).

SCHEME I



a, R = O
b, R = β-OH, H
c, R = β-OH, CH_3

culated and observed angular methyl shifts for the 8 *vs.* the 8(14) olefins.[11]

The third by-product **5a** of the photooxygenation (8% yield) was also identical with a pyrolysis product of the epidioxide **2a**. It was separated in a pure state from the oxide **9a** by acetylation and careful rechromatography. Spectral characteristics quickly marked it as the double bond isomer of **9a**, the 8(14) olefin **5a**.[11] Evidence that **5a** was not the C-7 epimer of **9a** was obtained by oxidation of the 7-hydroxyl to a ketone different from ketone **10** (Scheme I).

Thermal isomerization of the epidioxide **2a**, effected by refluxing decane, yielded a ketone (**13**) isomeric to its companion hydroxy oxides **5a** and **9a**. The structure of the ketone **13** was demonstrated by potassium iodide reduction to the known unsaturated ketone **14**.[12] Thermal production of the photooxides implies that photochemical epimerization of C-13 has not occurred in spite of the 17-keto group. The formation of both epoxides (**5a**, **9a**) is analogous to the Δ^7 cholesterol work.[6]

The C-3 acetates of the three photooxygenation byproducts **5a**, **6a**, and **9a** underwent rapid basic hydrolysis to the corresponding hydroxy derivatives at room temperature. A sensitivity to base of these materials was shown by decreased yields with prolonged treatment.

The oxides **5a** and **9a** reasonably arise in the photooxygenation from the transformation of the epidioxide **2a** (as suggested by mechanistic considerations[6] and the thermal isomerization studies) rather than by a competing alternate oxidation of the diene **1a** itself. Conversion of the pure epidioxide **2a** to the oxide pair (**5a**, **9a**) with alcoholic acid or base failed. However, when the pure epidioxide itself was photooxygenated, the oxides **5a** and **9a** were produced slowly, demonstrating this to be a photochemically induced conversion.

The higher yield of oxide formation in the androstadienes as compared to the ergosterol derivatives[13] is

(11) Using the values in Zürcher's tables (see ref 7) the calculated signals for the 18- and 19-methyl signals are 47 and 72 Hz (found, 47 and 68) for the 8(9) olefin and 62 and 55 Hz (found, 64 and 52) for the 8(14) olefin.

(12) The comparison sample was kindly supplied by Dr. C. W. Marshall of these laboratories; *cf.* C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Amer. Chem. Soc.*, **79**, 6303 (1957).

(13) W. Furst, *Arch. Pharm. (Weinheim)*, **298**, 795 (1965); *Chem. Abstr.*, **64**, 4865*f* (1966).

reasonably ascribed to the longer reaction necessary in the former; the difference in reaction rate may be a result of the change in C-17 substituents. Methylene blue sensitized photooxygenation afforded a faster photooxygenation of the diene **1a** with a resultant higher yield of epidioxide **2a**; formation of the oxides **5a** and **9a** was not seen in this case.

Additional information about the mechanism of formation of the photoxygenation products, especially the dienone **6a**,[14] was sought by oxidizing the diene **1a** with singlet oxygen generated from hypochlorite and hydrogen peroxide.[15] The chief product of this reaction was the epidioxide **2a**. Careful investigation of the side products showed that the oxides **5a** and **9a** were absent, in agreement with the postulated photochemical nature of their formation. No dienone **6a** was found, suggesting that its origin may involve an activated oxygen species other than singlet oxygen, such as the $^1\Sigma^+_g$ state of oxygen[16] or the sensitizer-oxygen activated complex described by Schenk.[17]

Since the epidioxide group of **2a** reacted readily with methylmagnesium bromide, the 17-methyl derivatives were prepared starting from the 17-methyldiene **1c**. Photooxygenation of **1c** afforded an array of products (**2c**, **5c**, **6c**, **9c**) similar to those obtained in the 17-ketone series. In addition, the epoxy ketone **13c** was isolated and its structure shown by spectral comparison with the keto oxide **13a**.

B. Trienone Formation.—Despite the relative stability of the epidioxide **2a** to acid and base, when stirred with palladium catalysts in ethanol the epidioxide underwent a facile change to provide 70% of the highly polar triol **3a**. The same compound was obtained (in low yield) by reduction of the epidioxide with zinc in ethanolic hydroxide.[18] The nmr of the triol in deuterated dimethyl sulfoxide showed two vinyl protons coupled only with each other; in addition, each of the hydroxyl protons appeared, the secondary hydroxyl as a doublet and each of the two tertiary hydroxyls as a singlet. Acetylation of the triol provided the 3-monoacetate which again exhibited the tertiary hydroxyl protons as singlets; in addition, the vinyl proton pattern was unchanged from that seen in the starting triol. The same acetate was also prepared by palladium treatment of the epidioxide **2a** acetate in ethanol.

Use of lithium tri-*tert*-butoxyaluminohydride to effect the reduction of the epidioxide group gave only the diol **2b**. The product retained the vinyl hydrogen nmr pattern of starting material. Acetylation of this material gave a diacetate which lacked hydroxyl bands in the ir, in agreement with structure **2b** diacetate.

Prolonged treatment of the triolone **3a** (or the epidioxide **2a**) with palladium black in ethanol promoted the slow formation of the trienone **4a** (λ_{max} 340 nm), an optimum concentration (60%) of this material being reached after 10 days. The structure of the trienone **4a** is clearly defined by the characteristic uv absorption[4] and corroborated by ir, nmr, and elemental analysis. Similar palladium treatment of 17-hydroxy or 17-methyl epidioxides (**2b**, **2c**) led to the respective trienones **4b**, **4c**.

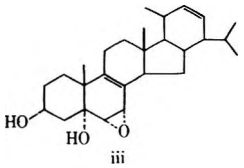
The reaction pathway from epidioxide to trienone would reasonably involve a discrete reductive cleavage of the epidioxide **2** to triolone **3**, involving a palladium-catalyzed transfer of hydrogen from the solvent. A subsequent hydrogen transfer would result in oxidation of the 3-hydroxyl group and loss of water to afford the trienone **4**. Attempts to follow the reaction path through the oxidation step were frustrated by the complexity and instability of the products obtained from the triolone **3a** with several mild oxidants.

One other intermediate, the 3-keto epidioxide **7**, might be envisioned in the conversion of the epidioxide **2** to the trienone **4**. That this was not so was shown by preparation of **7** (see below) and the demonstration of its stability to prolonged treatment with palladium black in ethanol.

C. Reactions of 3-Keto Epidioxide 7.—Oxidation of the epidioxide **2a** (or **2c**) with chromic acid proceeded smoothly to give the corresponding ketone **7a** (or **7c**). Evidence that the epidioxide group was intact was obtained from the unchanged nmr pattern of the C-6 and C-7 protons. Initial attempts to prepare **7a** by chromium trioxide–pyridine oxidation of the alcohol **2a** gave only minor amounts of the desired product. The major component, also obtained when **7a** was dissolved in pyridine or in dilute methanolic base, was shown to be the isomeric 4α,5-epoxide **8**.[19] The 3- and 17-carbonyl groups as well as a new hydroxyl group showed in the infrared. The nmr signals of the vinylic 6 and 7 protons were shifted from those of the starting ketone **7a**. In addition, a sharp singlet (218 Hz) appeared and was attributed to the proton on the oxirane ring. Formation of the epoxide from the ketone **7a** was followed directly in the nmr by use of deuteriopyridine as solvent; at room temperature the signals of starting material were completely replaced by those of the product within 2 hr with the intervention of no evident intermediate. With either reagent grade or anhydrous pyridine, the reaction was much slower, requiring 4 days at room temperature or 30 min at 90° for completion. The peculiar accelerative properties of the deuteriopyridine were not investigated further.

The epoxide **8** was labile in base, affording a mixture which possessed an ultraviolet maximum (298 nm), in accord with the 4,8-dihydroxydienone structure **15**. With more vigorous base treatment the 4-hydroxytrienone **11** was obtained; the uv spectrum (λ_{max} 361 nm) and the hydroxyl band in the infrared allowed

(14) Furst (ref 13) surprisingly isolated no dienone from the photooxygenation of ergosterol. He did find as a major component the epoxide iii



iii

which may represent an intermediate in an alternate, mechanistically more complex route to the dienone. No trace of an analog of iii was seen in the present studies, presumably because of its lability.

(15) C. S. Foote, S. Wexler, W. Ando and R. Higgins, *J. Amer. Chem. Soc.*, **90**, 975 (1968); C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968).

(16) D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Amer. Chem. Soc.*, **89**, 5455 (1967). The author wishes to thank a referee for pointing out this possibility.

(17) R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 604.

(18) A. Windaus and O. Linsert, *Justus Liebigs Ann. Chem.*, **465**, 148 (1928).

(19) Blandon has postulated, but not isolated, an analogous intermediate in the ergosterol series: P. Bladon and T. Sleigh, *J. Chem. Soc.*, 6991 (1965).

ready assignment of structure[20] to this compound. Since a by-product of the base treatment contained methoxyl groups, tetrahydrofuran was substituted as solvent; the trienone **11** was then accompanied by the seco acid **12** (see below).

Use of acid catalysts to effect conversion of the 3-keto epidioxide **7** to the trienone system **4** afforded instead an acidic product **12**. A 50% yield of this compound was obtained by use of acetic acid at room temperature either from the epidioxide **7** in 5 days or from the oxide **8** in 2 hr. The acid was isomeric with starting material and showed carboxyl and conjugated aldehyde functions as well as the undisturbed ring D ketone (ir and nmr analysis). The nmr also showed two adjacent vinylic protons (C-6, -7) coupled only with each other. The uv spectrum (λ_{max} 320 nm) was consistent with a homoannular diene conjugated with the aldehyde.[21] The seco acid structure **12** is in full accord with this data.

Formation of the acid **12** from the epidioxide **7a** probably proceeds by an initial conversion to the epoxide **8**; subsequent attack by hydroxide (in the base-catalyzed reaction) at the C-3 carbonyl group may occur, followed by C_3–C_4 bond rupture, shift of electrons, and expulsion of the 8-hydroxyl to give **12**. The acid-catalyzed transformation would proceed by an analogous route.

Chemical support for this seco acid structure was afforded by reactions of its functional groups: the carboxyl group formed a methyl ester with diazomethane, a change having no effect on the spectral properties of the dienic aldehyde system; the diene system readily added 2 mol equiv of hydrogen to provide an aldehydic acid lacking ultraviolet absorption; the aldehyde group gave a complex acetal mixture with methanolic acid.

Experimental Section[22]

3β-Acetoxy-5α,8-epidioxyandrost-6-en-17-one (2a Acetate). A. Eosin-Sensitized Photooxygenation. Procedure A.—A stream of oxygen was bubbled through a solution of 53 g of 3β-acetoxyandrosta-5,7-dien-17-one[23] and 0.5 g of eosin yellow in 4 l. of 2B ethanol illuminated with a 500-W tungsten lamp for 12 hr. The solvent volume was reduced to 0.5 l. and the resulting crystal mass was filtered and recrystallized from methylene chloride–methanol to give 20.1 g of the acetate **2a**: mp 253–260°; 5.72 μ; 56 (18-CH_3), 60 (19-CH_3), 381 (d, J = 8 Hz, C=CH) 393 Hz (d, J = 8 Hz, C=CH); $[\alpha]_D$ 51°.[24]

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.81; H, 7.65.

The stability of the diene acetate **1a** was tested by passing oxygen through a boiling ethanol solution. A slow decomposition resulted, affording a mixture of products; none of the photooxygenation products (**2a**, **5a**, **6a**, **9a**) could be discerned in this mixture (tlc and nmr analysis).

B. Methylene Blue Sensitized Photooxygenation.—The acetate of **1a** (10.2 g) in 0.8 l. of *n*-propyl alcohol containing 25 mg of methylene blue was photooxygenated as above for 1 hr. The cooled solution gave by direct crystallization 4.7 g of the pure acetate **2a**. Chromatography[25] gave another 0.7 g of **2a**.

3β-Hydroxy-5α,8-epidioxyandrost-6-en-17-one (2a). A. Photooxygenation.—3β-Hydroxyandrosta-5,7-diene (2.0 g, **1a**)[23] by use of procedure A for 7 hr was converted to 0.85 g of the alcohol **2a**, mp 184–190°. Recrystallization from acetone–hexane gave a pure sample: mp 200–202°; 2.72, 5.72 μ; $[\alpha]_D$ 32°. The nmr signals of vinyl protons and methyl groups were the same as for the acetate of **2a**.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.54; H, 8.13.

B. Nonphotochemical Oxygenation.—To a solution of 10 g of the diene **1a** in 1 l. of methanol at −5° was added 35 ml of 30% aqueous hydrogen peroxide. Sodium hypochlorite solution (5.25%, 350 ml) was added over a 35-min period. After an additional 10 min, the solution was poured into ice water and the product extracted with methylene chloride. The extract was washed with water and then aqueous potassium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated.[26] The product was chromatographed and afforded fractions containing 4.2 g of the epidioxide **2a**, identical with the above sample. Later eluents provided 4.0 g of a more polar mixture which was acetylated and rechromatographed; neither nmr nor tlc analysis showed evidence of the presence of the dienone **6a** or the oxides **5a**, **9a**.

C. Saponification.—A solution of 12.6 g of **2a** acetate in 400 ml of 3A ethanol and 40 ml of 10% aqueous potassium hydroxide after 20 hr at room temperature was diluted with water to afford 8.9 g of the epidioxide **2a**. Distillation of the ethanol from the filtrate followed by filtration afforded an additional 3.0 g of the same compound.

By-products of the Photooxygenation.—Chromatography of the mother liquors (31 g) of the first experiment (procedure A) gave by elution with 15% ethyl acetate–benzene first additional epidioxide **2a** followed closely by fractions containing 6.3 g of semicrystalline material. Trituration of this material with ether and recrystallization of the insoluble portion from aqueous methanol yielded 2.25 g of **3β-acetoxyandrost-5,8-diene-7,17-dione (6a)**: mp 172–174°; 5.72, 6.01 μ; 245 nm (15,200); 50 (18-CH_3), 84 (19-CH_3), 367 Hz (7-H).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.62; H, 7.64.

Elution with 50% ethyl acetate–benzene gave material which was recrystallized from acetone to yield 1.46 g of **3β-acetoxy-7α-hydroxy-5α,6-epoxyandrost-8-en-17-one (9a)**: mp 185–191°; 2.78, 5.72 μ; 47 (18-CH_3), 72 (19-CH_3), 201 and 203 (6-H), 262 Hz (7β-H, $W_{1/2}$ = 7 Hz); $[\alpha]_D$ 24°.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.58; H, 8.00.

To assist in purification of the components eluted at 50% ethyl acetate–benzene, the noncrystalline eluates and mother liquors were acetylated with acetic anhydride–pyridine at room temperature and the product was rechromatographed. The material eluted at 25% ethyl acetate–benzene was further purified by preparative tlc. The first component obtained was recrystallized from acetone–hexane to yield **3β,7α-diacetoxy-5α,6-epoxyandrost-8-en-17-one (9a)**: mp 206–211°; 5.75 μ; 47 (18-CH_3), 73 (19-CH_3), 121 (OAc), 123 (OAc), 203 and 205 (6-H), 329 Hz (7-H, $W_{1/2}$ = 6 Hz).

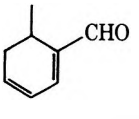
Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.56; H, 7.62.

This compound was also prepared in high yield by acetylation of the 3-monoacetate of **9a**.

A second component from the preparative tlc was crystallized from acetone–hexane to yield **3β,7α-diacetoxy-5α,6-epoxyandrost-8(14)-en-17-one (5a)**: mp 166–172°; 5.75 μ; 57 (18-CH_3), 62

(20) See ref 19 for a hydroxytriene analogous to **11**.

(21) C. Grundmann, *Chem. Ber.*, **81**, 513 (1948), has recorded max 303 mμ (7900) for



An additional increment of 18 mμ can be added to this value for the additional δ substituent (see ref 5, p 19). D. N. Kirk and J. M. Wiles [*Chem. Commun.*, 1015 (1970)] have described a similar type of cleavage.

(22) We wish to thank Dr. R. T. Dillon and staff for elemental and spectral analyses reported. Infrared spectra (μ) were determined in chloroform (5%), ultraviolet (nm) in methanol, and nmr (Hz) in deuteriochloroform (on a Varian A-60 spectrometer with tetramethylsilane as an internal standard, $\Delta\nu$ = 0). Rotations were run in chloroform (1%).

(23) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).

(24) This compound was first prepared in these laboratories by Dr. R. H. Bible. The author also acknowledges valuable discussions with Dr. Bible pertaining to the interpretation of several nmr spectra.

(25) The chromatographies described throughout this paper were run by the Chromatography Department under the direction of Mr. R. T. Nicholson. These were routinely run on a weight of silica gel (Davison) 60 times that of the compound, unless specified otherwise.

(26) This represents a standard method of isolating the products and was used routinely throughout the bulk of this work. The temperatures used in removal of solvents were normally kept below 50°, vacuum being used where necessary.

(19-CH_3), 121 (OAc), 127 (OAc), 195 and 198 (6-H), and multiplets centered at 343 and 346 Hz (7-H).

Anal. Found: C, 68.55; H, 7.42.

The remainder of the materials from these chromatograms were intractable mixtures which displayed no clear methyl signals in the nmr.

The methylene blue sensitized photooxygenation mother liquors (5.1 g) were also chromatographed and yielded, besides additional epidioxide acetate **2a**, fractions (1.2 g) consisting largely of the dienone acetate **6a** (nmr and tlc analysis). Later eluents were acetylated and rechromatographed but contained no discernible amount of the oxides **5a** or **9a** nor were any other discrete products seen (nmr, tlc).

3β-Hydroxyandrosta-5,8-diene-7,17-dione (6a).—Aqueous potassium hydroxide (10%, 0.5 ml) was added to a solution of 0.70 g of **6a** acetate in 5 ml of methanol. After 1 hr, a precipitate formed and was separated yielding 0.57 g of the crude alcohol **6a**. Recrystallization from methylene chloride–methanol yielded the pure material: mp 252–254°; 2.75, 5.72, 6.01 μ; 248 nm (14,200); 49 (18-CH_3), 83 (19-CH_3), 364 Hz (7-H); $[\alpha]_D$ 42°.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.81; H, 8.05. Found: C, 75.97; H, 7.90.

3β,7α-Dihydroxy-5α,6-epoxyandrost-8-en-17-one (9a). Procedure B.—A slurry of 0.10 g of **9a** 3-monoacetate in 2 ml of methanol was treated with 0.2 ml of 10% aqueous potassium hydroxide. The compound dissolved immediately and after 3 min was isolated by methylene chloride extraction. The product was crystallized from ether and from acetone–hexane to yield 50 mg of the diol **9a**: mp 196–203°; 2.75, 5.75 μ; 47 (18-CH_3), 68 Hz (19-CH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.72; H, 8.33.

Longer base treatment decreased the yield of isolable diol **5a**. Treatment of the 3-monoacetate of **5a** with acidic ethanol led to an intractable mixture.

3β,7α-Dihydroxy-5α,6-epoxyandrost-8(14)-en-17-one (5a).—The diacetate of **5a** (120 mg) was treated according to procedure B. The crude product was recrystallized from ethyl acetate to yield 40 mg of the diol **9a**: mp 178–183°; 2.75, 5.72 μ; 54 (18-CH_3) and 66 Hz (19-CH_3).

Anal. Found: C, 71.12; H, 7.96.

Structure Proof of Epoxide 9a. A. Oxidation of the Epoxide 9a.—A solution of 0.38 g of the 3-monoacetate of **9a** in 5 ml of pyridine was added to the Sarett reagent[27] prepared from 0.5 g of chromium trioxide. After 3 hr at room temperature the solution was diluted with water and extracted with ether. The crystalline product was recrystallized from acetone–hexane and then from ether (Darco) to yield **3β-acetoxy-5α,6-epoxyandrost-8-ene-7,17-dione (10)**: mp 189–194°; 5.75, 5.98 μ; 259 nm (6800); 47 (18-CH_3), 78 (19-CH_3), 201 Hz (6-H).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.10; H, 7.27.

A similar oxidation of the 8(14) olefin **5a** 3-acetate gave a different product (methyl signals 57, 72 Hz), but insufficient material was available to complete its purification and obtain a satisfactory elemental analysis.

B. Reduction of the Oxido Ketone 10a. Procedure C.—A solution of 60 mg of the unsaturated keto oxide **10a** in 2 ml of acetic acid saturated with potassium iodide was heated at 95° for 15 min resulting in the fast liberation of iodine. The solution was cooled and diluted with aqueous sodium thiosulfate. The product (45 mg of crystals) was isolated by methylene chloride extraction and was identical spectrally with the known 5,8-dienone **6a**.

Rearrangement of the Epoxide 2a.—A solution of the 0.38 g of the epidioxide **2a** (3-acetate) was treated as in procedure A for 7.5 hr. The crude product was chromatographed and yielded 0.18 g of starting material. A mixture (0.12 g) of compounds which eluted next consisted predominantly of the oxide 3-monoacetates (**5a**, **9a**) in a 6:4 ratio; the identification was made clear by nmr analysis of the characteristic methyl and C-6 proton signals and by tlc.

The stability of the epidioxide group was shown in separate experiments in which the compound was boiled in neat triethylamine[10] (20 hr), in aqueous ethanol containing either potassium hydroxide (22 hr) or hydrochloric acid (6 hr) with essentially no effect (nmr and tlc analysis). Prolonged contact at room temperature with alumina or silica gel also caused no appreciable change.

Thermal Isomerization of the Hydroxy Epidioxide 2a.—The epidioxide **2a** (0.75 g) in 60 ml of redistilled decane[10] was boiled under nitrogen for 36 hr. The solvent was distilled and the residue chromatographed. Fractions eluted at 20% ethyl acetate–benzene were recrystallized from aqueous acetone to give 65 mg of **3β-hydroxy-5α,6-epoxyandrostane-7,17-dione (13a)** solvated with 0.25 mol equiv of water: mp 168–173°; 2.75, 5.73, 5.88 μ; 54 (18-CH_3), 65 (19-CH_3), 185 Hz (6β-H).

Anal. Calcd for $C_{19}H_{26}O_4 \cdot 0.25H_2O$: C, 70.67; H, 8.28. Found: C, 70.62; H, 8.09.

Treatment of the oxido ketone **13a** according to procedure C at room temperature for 4 hr gave a product identical spectrally with an authentic sample of the unsaturated ketone **14a**.[12]

Further elution of the chromatographic column with 30% ethyl acetate–benzene gave 0.35 g of a 6:4 mixture of the epoxides **5a** and **9a** (nmr analysis).

5α,8-Epidioxyandrost-6-ene-3β,17β-diol (2b).—Lithium tri-*tert*-butoxyaluminohydride (3.56 g) was added to a solution of 1.78 g of the ketone **2a** in 30 ml of tetrahydrofuran at 5°. After 10 min the solution was removed from the cooling bath and allowed to stand at room temperature or 2 hr. The solution was poured into ice water containing 10 ml of acetic acid, the organic solvent was evaporated in a stream of nitrogen, and the product (1.62 g) was isolated by ethyl acetate extraction. The pure compound, obtained by crystallization from acetone, had mp 125–135° and 195–210°; 2.73 μ; 53 (18 and 19-CH_3), 376 (d, J = 9 Hz, C=CH), 390 Hz (d, J = 9 Hz, C=CH) (DMSO-d_5).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.90; H, 9.20.

Nmr analysis of the mother liquors showed no sign of the tetrol **3b**.

Acetylation of the diol **2b** afforded 5α,8-epidioxyandrost-6-ene-3β,17β-diol diacetate (**2b**): mp 200–202°; 5.79 μ (no hydroxyl absorption); 55 (18,19-CH_3), 121 (OAc), 123 (OAc), 377 (d, J = 8 Hz, C=CH), 393 Hz (d, J = 8 Hz, C=CH).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.56; H, 8.18.

17α-Methylandrosta-5,7-diene-3β,17-diol (1c).—A solution of 9.5 g of the 17-ketone **1a** in 200 ml of tetrahydrofuran was added to a solution of 300 ml of ether containing 0.16 mol of methylmagnesium bromide. After 18 hr the reaction mixture was diluted with water and then dilute hydrochloric acid. The ether was distilled and the crystal mass obtained, after separation by filtration, was recrystallized from aqueous methanol to yield 8.7 g of crude adduct. Recrystallization from methanol–ethyl acetate gave pure **1c**: mp 211–213°; 2.75 μ; 270 (10,300), 280 (10,900), 287 nm (6180); 49 (18-CH_3), 58 (19-CH_3), 74 (17-CH_3), 220–240 Hz (broad multiplet, 6,7 H's).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.50; H, 9.88.

3β-Acetoxy-17α-methylandrosta-5,7-dien-17-ol was prepared by acetylation of the alcohol **1c** with pyridine–acetic anhydride; crystallization from methylene chloride–methanol gave a hemimethanolate: mp 134–139°; 2.75, 5.78 μ; 270 (10,400), 281 (10,750), 293 nm (6250); 48 (18-CH_3), 58 (19-CH_3), and 74 Hz (17-CH_3).

Anal. Calcd for $C_{22}H_{32}O_3 \cdot 0.5CH_3OH$: C, 74.96; H, 9.38. Found: C, 75.27; H, 9.51.

5α,8-Epidioxy-17a-methylandrost-6-ene-3β,17-diol (2c).—The diene **1c** (15 g) was treated according to procedure A and afforded by direct crystallization 3.3 g of the crude epidioxide **2c**. Recrystallization from acetone gave the pure material: mp 196–201°; 2.74 μ; 54 (19-CH_3), 58 (18-CH_3), 75 (17-CH_3), 372 (d, J = 8 Hz, C=CH), 393 Hz (d, J = 8 Hz, C=CH).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.55; H, 8.83.

The epidioxide **2c** was stable to reduction with lithium aluminum tri-*tert*-butoxyhydride at room temperature for 24 hr.

Running the photooxygenation with eosin blue in dimethylformamide or in methanol–benzene[9] slowed the reaction and decreased the yield of epidioxide; no increased proportion of the dienone was found as compared to the eosin yellow photooxygenation.

3β-Acetoxy-5α,8-epidioxy-17α-methylandrost-6-en-17-ol (2c) was prepared by procedure A from **1c** (3-acetate) and had mp 197–203°; 2.71, 572 μ; 55 (19-CH_3), 58 (18-CH_3), 75 (17-CH_3), 375 (d, J = 8 Hz, C=CH), 397 Hz (d, J = 8 Hz, C=CH); $[\alpha]_D$ −12°.

(27) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.50; H, 8.55.

Alkaline hydrolysis of this material gave the alcohol **2c** in good yield.

3β,17β-Dihydroxy-5α,6-epoxy-17α-methylandrostan-7-one (13c).—Photooxygenation of mother liquors upon acetylation and rechromatography afforded impure oxide **13c** 3-acetate. Room temperature hydrolysis of this material (procedure B) and rechromatography afforded pure oxide **13c**: mp 190–192° from methylene chloride–hexane; 2.75, 5.89 μ; 52 (18-CH_3), 65 (19-CH_3), 183 Hz (6-H).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.86; H, 9.19.

In the same manner, **3β,17β-dihydroxy-17-methylandrosta-5,8-dien-7-one (6c)** was obtained. Recrystallization from aqueous acetone afforded a monohydrate: mp 119–122°; 2.75, 6.10 μ; 247 nm (7700); 50 (18-CH_3), 75 (17-CH_3), 82 (19-CH_3), 364 Hz (6-H).

Anal. Calcd for $C_{20}H_{28}O_3 \cdot H_2O$: C, 71.82; H, 9.04. Found: C, 71.68; H, 8.99.

No pure samples of the oxides **5c** or **9c** were obtained.

3β,5α,8α-Trihydroxyandrost-6-en-17-one (3a).—A solution of 3.1 g of the epidioxide **2a** in 100 ml of 2B ethanol was stirred with 5 g of palladium black (Fischer) at room temperature. After 18 hr the mixture was filtered and the filtrate concentrated. Crystallization of the residue from acetone afforded 2.02 g of the triolone **3a**; mp 222–226°; 3.02, 5.72 μ; 47 (19-CH_3), 53 (18-CH_3), 259 (d, 3-OH), 306 (OH), 331 Hz (OH) (DMSO-d_5).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.47; H, 8.60.

Chromatography of the mother liquors afforded 0.20 g of the starting material **2a** but very little of the trienone **4a** was found.

This reaction could also be effected at a comparable rate with 10% palladium on charcoal. Zinc–potassium hydroxide in ethanol reduced the epidioxide but the triolone **3c** was at best a minor component of the product (nmr and tlc analysis). Attempts to oxidize the triolone **3c** with Jones reagent,[28] the Sarett reagent,[27] pyridine chromate in methylene chloride,[29] or aluminum isopropoxide–cyclohexanone led to mixtures from which no pure products were isolated.

3β,5α,8α-Trihydroxyandrost-6-en-17-one 3-acetate was prepared from the triolone **3a** with acetic anhydride–pyridine and had mp 198–201°; 2.89, 5.70 and 5.83 μ (KBr); 52 (18-CH_3), 58 (19-CH_3), 122 Hz (OAc) (DMSO-d_5).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.28. Found: C, 69.48; H, 8.34.

The same acetate (of **3a**) was obtained by treatment of the epidioxide acetate **2a** with palladium black in ethanol for 42 hr; the yield was lower than for the alcohol **3a** due to formation of unidentified side products.

Androsta-4,6,8(14)-triene-3,17-dione (4a). A. From the Epidioxide 2a.—The epidioxide **2a** (2.14 g) in 200 ml of 2B ethanol was stirred with 10 g of palladium black (Englehard) for 10 days. The mixture was filtered and the solvent evaporated. Uv analysis implied 60% of the material was the trienone **4a**. The product was crystallized from ether and then from acetone–hexane to yield 0.93 g of the trienone **4a**: mp 143–153°; $E_{340\ nm}$ 19,500. Further recrystallization from acetone–hexane gave material, mp 163–166°, solvated with 0.5 mol equiv of acetone: 5.72, 605 μ; 340 nm (26,400); 63 (18-CH_3), 73 (19-CH_3), 347 (4-H), 370 (d, J = 9 Hz, C=CH), 404 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{19}H_{22}O_2 \cdot 0.5C_3H_6O$: C, 79.06; H, 8.09. Found: C, 79.04; H, 8.00.

The polar by-products contained the triolone **3a** and ethoxyl-containing compounds (ethoxyl determination, 3.76%). Retreatment of this material with palladium black did not increase the amount of trienone present (uv analysis).

Use of freshly prepared sponge palladium black gave a mixture of compounds containing neither triolone **3a** or trienone **4a** (tlc and nmr analysis).

B. From the Triolone 3a.—A solution of 0.20 g of the triolone **3a** in 10 ml of 2B ethanol was stirred with 0.50 g of palladium black at room temperature for 3 days. The mixture was filtered and the filtrate concentrated to give a mixture containing 50% of the trienone **4a** (uv, nmr, and ir analysis).

17β-Hydroxyandrosta-4,6,8(14)-trien-3-one (4b).—A solution of 1.6 g of the diol **2b** in 50 ml of 2 B ethanol was stirred with 3 g of palladium black for 6 days. The product (1.52 g, $E_{346\ nm}$ 8700) was isolated and chromatographed. Fractions eluted with 20% ethyl acetate–benzene were recrystallized from acetone–hexane to afford 0.21 g of the triene **4b** as a hemiacetonate: mp 159–165°; 2.75, 6.08 μ; 346 nm (18,600); 61 (18, 19-CH_3's), 345 (4-H), 363, 372, 392, 401 Hz (6,7 H's).

Anal. Calcd for $C_{19}H_{24}O \cdot 0.5C_3H_6O$: C, 78.55; H, 8.68. Found: C, 78.16; H, 8.54.

The bulk of the remaining material from the chromatogram was more polar, indicating incomplete reaction. Very little saturated ketone was visible in the ir spectra of this material.

17β-Hydroxy-17-methylandrosta-4,6,8(14)-trien-3-one (4c).—The epidioxide **2c** (0.58 g) and 2 g of palladium black were stirred in 30 ml of 2B ethanol for 6 days. The mixture was filtered, the filtrate concentrated, and the resulting residue chromatographed. The product was eluted at 20% ethyl acetate–benzene and was recrystallized from acetone–hexane to give 50 mg of the trienone **4c**, as a hemietherate: mp 181–186°; 2.76 6.05 μ; 349 nm (25,400); 62 (18-CH_3), 69 Hz (19-CH_3).

Anal. Calcd for $C_{20}H_{26}O_2 \cdot 0.5C_4H_{10}O$: C, 78.76; H, 9.31. Found: C, 79.14; H, 9.22.

5α,8-Epidioxyandrost-6-ene-3,17-dione (7a). Procedure D.—Jones reagent[28] (10 ml) was added over a 5-min period to a solution of 8.6 g of the alcohol **2a** in 400 ml of acetone at −10°. After 30 min the solution was diluted with 10 ml of 2-propanol and then with water. The resulting precipitate was collected, air-dried, and recrystallized from methylene chloride–acetone to yield 7.19 g of the diketone **7a**, mp 173–177°. A second recrystallization raised the melting point to 185–189°; 5.72, 5.79 μ; 61 (18-CH_3), 65 (19-CH_3), 383 (d, J = 9 Hz, C=CH), 396 Hz (d, J = 9 Hz, C=CH); $[\alpha]D$ +77°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.07; H, 7.46.

Treatment of the epidioxide **7a** with palladium black in ethanol at room temperature for 6 days gave no evidence of reaction.

17β-Hydroxy-5α,8-epidioxy-17-methylandrost-6-en-3-one (7c).—Oxidation of 190 mg of the alcohol **2c** according to procedure D gave after recrystallization from acetone–hexane 70 mg of the ketone **7c**: mp 175–180°; 2.75, 5.82 μ; 60 (18-CH_3), 65 (19-CH_3), 77 (17-CH_3), 380 (d, J = 9 Hz, C=CH), 399 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.16; H, 8.67.

8α-Hydroxy-4α,5-epoxyandrost-6-ene-3,17-dione (8).—The epidioxide **7a** (2 g) was dissolved in 50 ml of pyridine (Reilly). After 5 days pentane was added, precipitating an oil which then crystallized. Recrystallization of this material from acetone gave 1.77 g of the oxide **8**: mp 162–166°; 2.78, 5.74, 5.82 μ; 53 (18-CH_3), 61 (19-CH_3), 218 (4-H), 358 (d, J = 6 Hz, C=CH), 406 (d, J 6 Hz, C=CH), 530 (CO_2H), 567 Hz (CHO).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.68. Found: C, 72.40; H, 7.65.

Although use of anhydrous pyridine had no effect on the rate of this reaction, use of deuteriopyridine (in an nmr cell) caused the reaction to be complete in less than 2 hr. The reaction was also run in pyridine at 90° for 30 min or with aqueous potassium hydroxide in tetrahydrofuran at 5° for 10 min, but these procedures gave lower yields of **8**. The oxide **8** was also the principal product of oxidation of the epidioxide **2a** with the Sarett reagent.[27]

4-Hydroxyandrosta-4,6,8(14)-triene-3,17-dione (11).—A solution of 0.30 g of the epidioxide **7a** in 20 ml of ethanol and 2 ml of 10% aqueous potassium hydroxide was heated at reflux in a nitrogen atmosphere for 15 min. The solution was cooled and diluted with aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water, air-dried, and recrystallized from methylene chloride–acetone to yield 0.16 g of the triene **11**: mp 210–212°; 2.89, 6.01 μ; 361 nm (25,200), 403 nm (20,600) (in 0.1 *N* KOH–MeOH); 62 (18-CH_3), 73 (19-CH_3), 402 Hz (6,7-H's).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.27; H, 7.52.

A similar treatment of the oxide **8** afforded the triene **11** in 30% yield.

In tetrahydrofuran–aqueous potassium hydroxide after 2 hr the neutral portion of the product (60% of the total) consisted largely of the triene **11**. The acidic portion was essentially pure seco acid **12** (see below). Room temperature treatment of the epidioxide **7a** in ethanol with aqueous potassium hydroxide for

(28) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(29) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

18 hr gave an amorphous mixture displaying the ultraviolet maximum of the 4,8-dihydroxydiene **15**, 295 nm (9900); isolation of the pure compound failed.

4,17-Dioxo-3,4-secoandrosta-5,7-dien-3-oic Acid (12). A. From the Epidioxide 7a.—The epidioxide **7a** (0.85 g) in 10 ml of acetic acid was heated at 95° for 1.5 hr and the solvent was distilled. The crystalline residue resulting after ether trituration was washed with cold ethyl acetate and recrystallized from methylene chloride–ethyl acetate to yield 0.15 g of the seco acid **12**: mp 169–170°; 3.0–3.2 (shoulder), 5.72, 5.81, 5.92 μ; 320 nm (13,600); no change in the uv maximum was seen in the presence of either acid or base; 47 (18-CH_3), 74 (19-CH_3), 361 (d, J = 9 Hz, C=CH), 405 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.11; H, 7.55.

The same reaction required 5 days at room temperature to go to completion. Uv analysis of the total product in either case implied *ca.* 50% was the seco acid **12**.

B. From the Oxide 8.—A solution of 0.10 g of the oxide **8** in 5 ml of acetic acid was allowed to stand at room temperature for 2 hr and was then diluted with water. Methylene chloride extraction afforded 60 mg of crude product [λ_{max} 316 mμ (6600)] having the characteristic nmr and ir absorption spectra of the seco acid **12**. When the reaction was run in deuterioacetic acid and followed directly in an nmr cell, the reaction required a longer period of time for completion (*ca.* 18 hr); no intermediate was visible and no other discernible product was formed.

Treatment of 75 mg of pure **12** in tetrahydrofuran with an excess of ethereal diazomethane afforded an amorphous methyl ester: 3.64, 5.72, 5.93 μ; 318 nm (11,550). The major nmr signals were the same as those of the acid **12** with the addition of the 218-Hz signal (OCH_3). Treatment of this ester (or the oxide **8**) with methanolic acid gave a complex acetal mixture lacking the diene chromophore.

Hydrogenation of the seco acid **12** in ethanol with a palladium/charcoal catalyst effected uptake of 2 mol equiv of hydrogen. The product was an amorphous aldehydro acid lacking uv absorption.

Registry No.—**1c**, 23971-00-8; **1c** 3-acetate, 29851-14-7; **2a**, 23970-97-0; **2a** acetate, 23970-96-9; **2b**, 23970-98-1; **2b** diacetate, 29851-17-0; **2c**, 23971-02-0; **2c** 3-acetate, 29851-19-2; **3a**, 29851-20-5; **3a** 3-acetate, 29851-21-6; **4a**, 23970-99-2; **4b**, 23971-01-9; **4c**, 29851-24-9; **5a**, 29851-25-0; **5a** diacetate, 29851-26-1; **6a**, 29851-41-0; **6a** acetate, 29851-40-9; **6c**, 29851-27-2; **7a**, 29851-28-3; **7c**, 29851-29-4; **8**, 29851-30-7; **9a**, 29851-31-8; **9a** 3-acetate, 29851-32-9; **9a** diacetate, 29851-33-0; **10**, 29851-34-1; **11**, 29851-35-2; **12**, 29936-63-8; **13a**, 29851-36-3; **13c**, 29851-37-4.

Acknowledgment.—The competent technical assistance rendered by Mrs. Barbara Tucker is gratefully acknowledged by the author.

Steroidal Adducts. IV.[1] Variable Selectivity in Hydride Reductions of a Steroidal Cyclic Anhydride

D. E. BURKE AND P. W. LE QUESNE*[2]

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48104

Received January 20, 1971

Variable selectivity has been observed in different hydride reductions of a steroidal cyclic anhydride to γ-lactones. There is strong selectivity with lithium aluminum hydride, less with sodium aluminum hydride, and none with sodium borohydride. Lactol formation *via* reduction of the anhydride with lithium aluminum tri-*tert*-butoxyhydride is also highly selective. These results support a proposed mechanism involving 1,4 attack by hydride on a complex involving an anhydride group, another carbonyl group, and a metal cation.

Steroids bearing appropriate functional groups are unsurpassed in their ability to reveal the stereochemical aspects of a wide variety of important reactions. In a previous paper in this series,[3] a study was made of the reduction of cyclic anhydrides by metal hydrides to γ-lactones, a reaction of considerable potential synthetic utility. In particular, the Inhoffen adduct **1**[4,5] of ergosteryl acetate and maleic anhydride was shown to be reduced selectively by sodium borohydride or lithium aluminum hydride to the lactone **2**. None of the isomeric **3** was obtained. Bloomfield and Lee[6] proposed for reductions of simple succinic anhydrides that differences in the steric environment of anhydride carbonyl groups induce preferential participation of these carbonyls in an intermolecular complex also involving a reagent cation. The complex is then selectively attacked by the hydride reagent. The 3′- and 4′-carbonyls of **1** are approximately equivalent in steric environment[3] (C-3′ is only slightly more hindered), and hence the high degree of selectivity observed in the reduction of **1** to **2** could not be ascribed to intermolecular complex formation alone. It can, however, be interpreted[3] in terms of a mechanism in which intramolecular complex **4** is formed, and the bulky solvated **4** is then attacked by hydride at the other anhydride carbonyl. This mechanism was also invoked[3] to explain the selective reduction of **1** by lithium aluminum tri-*tert*-butoxyhydride to the lactol **5**. (A related reduction in the aromatic series, of a dimethoxyphthalic anhydride to a hydroxyphthalide, has also been reported.)[7]

To test the validity of this mechanism, we have investigated the hydride reduction of the methoxy anhydride **6**. This compound, lacking the acetoxycarbonyl group to participate in an intramolecular complex, might be expected to give both possible lactones **7** and **8** on hydride reductions provided that intermolecular complex formation is absent or itself unselective.

The methoxy anhydride **6** was prepared from the Inhoffen adduct **1**. The known hydroxydicarboxylic diester **9**[5,8] with diazomethane and aluminum chloride[9]

(1) For part III, see A. L. Andrews, R. C. Fort, and P. W. Le Quesne, *J. Org. Chem.*, **36**, 83 (1971).

(2) To whom inquiries should be addressed.

(3) M. E. Birkelbaw, P. W. Le Quesne, and C. K. Wocholski, *J. Org. Chem.*, **35**, 558 (1970).

(4) H. H. Inhoffen, *Justus Liebigs Ann. Chem.*, **508**, 81 (1934).

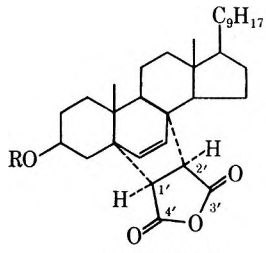
(5) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 297 (1968).

(6) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967).

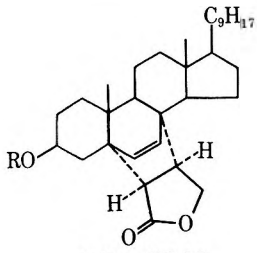
(7) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968).

(8) D. N. Jones and I. Thomas, *J. Chem. Soc.*, 5206 (1964).

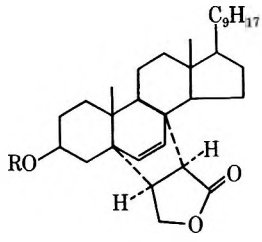
(9) E. Müller, R. Heischkeil, and M. Bauer, *Justus Liebigs Ann. Chem.*, **677**, 55 (1964).



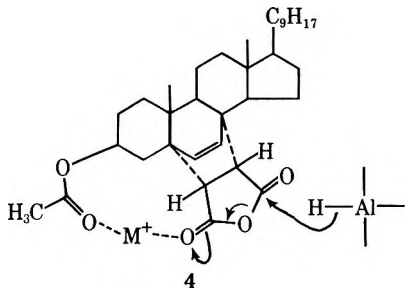
1, R = CH_3CO
6, R = CH_3



2, R = CH_3CO
7, R = CH_3
12, R = H

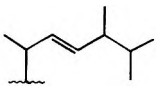


3, R = CH_3CO
8, R = CH_3

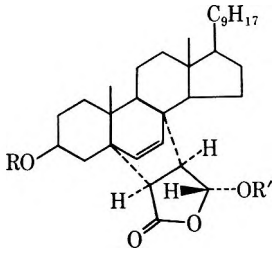


4

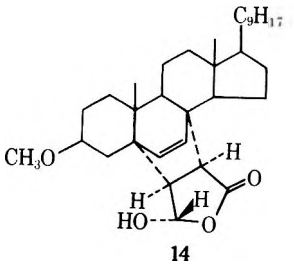
C_9H_{17} =



gave the methoxy dimethyl ester **10**, $C_{35}H_{54}O_5$, mp 92–93°, which on hydrolysis with potassium hydroxide in aqueous propylene glycol followed by reflux with acetic



5, R = CH_3CO; R′ = H
13, R = CH_3O; R′ = H
15, R = CH_3O; R′ = CH_3CO



14

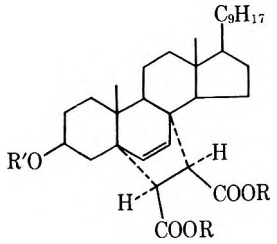
anhydride gave the desired methoxy anhydride **6**, $C_{33}H_{48}O_4$, mp 168–169.5°. That this compound has the same stereochemistry as the Inhoffen adduct **1** was established by comparison of their nmr spectra which are very closely analogous (see Table I).[10]

By treatment of the methoxy anhydride **6** with sodium borohydride in refluxing dioxane,[3] and chromatography of the crude product on alumina, a lactonic fraction was obtained which was shown by tlc to contain two compounds. These were separated by preparative tlc on silica gel and shown to be isomeric methoxy lactones, $C_{33}H_{50}O_3$. These compounds, mp 161–163° (slower moving on tlc) and mp 168–170.5° (faster moving in tlc), were obtained in virtually equal amounts and were assigned structures **7** and **8**, respectively, from the following data. First, both compounds with lithium aluminum hydride in refluxing dioxane gave the same methoxydiol **11**, $C_{33}H_{54}O_3$, mp

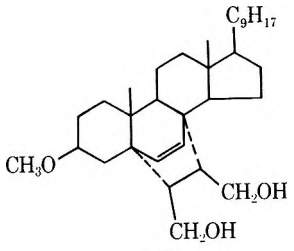
TABLE I

NMR SPECTRA OF ANHYDRIDES 1 AND 6 (τ UNITS)

Protons attached to	Anhydride 1	Anhydride 6
C-6, C-7 H	AB q, 3.86, 4.28 ($J_{6,7}$ = 8 Hz)	AB q, 3.83, 4.49 ($J_{6,7}$ = 8 Hz)
C-22, C-23 H	m, 4.90	m, 4.87
C-1′, C-2′ H	AB q, 6.58, 7.18 ($J_{1',2'}$ = 9 Hz)	AB q, 6.58, 7.17 ($J_{1',2'}$ = 9 Hz)
CH_3COO	s, 8.00	
CH_3O		s, 6.58
C-18 CH_3	s, 9.28	s, 9.28
C-19 CH_3	s, 8.98	s, 8.96



9, R = CH_3; R′ = H
10, R = R′ = CH_3



11

190.5–191.5°. Secondly, treatment of the hydroxy lactone **12** of known structure[3] with diazomethane–aluminum chloride gave the slower moving methoxy lactone unambiguously. In accord with this, the ORD curve of the methoxy lactone **7**, was virtually superimposable on that of the acetoxy lactone **2** (see Experimental Section). The CD of **7** was also negative, as predicted from the lactone sector rules.[11] In contrast, the CD curve of the isomeric lactone **8** was positive, also in accord with predictions from the lactone sector rules. The ORD curve of this compound, however, has a positive peak (230 nm) followed by a negative trough (208 nm). This complexity may be regarded as an effect of the combined asymmetry of the whole molecule.[12] Thirdly, the nmr spectra of the two lactones, although similar, showed differences in accord with the structures assigned. The salient features are shown in Table II.

With lithium aluminum hydride in tetrahydrofuran at −55°, the methoxy anhydride **6** gave both lactones **7** and **8**, but under these conditions the lactone **7** greatly predominated (~13:1). Sodium aluminum hydride under the same conditions also gave both lactones, with slightly but reproducibly lesser selectivity (10:1).

These products were obtained in moderate (30–60%) yield. Other products were mixtures and were not

(10) Note that in ref 3 the *J* values quoted are *half* the values intended; this error does not, however, invalidate the structural conclusions drawn.

(11) J. P Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211, 7229 (1965).

(12) Compare C. Djerassi, in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Sadtler Research Laboratories, Philadelphia, Pa. 1967, p 16.

TABLE II
NMR SPECTRA OF LACTONES 7 AND 8

Protons attached to	Lactone 7	Lactone 8
C-6, C-7	AB q, 3.86, 4.32 (J_{AB} = 8 Hz)	AB q, 3.94, 4.24 (J_{AB} = 8 Hz)
C-22, C-23	m, 4.88	m, 4.89
C-3′ (2 H)	m, 6.1	
C-4′ (2 H)		m, ~6.1
C-1′	d, 7.64 (J = 9 Hz)	m, ~6.3
CH_3O	s, 6.72	s, 6.63
C-2′	m, 6.24	d, 7.08 (J = 10 Hz)
C-18	s, 9.28	s, 9.24
C-19	s, 8.97	s, 8.98

well characterized, but preliminary examination suggested the presence of acidic compounds.

Dreiding models of anhydride **6** do not indicate a large difference in the steric accessibility of the two carbonyl groups (the C-3′ group is slightly more hindered). The pronounced selectivity observed with lithium aluminum hydride at −55° probably, therefore, reflects a preferential complex formation involving the slightly less hindered C-4′ carbonyl, a lithium cation, and a carbonyl group from another molecule. The small lithium cation would be highly solvated, adding to the effective steric bulk of such a complex and enhancing the selectivity of its formation. The lesser selectivity of sodium aluminum hydride reduction may reflect lesser solvation of the metal cation in the complex. In the sodium borohydride reaction, the sodium cation, the much higher temperature, and perhaps the different solvent (dioxane) would tend to lessen the selectivity of intermolecular complex formation.

These data taken together support the formation of intermolecular complexes containing metal cations in the reduction of the methoxy anhydride **6**, as suggested for simpler compounds in Bloomfield and Lee's hypothesis,[6] and are also clearly consonant with the intramolecular complex formation proposed for the Inhoffen adduct **1**.[3]

Treatment of the anhydride **6** with lithium aluminum tri-*tert*-butoxyhydride gave mainly one compound, $C_{33}H_{50}O_4$, mp 234–237° dec. This compound is assigned the lactol structure **13** from comparison of its spectra (and those of its acetate **15**, $C_{35}H_{52}O_5$, mp 170–172°) with those of the acetoxy lactol **5** and from its reduction by sodium borohydride in ethanol to the lactone **7**. The ir spectrum of the lactol **13** in the solid state indicated the presence of both lactol and aldehydo acid tautomers but in chloroform solution only the ring-closed form. The stereochemistry of the lactol OH appeared from the nmr spectrum of the acetate **15** to be the same as in the lactol **5** and its derivatives.[3] Accompanying the lactol in the lithium aluminum tri-*tert*-butoxyhydride reduction product were traces of the lactone **7**, detected by tlc, and a further compound, not obtained in sufficient quantity for isolation. Its polarity in tlc indicated that it was probably the lactol **14**, which is supported by the reduction of a mixture with the lactone **7** by ethanolic sodium borohydride to a mixture of the lactones **7** and **8**. These results show that lithium aluminum tri-*tert*-butoxyhydride also reduces the anhydride **6** with high selectivity, which further supports the mechanistic postulates made above, since with this extremely bulky attacking anion the reduction takes place almost exclusively of the *more* hindered carbonyl of the substrate. The variability of these anhydride reductions is potentially useful in the design of syntheses of a variety of natural products.

Experimental Section

General experimental directions are given in ref 3.

Methylation of the Hydroxy Dimethyl Ester 2.—Ethereal diazomethane was gradually added at 0° (N_2) to a solution of the hydroxy dimethyl ester **9** (13 g) in anhydrous ether (250 ml) containing aluminum chloride (0.2 g) until the yellow color persisted. Further aluminum chloride (0.2 g) was then added and the solution stirred at 0° for 30 min. Excess diazomethane was destroyed by dropwise addition of acetic acid, and 2 *N* HCl was then added. The ether layer was dried (Na_2SO_4) and concentrated to an oil, which crystallized from a concentrated solution in methanol, giving the methoxy dimethyl ester **10** (12 g) as stout prisms: mp 92–93°; $[\alpha]^{23}D$ −54° (*c* 1.0, $CHCl_3$); ir ν^{KBr} 1748 cm^{-1} (ester C=O); nmr τ 3.76, 4.01 (2 H, AB q, J = 8 Hz, C-6, C-7 H), 4.85 (2 H, m, C-22, C-23 H), 6.45, 6.55 (3 H each, singlets, $COOCH_3$), 6.63, 7.21 (2 H, AB q, J = 10 Hz, C-1′, C-2′ H), 6.73 (3 H, singlet, C-3 OCH_3), 8.96 (3 H, s, C-19 CH_3), 9.23 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{33}H_{54}O_5$: C, 75.77; H, 9.81. Found: C, 75.67; H, 9.88.

Synthesis of the Methoxy Anhydride 6.—The methoxy dimethyl ester **10** (6g) was dissolved in warm propylene glycol (90 g) (N_2), and after gradual addition of 50% aqueous potassium hydroxide (17.4 g) the mixture was heated under reflux (N_2) for 3–4 hr. The reaction mixture was poured into a large volume of 2 *N* HCl which caused an acidic product (5.8 g) to be precipitated.

This material (2 g) was heated under reflux with acetic anhydride (15 ml) for 1 hr. Cooling the mixture caused crystallization of the anhydride **6** (1.7 g), essentially pure. One recrystallization from acetic anhydride gave the analytical sample as needles: mp 159–170°; $[\alpha]^{23}D$ −32° (*c* 1.0, $CHCl_3$); ir ν^{KBr} 1850, 1775 cm^{-1} (anhydride C=O); nmr given fully in text. *Anal.* Calcd for $C_{33}H_{48}O_4$: C, 77.91; H, 9.51. Found: C, 77.87; H, 9.37.

Reaction of the Methoxy Anhydride 6 with Sodium Borohydride.—Sodium borohydride (250 mg) was added to a solution of the methoxy anhydride **6** (1.7 g) in freshly distilled dioxane (17 ml) and the mixture heated under reflux for 3 hr. The solution was let cool, diluted with water, and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated to a clear oil which was chromatographed in benzene on alumina (Fisher, alumina for chromatography, 50 g). Elution with benzene rapidly gave a lactonic fraction (by ir, 0.7 g). This material was chromatographed on two E. Merck 2.0-mm silica gel preparative layer plates. Each plate was developed nine times with pentane–ether (9:1), giving two well-resolved bands (uv visualization). Each band from both dried plates was excised, powdered, and mixed with the equivalent from the other plate. The adsorbents were then exhaustively extracted (Soxhlet) with ether. The ethereal extract of the material from the slower moving band crystallized on concentration to give the methoxy lactone **7** as needles (275 mg): mp 161–163°; $[\alpha]^{23}D$ −87° (*c* 1.0, $CHCl_3$); ORD, negative Cotton effect, $[\alpha]_{MeOH}$ −4200° at 215 nm, the first extreme; λ_0 208 nm; CD, negative, trough not observable under the conditions employed; ir ν^{KBr} 1760 cm^{-1} (γ-lactone); nmr given in text. *Anal.* Calcd for $C_{33}H_{50}O_3$: C, 80.11; H, 10.19. Found: C, 80.30; H, 10.17. (Note that the ORD data for the acetoxy lactone **2** were incorrectly given in ref 3; the correct data are $[\alpha]_{MeOH}$ −3900° at 220 nm, the first extreme; λ_0 208 nm). The ethereal extract of the faster moving band also crystallized on concentration to give the methoxy lactone **8** as needles (290 mg): mp 168–170.5°; $[\alpha]^{23}D$ −9° (*c* 1.0, $CHCl_3$); ORD, positive followed by negative Cotton effects, peak at 230 nm, $[\alpha]_{MeOH}$ +200°, trough at 209 nm, $[\alpha]_{MeOH}$ −3450°; λ_0 224 nm; CD, positive Cotton effect, peak at 229 nm, $[\theta]_{MeOH}$ +5000°; ir ν^{KBr} 1750 cm^{-1} (γ-lactone); nmr given in text. *Anal.* Calcd for $C_{33}H_{50}O_3$: C, 80.11; H, 10.19. Found: C, 80.23; H, 10.10.

Methylation of the Hydroxy Lactone 12 to the Methoxy Lactone 7.—To a solution of the hydroxy lactone **12** (50 mg) in anhydrous

ether (10 ml) at 0°, anhydrous aluminum chloride (10 mg) was added, followed by excess ethereal diazomethane, until the yellow color persisted briefly. Further aluminum chloride and diazomethane solution were then added. After 30 min of stirring at 0°, glacial acetic acid was added dropwise to destroy excess diazomethane. Work-up as in the methylation of **9** described above gave a material shown by tlc to comprise the methoxy lactone **7** and a small amount of the hydroxy lactone **12**. No methoxy lactone **8** was observed.

Reductions of Lactone 7 and 8 with Lithium Aluminum Hydride.—The lactone **7** (50 mg) was heated under reflux in dioxane (5 ml) with lithium aluminum hydride (10 mg) for 4 hr. The reaction was quenched with aqueous dioxane and worked up *via* 2 *N* HCl and ether. The product was the methoxy diol **11** (20 mg), which crystallized from ethyl acetate–hexane as needles: mp 190.5–191.5°; $[\alpha]^{23}D$ −60° (c 1.0, $CHCl_3$); ν^{KBr} 3400 cm^{-1} (OH). *Anal.* Calcd for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.32; H, 10.90.

Lactone **8**, reduced in the same way, gave the same methoxydiol.

Reductions of the Methoxy Anhydride 6 with Lithium Aluminum Hydride and Sodium Aluminum Hydride. 1. With Lithium Aluminum Hydride.—A solution of the methoxy anhydride **6** (500 mg) in tetrahydrofuran (5 ml) was added dropwise to a stirred solution of lithium aluminum hydride (40 mg) in tetrahydrofuran (5 ml) at −55° (acetone–CO_2 bath). The mixture was let warm to −5° during 90 min and stirred at this temperature for 30 min, after which it was acidified (6 *N* HCl) and partitioned between water and ether. The organic material obtained by concentration of the dried (Na_2SO_4) ether layer was chromatographed as described for the reduction of **6** with sodium borohydride above. Lactones **7** and **8** were obtained pure in yields of 200 and 15 mg, respectively. They were identified by tlc and ir.

2. With Sodium Aluminum Hydride.—From 525 mg of anhydride **6** and 100 mg of sodium aluminum hydride (Ventron), lactone **7** and **8** were obtained in yields of 275 and 30 mg, respectively, using the same procedure as above.

Reduction of the Methoxy Anhydride 6 with Lithium Aluminum Tri-*tert*-butoxyhydride.—A solution of the anhydride **6** (1 g) in tetrahydrofuran (25 ml) was added dropwise to a stirred solution of lithium aluminum tri-*tert*-butoxyhydride (2.0 g) in tetrahydrofuran (25 ml) at 0°. After 5 hr at 0°, the reaction was quenched with excess 2 *N* HCl, and the mixture partitioned between water and ether. The ether layer was dried ($MgSO_4$) and concentrated, and the organic product chromatographed on preparative silica gel plates as in experiments described above, except that pentane–ethyl acetate (10:1) was used as developing solvent. After four developments, three bands were discerned: one at the origin and two above it. Extraction of the lower two of these as above gave the same material which was the lactol **13**, obtained from ether as fine needles (650 mg): mp 234–237° dec; $[\alpha]^{23}D$ −51° (c 1.0, $CHCl_3$); ir ν^{KBr} 3404, 3230 (OH), 1770 (γ-lactone), 1735 cm^{-1} (aldehyde and acid C=O); ν^{CHCl_3} 3300 (OH), 1765 cm^{-1} (γ-lactone). *Anal.* Calcd for $C_{33}H_{50}O_4$: C, 77.60; H, 9.87. Found: C, 77.68; H, 9.69. Treatment of this compound (50 mg) with acetic anhydride (2 ml) under reflux (N_2) for 3 hr and removal of solvent under reduced pressure gave a slowly crystallizing oil, which after two recrystallizations from ethyl acetate–hexane gave the pure lactol acetate **15** as needles: mp 170–172°; ir ν^{KBr} 1780 (γ-lactone C=O), 1755 cm^{-1} (lactol acetate C=O); nmr τ 3.69, 4.12 (2 H, AB quartet, J = 10 Hz, C-6, C-7 H), 3.87 (1 H, broadened singlet, C-3′ H), 4.82 (2 H, m, C-22, CH23 H), 6.63 (3 H, singlet, C-3 OCH_3), 7.85 (3 H, singlet, lactol CH_3COO), 8.91 (3 H, singlet, C-19 CH_3), 9.24 (3 H, singlet, C-18 CH_3). *Anal.* Calcd for $C_{35}H_{52}O_5$: C, 76.04; H, 9.48. Found: C, 76.13; H, 9.50. The highest band in the preparative tlc from the reduction was present in very small amount. Analytical tlc of this band showed it to contain two compounds, one identical with the methoxy lactone **7**. Reduction of a very small sample of this mixture with sodium borohydride in ethanol and work-up as above gave (tlc) a mixture containing methoxy lactone **7** and **8** only.

Similar sodium borohydride reduction of the pure lactol **13** gave the methoxy lactone **7**.

Registry No.—**1**, 30345-18-7; **2**, 30345-11-0; **6**, 30345-12-1; **7**, 30345-13-2; **8**, 30409-20-2; **10**, 30345-14-3; **11**, 30345-15-4; **13**, 30345-16-5; **15**, 30345-17-6.

Acknowledgments.—We thank Mr. Yoichi Shimokawa for assistance with ORD–CD measurements, and we gratefully acknowledge partial support of this work through institutional research grants from the American Cancer Society to The University of Michigan.

Steroids. VIII.[1] A-Nor Steroids *via* Pinacol-Type Rearrangement

AJAY K. BOSE* AND NATHAN G. STEINBERG

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030

Received December 23, 1970

Pinacol-type rearrangement of 2α-hydroxy-3α-mesyloxy-2β-methylcholestane led to 2β-acetyl-1-norcholestane, the structure and stereochemistry of which was confirmed by Baeyer–Villiger oxidation to the known 2β-acetoxy-*A*-norcholestane and subsequent saponification and oxidation to the known *A*-norcholestan-2-one. Analogous rearrangement of 3β-hydroxy-4β-mesyloxy-3α-methyl-5β-cholestane gave 3ξ-acetyl-*A*-nor-5β-cholestane.

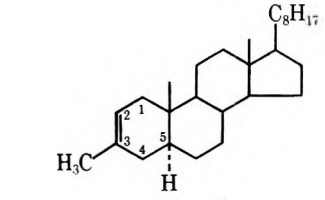
In the course of a synthesis of steroids with modified ring systems,[2] it was necessary to contract the A ring of certain steroids and introduce the progesterone side chain. The synthesis of A-nor steroids has been effected previously through the Favorskii reaction or the benzilic acid rearrangement.[3-7] Since these methods were not particularly suited to our objectives, a pinacol-type rearrangement was studied. This approach has been used for the modification of the D ring of steroids.[8,9] After the completion of our work, the preparation of A-homo-B-nor and A-nor-B-homo steroids[10] and ring-contracted pinane derivatives[11] through a pinacol-type rearrangement was described.

Reaction of 3-cholestanone with methylmagnesium bromide gave a tertiary alcohol which could be dehydrated readily[12] to an olefin **1**. The nmr spectrum of **1**

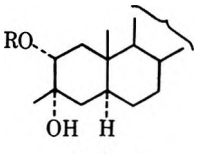
(1) For part VII, see A. K. Bose and N. G. Steinberg, *Syn.*, 595 (1970).
(2) N. G. Steinberg, Ph.D. Thesis, Stevens Institute of Technology, 1969.
(3) F. Winternitz and A. C. dePaulet, *Bull. Soc. Chim. Fr.*, 288 (1954).
(4) D. E. Evans, A. C. dePaulet, C. W. Shoppee, and F. Winternitz, *Chem. Ind. (London)*, 355 (1955).
(5) D. E. Evans, A. C. dePaulet, C. W. Shoppee, and F. Winternitz, *J. Chem. Soc.*, 1451 (1957).
(6) J. Bielman and N. Rajic, *Bull. Soc. Chim. Fr.*, 441 (1962).
(7) For an excellent summary, see N. L. Wendler in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 1084.
(8) N. L. Wendler and D. Taub, *J. Amer. Chem. Soc.*, **82**, 2836 (1960).
(9) G. Stork and J. E. McMurry, *ibid.*, **89**, 5465 (1967).
(10) M. Nussim and Y. Mazur, *Tetrahedron*, **24**, 5337 (1968).
(11) R. G. Carlson and J. K. Pierce, *Tetrahedron Lett.*, 6213 (1968).
(12) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

was consistent with the 3-methyl-2-cholestene structure, since the olefinic proton signal appeared as a multiplet rather than a doublet. The corresponding olefin **8** from 3-coprostanone could be assigned the 3-methyl-5β-cholest-3-ene structure as the olefin signal was a doublet (J = 2 Hz).

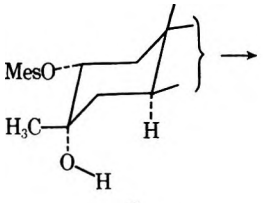
The pinacol-type rearrangement of 3-methyl-2,3-diol (**2**) could lead to various products depending on the configurational and conformational factors.[13] Besides the desired 2-acetyl-*A*-norcholestane (**4**), other products could be 2,3-epoxide and 2-methyl-3-cholestanone. It is known[14] that the optimum conditions for ionic rearrangement in substituted cyclohexanes exist when the four atoms involved in the rearrangement are coplanar and the migrating and departing groups are trans and antiparallel. In the light of these requirements, the best chances for obtaining **4** would exist when the 2,3-diol is cis and α oriented.



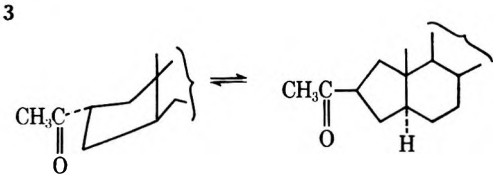
1



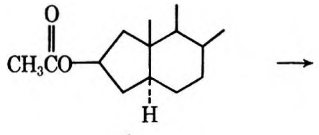
2, R = H
3, R = Mes



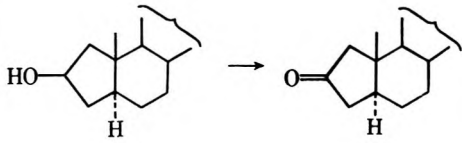
3



4a **4b**



5

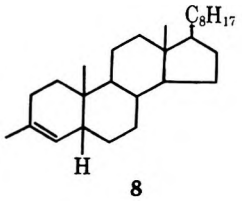


6 **7**

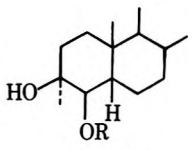
Stereospecific formation of a diol **2** occurred on osmylation of **1**. Confirmation of the expected 2α,3α configuration for the diol was provided by its nmr spectrum: the 2β proton appeared as a quartet (J_{aa} = 12 Hz, J_{ae} = 6 Hz). The 2α-mesylate derivative **3** underwent ring contraction to give a single isomer of 2-acetyl-*A*-norcholestane (**4**) in 73% yield when warmed with a solution of 5% methanolic potassium hydroxide. The 2α configuration would be expected for the acetyl group in **4** on the basis of the reaction mechanism; however, epimerization in the presence of a base could result in the formation of the β isomer **4b**.

Shoppee and Sly[15] had prepared 2α- and 2β-acetyl-*A*-nor-5α-cholestane but the configurational assignment was later reversed by Fuchs and Loewenthal,[16] a revision subsequently confirmed by Dauben, *et al.*[17] Baeyer–Villiger oxidation of **4** gave the previously described 2β-acetoxy-*A*-nor-5α-cholestane in good yield which was hydrolyzed and oxidized to the known *A*-norcholestan-2-one. The product isolated by us from the ring contraction of **3** must therefore be assigned the structure **4b**.

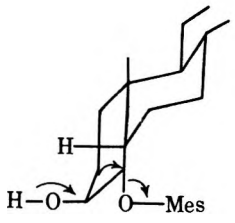
It could be expected by analogy that ring contraction of an appropriate 5β-steroid compound by the sequence described above would lead to an A-nor derivative with an acetyl side chain on C-3 (**11**). Reaction of 3-coprostanone with methylmagnesium iodide followed by dehydration gave a single cycloalkene **8**, demonstrating regiospecificity of the dehydration step. Osmylation



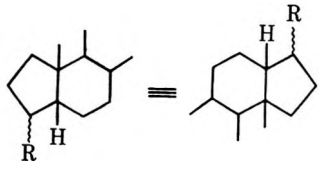
8



9, R = H



10



11, R = CH_3CO
12, R = CH_3CO_2

of **8** afforded in good yield a cis diol **9**, the stereochemistry of which was determined by nmr spectroscopy. The methine proton at C-4 exhibited a doublet at τ 6.38 with a coupling constant of 11 Hz indicative of diaxial coupling with the 5β proton. The compound **9** must therefore be the 3β,4β diol. Conversion of **9** to the mesylate **10** followed by alkali treatment yielded 3ξ-acetyl-5β-cholestane (**11**). Baeyer–Villiger oxidation of **11** gave 3-acetoxy-5β-cholestane (**12**) as an oil which appeared to be homogenous on tlc. Although the initial product from the ring contraction of **10** would be expected to be the 3β-acetyl compound on mechanistic grounds, inversion (at least in part) may have occurred under the basic reaction conditions.

Since bile acids belong to the 5β series and are readily available, the pinacol-type rearrangement described here provides easy access to 18-nor-14β-methylprogesterone derivatives **11**. Work along these lines is in progress.

Experimental Section

Infrared spectra were obtained in Nujol mull on a Perkin-Elmer Model 137B spectrophotometer; nmr spectra were re-

(13) For example, see ref 11.
(14) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(15) C. W. Shoppee and J. C. P. Sly, *ibid.*, 345 (1959).
(16) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).
(17) W. G. Dauben, G. A. Boswell, and W. H. Templeton, *J. Amer. Chem. Soc.*, **83**, 5006 (1961).

corded in deuteriochloroform solution on a Varian DP-60 spectrometer using tetramethylsilane as an internal standard. Melting points were determined on Mel-Temp block and are uncorrected. Thin layer chromatography was performed on silica gel G coated plates and spots were visualized with iodine vapor.

3-Methylcholest-2-ene (1).—To a stirred solution of 6.06 g (15.8 mmol) of cholestan-3-one in 21 ml of anhydrous tetrahydrofuran was added 21 ml of 3 *N* methylmagnesium bromide. After refluxing the mixture in a nitrogen atmosphere for 1 hr and then cooling, the excess of Grignard reagent was decomposed by dropwise addition of saturated ammonium chloride solution. The layers were separated, and the aqueous layer was extracted three times with chloroform. The organic extracts were combined, washed successively with saturated aqueous sodium chloride and water, and dried (Na_2SO_4). Evaporation *in vacuo* gave 5.8 g (91%) of the *tert*-alcohol (ir, 2.8 μ) as an oil, which could not be induced to crystallize.

A solution of 4.0 g (9.95 mmol) of this alcohol in 60 ml of glacial acetic acid was heated at reflux for 10 hr. After cooling, a crude solid precipitated which was collected and washed with a small amount of acetic acid and water and then chromatographed over neutral alumina. Elution with chloroform afforded 3.5 g (92%) of a colorless solid, mp 82–83° (lit.[12] mp 82–83°). The nmr spectrum displayed a one-proton multiplet at τ 4.8 (olefin).

3β-Methylcholestane-2α,3α-diol (2).—A solution of 2.28 g of 1 in 20 ml of dioxane was treated with a solution of 2.28 g of osmium tetroxide in 5 ml of benzene. The solution was stirred at room temperature for 2 days, treated with 92 ml of absolute alcohol for 45 min, and then reduced with a solution of sodium sulfite at 5° for 3 hr. The reaction mixture was filtered through Super-cel, and the cake thoroughly washed with absolute alcohol and then with ether.

The filtrates were combined and evaporated to dryness *in vacuo*. The crude product was once again taken up in ether, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue, on crystallization from ethyl acetate, afforded 1.5 g (61%) of **2**, mp 162–164°. An analytical sample, mp 188–189°, was obtained by chromatography over neutral alumina and recrystallization from ethyl acetate–acetone. The nmr spectrum revealed a one-proton quartet at τ 6.5, J = 12 Hz (5a,a) and J = 6 Hz (5a,e).

Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.01; H, 11.61. Found: C, 80.09; H, 11.51.

2β-Acetyl-*A*-nor-5α-cholestane (4).—To a stirred solution of 1.0 g (2.4 mmol) of **2** dissolved in 10 ml of pyridine was added 1.5 ml of methanesulfonyl chloride at −5–0°. After 2 hr at that temperature, the reaction mixture was poured into water and allowed to stand for 30 min. The resulting precipitate was dissolved in chloroform, washed three times with water, and dried (Na_2SO_4). Removal of solvent afforded 1.2 g (100%) of **3** which was used without purification for the next step.

A mixture of 1.2 g of crude **3** in 40 ml of methanol and 1.8 g of potassium hydroxide in 4 ml of distilled water was refluxed for 1 hr, under nitrogen. The reaction mixture was cooled to 0–5°, acidified to pH 1 with 2.5 *N* aqueous HCl, and extracted with three portions of chloroform. The usual work-up gave 0.98 g of a crude product which was chromatographed over neutral alumina to afford 0.68 g (71%) of **4**, mp 56–57.5°, characterized by infrared absorption at 5.78 μ (CO) and a methyl signal [$CH_3C(=O)$] at τ 7.98 in the nmr spectrum. An analytical sample, mp 62–64°, was prepared by recrystallization from methanol.

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.60; H, 12.32.

2β-Acetoxy-*A*-nor-5α-cholestane (5).—A solution of 100 mg of **4** and 188 mg of *m*-chloroperbenzoic acid in 5 ml of chloroform was maintained at 0–5° for 7 days and then treated with 5% aqueous potassium iodide, followed by 5% aqueous solution of sodium thiosulfate. After three washes with water, the organic layer was dried ($MgSO_4$) and evaporated to give a material with strong ir absorption at 5.78 μ (ester CO) which upon crystallization from methanol afforded 80 mg (77%) of **5**, mp 75–76° (lit.[17] 75–77°).

***A*-nor-5α-cholestan-2-one (7).**—A solution of 100 mg of **5** in methanol and 2 ml of a 10% solution of potassium hyroxide was refluxed under nitrogen for 1 hr. After the usual work-up 95 mg of product **6** was obtained which was dissolved in acetone and oxidized with Jones reagent at 0–5°. Methanol was added to destroy the excess of Jones reagent. The reaction mixture was diluted with water and then extracted with ether. The combined organic extracts were washed with water, 10% aqueous sodium bicarbonate, and again with water. Drying ($MgSO_4$) and concentration *in vacuo* afforded 90 mg of an oil which was chromatographed on 6.0 g of silica gel to yield 35 mg of the title compound, mp 95–96°. The infrared spectrum showed an absorption peak at 5.75 μ; in the mass spectrum the molecular ion appeared at m/e 372 (M calculated for $C_{26}H_{44}O$). The 2,4-dinitrophenylhydrazone had mp 166–167.5° (lit.[15] mp 165–167°).

3-Methyl-5β-cholest-3-ene (8).—Following the method for the preparation of **1**, coprostanone was converted to **5** in about 90% yield and isolated as an oil characterized by the presence of a methyl signal as a doublet (J = 2 Hz) at τ 8.32 in the nmr spectrum.

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.54. Found: C, 87.48; H, 12.60.

3α-Methylcoprostane-3β,4β-diol (9).—A solution of 730.3 mg (1.9 mmol) of **5** in 10 ml of dioxane was treated with a solution of 1.5 g of osmium tetroxide in 8 ml of benzene. After 2 days at room temperature, the reaction mixture was thoroughly washed with absolute alcohol (20 ml) and then treated with a solution of sodium sulfite at 5° for 3 hr. The reaction mixture was filtered through Super-cel, and the cake was washed with absolute alcohol and then ether. The organic combined filtrate and washes were evaporated to dryness *in vacuo*. The resulting crude product was dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated to give 391.8 mg of oil. This oil was dissolved in chloroform, adsorbed on 12 g of neutral alumina, and eluted successively with chloroform and then chloroform–methanol (99:1), from which 262 mg (33%) of oil was obtained which gave a single spot on tlc: nmr τ 5.38 (J_{aa} = 11 Hz); mass spectrum molecular ion at m/e 418 (M calculated for $C_{28}H_{50}O_2$).

3β-Mesyl-3α-methylcoprostan-3β-ol (10).—A solution of 216.8 mg (0.63 mmol) of **9** was dissolved in 2.5 ml of pyridine and treated with 0.6 ml of methanesulfonyl chloride at 0–5°, with constant stirring. The reaction mixture was allowed to stand for 3 hr at 0–5° and poured into water. After 30 min, the resulting oil was dissolved in chloroform, washed three times with water, dried (Na_2SO_4), and evaporated to give 247 mg of an oil. The infrared spectrum of the mesylated product showed mesylate absorption at 7.5 (s) and 8.5 μ, as well as hydroxyl absorption at 2.85 μ. This product was satisfactory for use in the next step.

3ξ-Acetyl-*A*-nor-5β-cholestane (11).—A solution of 240 mg (0.49 mmol) of **10** in 1 ml of methanol was treated with a solution of 230 mg of potassium hydroxide in 0.5 ml of water and refluxed for 1 hr, under an inert atmosphere. The reaction was cooled to 0–5°, acidified to pH 1 with 2.5 *N* aqueous hydrochloric acid, and extracted three times with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to give 188 mg of product **11** which was dissolved in hexane, adsorbed on 6.0 g of neutral alumina, and eluted successively with hexane, and hexane–benzene (1:1). The latter eluent mixture afforded 148 mg (75.5%) of an oily product which was homogeneous by tlc. The infrared spectrum showed absorption peaks at 5.85 μ; nmr τ 7.87 (s, 3 H, [$CH_3C(=O)$]; mass spectrum molecular ion m/e 400 (M calculated for $C_{28}H_{48}O$).

Registry No.—**2**, 20297-26-1; **4b**, 2493-91-6; **5**, 14772-59-9; **7**, 2310-36-3; **8**, 30255-99-3; **9**, 30256-00-9; **10**, 30256-01-0; **11**, 30256-02-1.

Stereochemistry of the Addition of Metalated Carboxylic Acids to Steroids[1]

MASATO TANABE* AND RICHARD H. PETERS

Stanford Research Institute, Menlo Park, California 94025

Received November 23, 1970

The stereochemistry of the addition of dilithiopropionate and α-halopropionate to dehydroisoandrosterone (**1a**) was studied. The stereochemistry at C_{17} and C_{20} of 17-hydroxybisnorcholanic acids previously determined was reassigned on the basis of new chemical and nmr spectroscopic evidence. The stereochemistry at C_{17} of 3β,17β-dihydroxy-20β-bisnorchol-5-enic acid (**3a**) and its 17α-hydroxy isomer **2a** was determined. Reduction with lithium aluminum hydride of **2a** and **3a** followed by tosylation of the alcohol **8a** and **9a**, which were again reduced by lithium aluminum hydride, yielded two isomeric C_{17} isopropyl compounds, **10** and **11**. Nmr characterization of **10** and **11** indicated that the expected major product resulted from α-side attack at the C_{17} ketone. Compound **11** was also prepared by Grignard reaction of 2-bromopropene and **1b**. The stereochemistry at C_{20} was determined by β-lactonization of acids **2a** and **3a** followed by decarboxylation to cis and trans olefins **6** and **7**.

The metalation of aliphatic carboxylic acids with lithium diisopropyl amide and the reaction of the dimetalated acids with alkylating agents have been reported.[2] We report on a study of the stereochemistry of the addition of dilithiopropionate to dehydroisoandrosterone (**1a**), since the equivalent Reformatsky reaction with α-bromopropionate has been studied in detail and all four compounds isomeric about C_{17} and C_{20} have apparently been isolated and characterized.[3,4]

Reaction of propionic acid with lithium diisopropylamide proceeded smoothly in tetrahydrofuran–hexane, and the dimetalated acid reacted with dehydroisoandrosterone **1a** to give acidic material in a yield of 50% (Scheme I). The nmr spectrum of the acidic fraction showed multiple C_{18} and C_{21} methyl resonances in a ratio of 4:1, indicating the formation of two isomers. The isomers were separated by fractional crystalization from acetone.

The major acidic isomer **3a** was esterified and acetylated to yield a methyl ester 3-acetate, mp 153–154°, $[\alpha]^{24}D$ −49° (acetone). These physical properties are in apparent accord with the isomer designated by Hey, *et al.*,[4] as methyl 3β-acetoxy-17α-hydroxy-20α-bisnorchol-5-en-21-oate, which was isolated as a minor Reformatsky reaction product.

If the previously assigned 17α-hydroxy stereochemistry is valid, this would indicate that the principal product resulted from attack at the more hindered β face of the C_{17} ketone by the dimetalated acid. This result is contrary to all previous addition reactions at C_{17} and suggested that the stereochemical assignment of the bisnorcholenic acids from the Reformatsky reaction should be reinvestigated.

The Reformatsky reaction of dehydroisoandrosterone **1a** with zinc and methyl α-bromopropionate in benzene gave the methyl esters, which were isolated in a 70% yield by a modified method compared to 26% when the products were isolated as acids.[4] Nmr inspection of the C_{18} angular methyl resonances revealed an approximately 3:2 mixture of the esters **3b** and **2b**. Saponification of the mixture of these methyl esters **3b** and **2b** yielded acid **2a** and only traces of acid **3a** along with the neutral ketone **1a**.

The low yield of the acid **3a** recovered under the saponification conditions indicates that retroaldolization of **3b** to starting ketone and propionic acid occurs. Since the retroaldol process changes the product distribution of the isomeric acids, owing to the disappearance of acid **3a** during saponification of its methyl ester **3b**, stereochemical assignments based solely on the relative distribution of acid isomers in the Reformatsky reaction are invalid.

To establish the stereochemistry of the acids **2a** and **3a**, the following series of transformations were conducted. Each acid was reduced with lithium aluminum hydride to afford the corresponding bisnorcholanetriols **8a** and **9a**. Reduction of the respective tosylates **8b** and **9a** with lithium aluminum hydride gave a pair of isomeric 17-hydroxy-3,5-cyclodinorcholanes, **10** and **11**, which had different physical properties and were different by thin layer chromatographic (tlc) behavior.

Since the transformation of **2a** to **10** and **3a** to **11** occurs with destruction of the asymmetric center at C_{20}, the nonidentity of **10** and **11** is evidence for a difference in their stereochemistry at C_{17}. For isomer **3a**, the major isomer formed by the reaction with dilithiopropionate, the nmr of its 17β-hydroxy-17α-isopropyl conversion product **11** shows an equivalence of the isopropyl methyl groups at τ 8.99 (J = 6.6 Hz) and the C_{18} angular methyl resonance appears at τ 9.06. In the nmr of the isopropyl derivative **10** derived from **2a**, which has the 17α-hydroxy-17β-isopropyl grouping, C_{18} angular methyl resonance now experiences greater shielding and resonates at higher fields at τ 9.20 and the isopropyl methyls show nonequivalence at τ 9.08 (J = 6.6 Hz), and τ 9.10 (J = 6.6 Hz). The 17β-isopropyl group is expected to show a greater nonequivalence of the isopropyl groups because of the severe nonbonded interactions with the β-oriented C_{18} angular methyl groups. The nmr data of **10** and **11** are consistent with the stereochemistry of acid **2a** as the 17α-hydroxy derivative and acid **3a** as the isomeric 17β-hydroxy compound.

The stereochemical assignments are in accord with the nmr pyridine solvent shifts of the C_{18} methyl resonance in **2a**, **3a**, **10** and **11**, Table I. The observed shift difference of 10 Hz is in agreement with previously observed values for vicinal deshielding by the 17β-hydroxy group.[5] Our assignment is also in accord with the observation that 17α-hydroxyl compounds

* To whom correspondence should be addressed.

(1) This work was supported by the Public Health Service under Grant AI 07397 from the National Institute of Allergy and Infectious Diseases.

(2) (a) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); (b) P. L. Creger, *ibid.*, **92**, 1396 (1970); (c) P. E. Pfeffer and L. S. Silbert, *Tetrahedron Lett.*, 699 (1970).

(3) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **24**, 1127 (1941).

(4) D. H. Hey, J. Honeyman, and W. J. Peal, *J. Chem. Soc.*, 185 (1954).

(5) P. Demarco, E. Farkas, D. Doddrell, B. Mylari, and E. Wenkert *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

SCHEME I

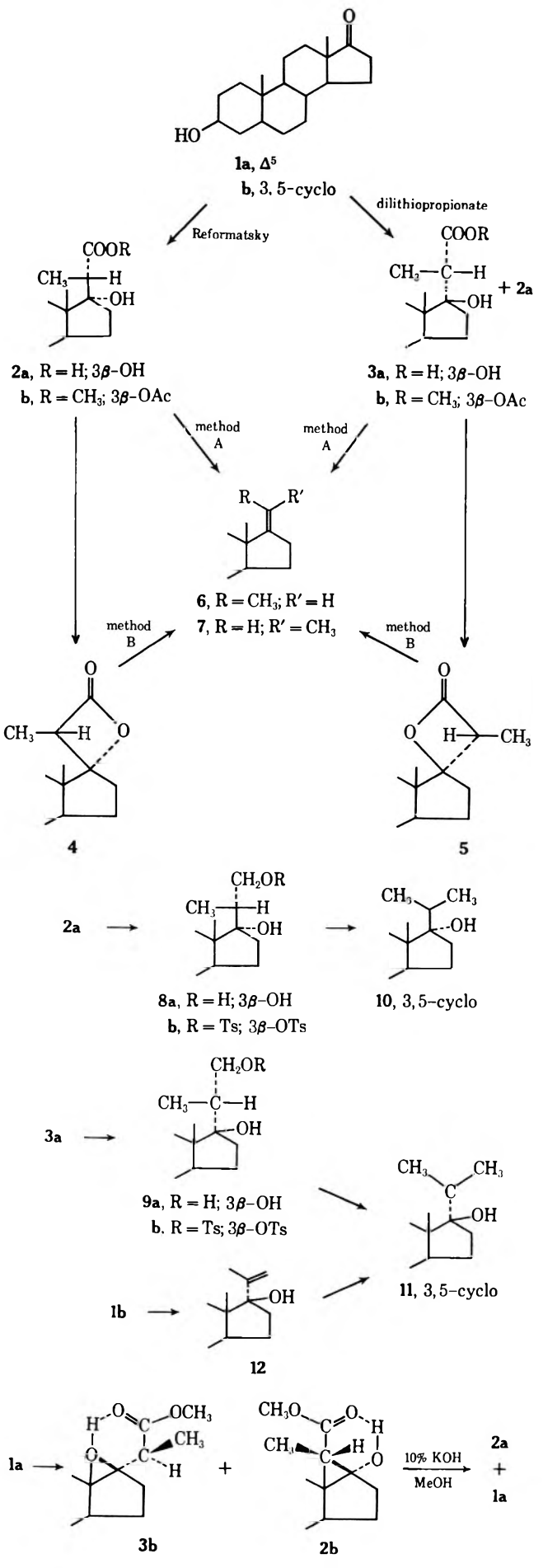
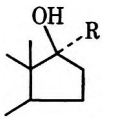
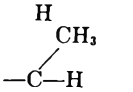
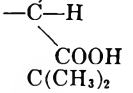


TABLE I

PYRIDINE SOLVENT SHIFTS



R	$\Delta_{18\text{-}CH_3}$[a]
H	10.0
	10.5
	10.0

[a] $\Delta_{18\text{-}CH_3} = Hz_{CD_5N} - Hz_{1:1CDCl_3\text{-}CD_3OD}$. The $\Delta_{18\text{-}CH_3}$ pyridine solvent shifts for the corresponding isomeric 17α-hydroxy compounds were not detectable.

have a more negative rotation value than the 17β isomer.[6]

An alternate synthesis of **11** was achieved by the addition of isopropenylmagnesium bromide to 3α,5β-cycloandrostan-17-one **1b**. Catalytic reduction of the intermediate 17-isopropenyl compound yielded material identical in all respects with **11**. This method of synthesis also supports the 17α-isopropyl stereochemistry for **11**, since all known Grignard additions to C_{17} ketones occur predominantly from the α side.[7]

With the C_{17} configuration firmly established, we determined the C_{20} stereochemistry of **2a** and **3a**. Advantage was taken of a recent observation[8] that a 17-hydroxybisnorcholanic acid decarboxylates with boiling acetic anhydride to yield *cis*-pregn-17(20)-ene, which was formed by decarboxylation of an intermediate β-lactone (5.48 μ). Iwasaki[8] provided conclusive chemical evidence for the 17(20) double bond stereochemistry by osmium tetroxide hydroxylation of 3β-hydroxy-5α-pregn-*cis*-17(20)-ene to yield 3β,20α-dihydroxy-5α-pregnane. Nmr studies[9] have also shown that, in 17(20)-enes with a *cis*-oriented ethylidene side chain, deshielding of the C_{18} angular methyl group occurs in contrast to the trans ethylidene side chain relative to the corresponding C_{17} ketone in the nmr. This spectral correlation is a useful method for establishing the geometry of the 17(20) double bond (Table II).

For rigid stereochemical correlation, the conclusion that a 17α-hydroxy-20β-bisnorcholanic acid will yield pregn-*cis*-17(20)-ene and the 17β-hydroxy-20β epimer will yield pregn-*trans*-17(20)-enes proceeding *via* a β-lactone is valid if isomerization does not occur during this transformation. A recent study[10] shows that the decarboxylation of β-lactones to olefins proceed as a stereospecific cis-elimination reaction.

Application of this β-lactone to olefin conversion for the establishment of C_{20} stereochemistry in bisnorcholanic acids was studied with the acid **3a** obtained from dilithiopropionate. Isolation of β-lactone **5** was achieved by reaction of the acid **3a** with ethyl chloro-

(6) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 179.

(7) (a) L. Fieser and M. Fieser, ref 6, p 467; (b) S. Pines, R. Firesteone, L. Re, M. Kozlowski, and M. Sletzinger, *Steroids*, **8**, 877 (1966).

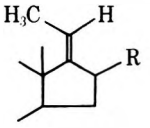
(8) M. Iwasaki, *ibid.*, **9**, 373 (1967).

(9) (a) W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964); (b) M. Leboeuf, A. Cave, and R. Goutarel, *Compt. Rend.*, **264**, 1090 (1967); (c) F. A. MacKeller and G. Slomp, *Steroids*, **11**, 787 (1968).

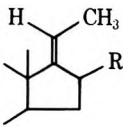
(10) D. S. Noyce and E. H. Baniff, *J. Org. Chem.*, **31**, 4043 (1966).

TABLE II

CIS–TRANS DESHIELDING EFFECTS



cis olefin



trans olefin

Compd	Cis 18-CH_3[a]	Cis $\Delta_{18\text{-}CH_3}$[b]	Trans 18-CH_3[a]	Trans $\Delta_{18\text{-}CH_3}$[b]
3β,16β-Diacetoxy-5α-pregn-17(20)-ene (R = OAc)	55.0[c]	+0.5	47.0[c]	−7.5
3β-Acetoxy-pregn-5,17(20)-diene (R = H)	54.5	+0.5	46.0	−7.0
3β-Acetoxy-5α-pregn-17(20)-ene (R = H)	52.5	+0.5	44.7	−7.3

[a] Values of chemical shifts in hertz downfield from TMS. [b] $\Delta_{18\text{-}CH_3}$ = [18-CH_3 of olefin] − [18-CH_3 of corresponding C_{17} ketone]. [c] These values are from ref 9a.

formate in the presence of triethylamine. The crystalline β-lactone exhibited a characteristic ir band at 5.46 μ. On treatment with *p*-toluenesulfonic acid in boiling xylene, decarboxylation occurred to give only 3β-hydroxy-pregna-5-*trans*-17(20)-diene, isolated as the acetate **7**.

A similar sequence of reactions on the acid **2a**, the major acidic product of the Reformatsky reaction, afforded the β-lactone **4**, which was decarboxylated to 3β-hydroxypregna-5-*cis*-17(20)-diene, then acetylated to give **6**, which had different physical properties and tlc mobility from **7**. The assignment of the C_{20} configuration in **6** and **7** is based on nmr data and is presented in Table I.

The retroaldozation of **3b** can now be rationalized on the basis of steric effects. Examination of models of a hydrogen-bonded form of the methyl ester **3a** [ν_{max} 3510 cm^{-1} (bonded OH)] shows the C_{20} methyl and the C_{12} methylene groups hinder attack of base at the C_{20} carbonyl group, whereas similar considerations with the ester **2b** shows the absence of steric encumbrance at the C_{20} carbonyl.

The addition of dianions of acids offers a convenient alternative to the Reformatsky reaction for the synthesis of β-hydroxy acids.[11,12]

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord instrument from Nujol mulls. Infrared spectra of **3b** in carbon disulfide solution were obtained on a Beckman infrared 7. Proton nmr spectra were obtained on a Varian A-60A instrument, using deuteriochloroform as a solvent and tetramethylsilane as an internal standard unless otherwise stated. Optical rotations were measured in 0.1–0.2% chloroform solutions at 24° unless stated differently. Melting points were taken with a Fisher-Johns hot-stage apparatus and are essentially uncorrected. Reagents were freshly distilled and all glassware was flame-dried. All extracts were dried over anhydrous sodium sulfate and evaporated at reduced pressure.

3β,17β-Dihydroxy-20β-bisnorchol-5-enoic acid (3a).—To a solution containing 12.6 ml of diisopropyl amine in 350 ml of tetrahydrofuran at 0–5° was added, dropwise, 56.5 ml of 1.6 *M* *n*-butyllithium in hexane. After the mixture was stirred for 0.5 hr, 3.4 ml of propionic acid in 60 ml of tetrahydrofuran was added dropwise and stirring was continued for 3.5 hr. To the slightly cloudy suspension, 6.49 g of **1a** in 60 ml of tetrahydrofuran was added. Stirring was continued at 0–5° for 2 hr and then at room temperature for 14 hr. Water (50 ml) was added, and the tetrahydrofuran was evaporated. Ethyl acetate was added and extracted with 4% NaOH. The neutral phase was evaporated to yield 3.08 g of starting ketone **1a**. The basic phase was acidified with 18% HCl and extracted with ethyl acetate. The ethyl acetate was evaporated to yield 4.05 g of acid.

Composition of the acid mixture as determined by nmr indicated an 18-CH_3 ratio of 4:1 for the 17β- to 17α-hydroxy isomers **3a** and **2a**, respectively. The crude acid was recrystallized from acetone to give 1.05 g of **3a**: mp 244–250°; $[\alpha]D$ −11° (dioxane); ir λ_{max} 3.0 (broad, OH), 5.92 μ (C=O); nmr (CD_3OD–$CDCl_3$, 1:1) τ 9.06 (18-CH_3), 8.96 (19-CH_3), 8.64 (d, *J* = 7 Hz, 21-CH_3).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.94; H, 9.57.

Methyl 3β-Acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate (3b).—To a solution of 0.25 g of **3a** in 50 ml of methanol was added an ethereal solution of diazomethane. After 1 hr, the reaction was quenched with acetic acid and evaporated. The residue was dissolved in ether, washed with saturated sodium bicarbonate and water, dried, and evaporated. The residue was acetylated and then recrystallized from ether–petroleum ether to give **3b**: mp 153–154° (lit.[4] mp 154–155°); $[\alpha]D$ −49° (acetone) ir λ_{max} 2.85 (OH), 5.75, 8.00 (acetate), 5.87 μ (C=O, methyl ester); nmr τ 9.10 (18-CH_3), 8.98 (19-CH_3), 8.71 (d, *J* = 7 Hz, 21-CH_3), 7.98 ($OCOCH_3$), 6.33 ($COOCH_3$).

3β,17α-Dihydroxy-20β-bisnorchol-5-enoic Acid (2a).—To a solution of 17.30 g of dehydroisoandrosterone acetate in 100 ml of dry benzene were added 20.0 g of activated zinc and 54.0 g of ethyl 2-bromopropionate. The reaction mixture was heated to slightly below reflux temperature until the reaction became exothermic; the external heating was withdrawn until the reaction subsided (15 min). The mixture was heated to reflux for 1.5 hr and, after cooling, 60 ml of 10% sulfuric acid and 60 ml of ether were added with vigorous stirring. The benzene–ether layer was separated and the water was extracted with additional ether. The combined benzene–ether solutions were washed with water, dried, and evaporated. The residue was dissolved in 200 ml of methanol containing 10% potassium hydroxide and was refluxed for 0.5 hr. The solution was cooled; 100 ml of water was added and concentrated to approximately 125 ml. The resulting suspension was extracted with ether; the ether was dried and evaporated to yield 11.4 g of **1a**. The aqueous phase was treated with 18% HCl until the solution's pH was approximately 3 and then extracted with ether. After evaporation, the residue was recrystallized from acetone to give 1.72 g of **2a**: mp 225–231° (lit.[4] mp 229–232°); ir λ_{max} 2.70 (OH), 2.90 (OH), 5.40 μ (C=O, acid); nmr ($CDCl_3$–CD_3OD, 1:1) τ 9.18 (18-CH_3), 8.95 (19-CH_3), 8.77 (d, *J* = 7 Hz, 21-CH_3).

Saponification of 3b.—A solution of 0.10 g of **3b** in 50 ml of a 10% potassium hydroxide–methanol solution was refluxed for 1.0 hr. After cooling, the methanol was evaporated and the residue was taken up in water and ether. The ether solution afforded 0.07 g of **1a**. The basic phase was acidified with 18% HCl and extracted with ether. The ether solution after evaporation gave 6 mg identical in all respects with **3a**.

Methyl 3β-Acetoxy-17α-hydroxy-20β-bisnorchol-5-enoate (2b) and Methyl 3β-Acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate (3b).—The Reformatsky reaction was carried out essentially as described previously, but with the use of 4.0 g of dehydroisoandrosterone acetate, 32.2 g of methyl α-bromopropionate, 8.0 g of activated zinc, and 120 ml of benzene. The resulting crude mixture was acetylated with acetic anhydride in pyridine to give a residue weighing 5.80 g. To a solution of 1.04 g of the residue in 125 ml of methanol were added 0.35 g of hydroxylamine hydrochloride and 0.42 g of sodium acetate. The solution was heated to reflux for 0.25 hr, cooled, and evaporated. The resulting residue was heated to boiling in chloroform and the insoluble oxime was collected by filtration. The chloroform solution was washed with water, dried, and evaporated to give 0.73 g of a white solid. An nmr spectra indicated that only esters were present and only two isomers were detectable. The composition, using C_{18} methyl chemical shifts was 65% methyl 3β-acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate [nmr ($CDCl_3$) τ 9.10 (18-CH_3), 8.98 (19-CH_3), 8.71 (d, *J* = 7 Hz, 21-CH_3)] and 35% methyl 3β-acetoxy-17α-hydroxy-20β-bisnorchol-5-enoate [τ 9.23 (18-CH_3), 8.95 (19-CH_3), 8.76 (d, *J* = 7 Hz, 21-CH_3)].

(11) A. E. Opara and G. Read, *Chem. Commun.*, 679 (1969).

(12) D. A. Cornforth, A. E. Opara, and G. Read, *J. Chem. Soc.*, 2799 (1969).

20β-Bisnorchol-5-ene-3β,17β,22-triol (9a).—To a solution of 1.3 g of lithium aluminum hydride in 80 ml of tetrahydrofuran was added 0.65 g of **3a** in 80 ml of tetrahydrofuran. The suspension was refluxed for 96 hr, cooled, and quenched with saturated sodium sulfate. The tetrahydrofuran was evaporated; ether and 10% sulfuric acid were added. The ether solution was washed with saturated sodium bicarbonate, 3% hydrochloric acid, and water, and then dried and evaporated to yield 0.90 g of 9a. An analytical sample was recrystallized from acetone: mp 214–217°; $[\alpha]_D$ −53° (MeOH); ir λ_{max} 2.95 μ (OH, broad).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.44; H, 10.45.

20β-Bisnorchol-5-ene-3β,17α,22-triol (8a).—The lithium aluminum hydride reduction of **2a** was carried out as previously described for **3a**, but with the use of 0.50 g of **2a** in 60 ml of tetrahydrofuran, and 1.0 g of lithium aluminum hydride in 60 ml of tetrahydrofuran. The resulting residue **8a** weighed 0.43 g, which afforded an analytical sample upon recrystallization from methanol, mp 201–202° (lit.[4] mp 200–208°).

20β-Bisnorchol-5-ene-3β,17β,22-triol 3,22-Ditosylate (9b) and 17β-Hydroxy-3α,5-cyclo-5α-dinorcholane (11).—A solution of 0.45 g of **9a** and 4.50 g of *p*-toluenesulfonyl chloride in 75 ml of pyridine was stirred for 24 hr at room temperature. The solution was poured into water and extracted with ether. The ether solution was washed with water, 3% HCl, and water. The ether solution after evaporation afforded 0.51 g of ditosylate (**9b**): ir λ_{max}^{film} 2.75 (OH), 6.22, 7.45, 8.50 μ (tosylate).

To a solution of 2.0 g of lithium aluminum hydride in 100 ml of tetrahydrofuran was added 0.1 g of **9b** in 50 ml of tetrahydrofuran. After stirring at room temperature for 48 hr, the reaction mixture was quenched by the slow addition of saturated sodium sulfate. The tetrahydrofuran was evaporated; ether and 10% sulfuric acid were added. The ether solution was separated, washed with 10% sulfuric acid and water, dried, and evaporated to afford 0.29 g of an oil. The oil (0.29 g) and 0.25 g of *m*-chloroperbenzoic acid[13] (78%) in 25 ml of methylene chloride were stirred at room temperature in the dark for 96 hr and then washed with saturated sodium bicarbonate, dried, and evaporated. Preparative thin layer chromatography, using a SiGF plate, developed in benzene–10% ether gave 11 as an oil: $[\alpha]_D$ +38°; ir λ_{max}^{film} 2.90 μ (OH); mass spectrum mol wt 316 (calcd for $C_{22}H_{36}O$), 316 (found); nmr τ 9.06 (18-CH_3, 19-CH_3), 8.99 (d, J = 6.6 Hz, isopropyl methyls, equivalent).

20β-Bisnorchol-5-ene-3β,17α,22-triol 3,22-Ditosylate (8b) and 17α-Hydroxy-3α,5-cyclo-5α-dinorcholane (10).—A solution of 0.23 g of **8a** and 0.33 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine was stirred for 16 hr at room temperature. The workup was as previously described. The resulting gum weighed 0.16 g: ir λ_{max}^{film} 2.75 (OH), 6.22, 7.45, 8.50 μ (tosylate).

The reduction of 8a was essentially as previously described but with the use of 0.16 g of **8b**, 0.64 g of lithium aluminum hydride, and 50 ml of tetrahydrofuran. The resulting residue weighed 0.068 g. An analytical sample was obtained by sublimation: $[\alpha]^{25}_D$ +24°; ir λ_{max}^{film} 2.75 μ (OH); mass spectrum mol wt 316 (calcd for $C_{22}H_{36}O$), 316 (found); nmr ($CDCl_3$) τ 9.20 (18-CH_3), 9.06 (19-CH_3), 9.08 (d, J = 6.6 Hz, isopropyl methyl), 9.10 (d, J = 6.6 Hz, isopropyl methyl).

Addition of Isopropenylmagnesium Bromide to 3α-5-Cyclo-5α-androstane (1b).—To 300 ml of tetrahydrofuran containing 3.6 g of magnesium turnings was initially added 6.5 g of 2-bromopropene followed by dropwise addition of 7.0 g of 2-bromopropene. To the solution of 11.7 g of anhydrous lithium perchlorate was added portionwise and stirring was continued for 20 min at room temperature. A solution of 9.2 g of **1b** in 100 ml of tetrahydrofuran was added and stirred for 18 hr. The reaction mixture was poured into 3% hydrochloric acid and extracted with ether. The ether solution was washed with water, dried, and evaporated to yield 8.4 g of a mixture. Crystallization from methanol yielded 3.61 g of **1b** and after evaporation 5.2 g of an oil. A solution of 150 ml of methanol containing 4.2 g of the filtrate of the oil residue, 2.1 g of hydroxylamine hydrochloride, and 2.1 g of sodium acetate was refluxed for 1 hr and then cooled. After evaporation, the residue was taken up in chloroform and washed with 3% hydrochloric acid and water, dried, and evaporated to yield a 5.1-g mixture of oxime and 11. The mixture (5.0 g) was chromatographed on 500 g of SiGF and the fraction eluted with 2% ether–benzene was put on a SiGF thick plate and developed in benzene–5% ether to afford 0.02 g of **12**: ir λ_{max}^{film} 2.90 μ (OH); nmr τ 9.08 (18-CH_3), 9.06 (19-CH_3), 8.17 (21-CH_3), 5.32, 4.97 (22-=CH_2).

A suspension of 0.02 g of ruthenium in 10 ml of ethanol containing 0.02 g of **12** and 2 drops of 0.1 *N* NaOH was hydrogenated over a period of 3.0 hr. The reaction was filtered through Celite and the ethanol was evaporated. The residue in chloroform was washed with water and evaporated to yield 0.02 g of **11**.

3β-Acetoxypregna-5-*trans*-17(20)-diene (7). Method A.—A solution of 0.25 g of **3a** in 15 ml of acetic anhydride was heated to reflux. After 2 hr, the reaction mixture was cooled and the acetic anhydride was evaporated. To the residue were added 5 ml of pyridine and ice. After the mixture was allowed to stand for 0.5 hr, water was added and the suspension was extracted with ether. The ether extract was washed with 10% sulfuric acid, 5% sodium bicarbonate, and water, dried, and evaporated to yield 0.20 g of **7**. The nmr of the residue indicated only trans olefin. Preparative chromatography using SiGF thick plates, developed in benzene–ether (1:1), followed by recrystallization from methanol yielded an analytical sample: mp 143.0–143.5°; $[\alpha]_D$ −72°; ir λ_{max} 5.75, 8.00 μ (acetate); nmr ($CDCl_3$) τ 9.24 (18-CH_3), 8.95 (19-CH_3), 8.46 (doublet of triplets, $J_{H_{21}, H_{20}}$ = 7 Hz, $J_{H_{20}, H_{16}}$ = 1.5 Hz), 7.97 (3, $OCOCH_3$), 4.94 (m, 20-H).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.33; H, 10.02.

3β-Acetoxypregna-5-*cis*-17(20)-diene (6). Method A.—The same procedure was followed as previously described, with the use of 0.18 g of **2a**. The residue obtained weighed 0.15 g. An nmr spectra of the crude residue indicated only cis olefin. The residue was sublimed to give an analytical sample: mp 73–77°; $[\alpha]^{22}_D$ −63°; ir λ_{max} 5.75 8.00 μ (acetate); nmr ($CDCl_3$) τ 9.08 (18-CH_3), 8.95 (19-CH_3), 8.33 (doublet of triplets, $J_{H_{21}, H_{20}}$ = 7 Hz, $J_{H_{20}, H_{16}}$ = 1.9 Hz), 7.97 ($OCOCH_3$), 4.87 (m, 20-H).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.92; H, 10.28.

3β,17β-Dihydroxy-20β-bisnorchol-5-enic Acid 22,17-Lactone (5).—To a solution of 0.25 g of **3a** in 10 ml of methylene chloride and 10 ml of triethylamine at 0.5° was added, dropwise, 0.2 ml of ethyl chloroformate. After stirring for 1.0 hr, the reaction mixture was warmed to room temperature for 2.0 hr and then added to water. The methylene chloride was separated and washed with 3% HCl, saturated sodium bicarbonate, and water. The methylene chloride was dried and evaporated to yield 0.28 g. Recrystallization from acetone gave 0.08 g of **5**: mp 137–140°; $[\alpha]^{20}_D$ −119°; ir λ_{max} 3.0 (OH), 5.50 μ (β-lactone carbonyl); nmr ($CDCl_3$–DMSO-d_6, 1:1) τ 9.05 (18-CH_3), 8.98 (19-CH_3), 7.77 (d, J = 8 Hz, 21-CH_3).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.58; H, 9.34.

3β-Acetoxypregna-5-*trans*-17(20)-diene (7). Method B.—To a solution of 0.25 g of **5** in 20 ml of xylene was added 1 mg of *p*-toluenesulfonic acid. After refluxing for 3 hr, the solution was diluted with ether and washed with 3% HCl, saturated sodium bicarbonate, and water. The ether solution was dried and evaporated to yield a residue of 0.5 g. The 3-acetate was identical with **7** synthesized by method A.

3β,17α-Dihydroxy-20β-bisnorchol-5-enic Acid 22,17-Lactone (4) and 3β-Acetoxypregna-5-*cis*-17(20)-diene (6). Method B.—The same procedure was followed as previously described for 0.25 g of **2a** to yield a residue of 0.23 g: ir λ_{max} 2.8 (OH), 5.50 μ (β-lactone carbonyl); nmr ($CDCl_3$–DMSO-d_6, 1:1); τ 9.08 (18-CH_3), 9.00 (19-CH_3), 8.65 (d, J = 8 Hz, 21-CH_3). The residue **4** was treated with xylene and *p*-toluenesulfonic acid as described previously. Only cis olefin was obtained. The acetate was identical with **6**. There was no depression of the melting point upon admixture.

Registry No.—**2a**, 29842-77-1; **2b**, 29842-78-2; **3a**, 29842-79-3; **3b**, 29842-80-6; **4**, 29842-81-7; **5**, 29842-82-8; **6**, 1167-32-4; **7**, 16374-33-7; **8b**, 29842-85-1; **9a**, 29842-86-2; **9b**, 29842-87-3; **10**, 29842-88-4; **11**, 29936-65-0; **12**, 29842-89-5; *cis*-3β,16β-diacetoxy-5α-pregn-17(20)-ene, 29842-90-8; *trans*-3β,16β-diacetoxy-5α-pregn-17(20)-ene, 29842-91-9; *cis*-3β-acetoxypregn-5,17(20)-diene, 1167-33-5; *trans*-3β-acetoxypregn-5,17(20)-diene, 29842-93-1.

(13) Impurities of 17β-hydroxydinorchol-5-ene were removed as the 5,6-epoxide.

The Synthesis of Bicyclo[4.3.0]nonanebarbituric and -thiobarbituric Acid Derivatives and a Bicyclo[4.4.0]decanebarbituric Acid Derivative

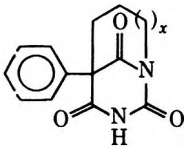
EDWARD E. SMISSMAN* AND JAMES W. AYRES[1]

The Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

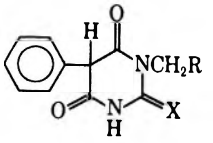
Received November 27, 1970

In attempting to prepare intramolecularly C-alkylated bicyclic barbituric and thiobarbituric acids from *N*-haloalkylbarbituric and *N*-haloalkylthiobarbituric acids, only O-alkylated compounds were obtained. The structures were assigned on the basis of spectral data and by degradation of the products to known entities.

Recent reports from this laboratory[2] indicate that barbituric acids with a displaceable group on an alkyl side chain attached to the C-5 carbon will undergo intramolecular alkylation to give O-alkylation in preference to N-alkylation. In a continuation of a program designed to prepare bicyclic barbituric acids **1** as selective CNS agents for potential use as anticonvulsants, the *N*-alkylbarbituric acids **2**, **4**, and **5** and the *N*-alkylthiobarbituric acid **3** were prepared[1] and investigated as possible precursors to compound **1**.

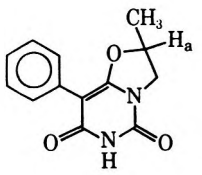


1, $x=0,1,2$

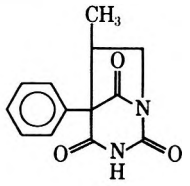


2, X = O; R = CH=CH$_2$
3, X = S; R = CH=CH$_2$
4, X = O; R = CH$_2$OH
5, X = O; R = CH$_2$CH$_2$Br
6, X = O; R = CHBrCH$_3$
7, X = O; R = CH$_2$Br

An acid-stable crystalline substance was obtained upon treatment of the *N*-allylbarbituric acid **2** with hydrogen bromide in acetic acid. Elemental analysis indicated the structure could be either **8** or **9**.

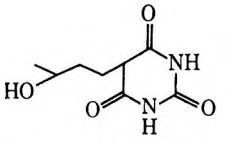


8

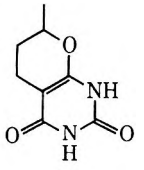


9

Structure **8** is supported by ir and nmr spectral data. Nuclear magnetic resonance analysis shows a one-proton multiplet centered at δ 5.1 which is consistent with H$_a$ (**8**) but is downfield from the chemical shift to be expected for any protons in **9**. The unexpected acid stability for the vinyl ether function in **8** was found in a similar system, the conversion of the barbiturate **10** to the bicyclic compound **11**, by Senda, Fujimura, and Izumi.[3]

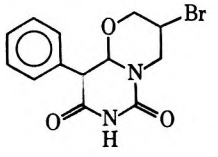


10

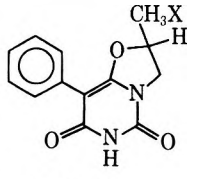


11

A plausible mechanism for the formation of **8** would involve enolization of **6**, followed by displacement of the secondary bromide by the enolic oxygen. When compound **2** was allowed to react with bromine in carbon tetrachloride and in ethylene glycol dimethyl ether, a crystalline product was obtained whose elemental analysis and spectral qualities were consistent with either structure **12** or **13**. The product was



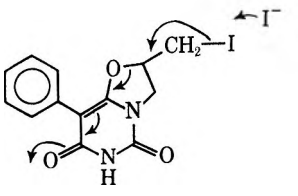
12



13, X = Br
14, X = OCOCH$_3$
15, X = OCOC$_6$H$_5$
16, X = I

shown to be 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) by nmr analysis of its acetate **14** and benzoate **15**. If the product were **12** rather than **13**, it would be expected that the absorbance of the methine proton rather than the methylene protons would be shifted on conversion to the esters **14** and **15**.

The iodo compound **16** was formed by allowing the bromo compound **13** to reflux with excess sodium iodide in acetone. Compound **2** was also obtained in this reaction, probably by an elimination with cleavage as shown below.

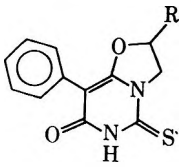


(1) Taken in part from the dissertation presented by J. W. Ayres, Aug 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *J. Org. Chem.*, **35**, 3823 (1970).

(3) S. Senda, H. Fujimura, and H. Izumi, Japanese Patent 6,824,193 (1968); *Chem. Abstr.*, **70**, 78001r (1969).

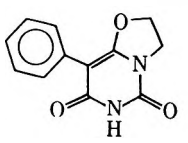
The sulfur-containing analogs **17–20** were prepared in a similar manner to the oxygen-containing compounds starting with **3**. The reaction of sodium benzoate in dimethylformamide with the bromide **18** did not pro-



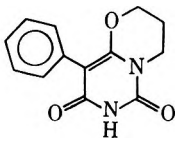
17, R = CH_3
18, R = CH_2Br
19, R = CH_2OCOCH_3
20, R = $=CH_2$

duce the corresponding benzoate as it had in the oxygen series but instead 4-keto-2-thio-5-phenyl-Δ^5-7-oxa-8-methylene-1,3-diazabicyclo[4.3.0]nonane (**20**) was obtained.

When the alcohol **4** was treated with 32% hydrogen bromide in acetic acid, the only product isolated was 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]-nonane (**21**). Presumably, this compound was obtained *via* the intermediate bromide **7**. Compound **5**



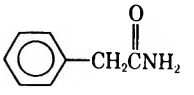
21



22

was converted to 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (**22**) by allowing it to stand in pyridine.

Further evidence for O-alkylation as opposed to C-alkylation in the above series of bicyclic compounds was provided by the degradation of compounds **18**, **21**, and **22**. These compounds were treated with 58% ammonium hydroxide and 21% ammonium sulfide at 150° in a steel reaction vessel. In each case, the only identifiable product obtained from this hydrolytic procedure was α-phenylacetamide (**23**), thus indicating that no alkylation had occurred on the carbon adjacent to the aromatic ring.



23

Experimental Section[4]

2,4-Diketo-8-methyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]-nonane (8).—A solution of *N*-allyl-5-phenylbarbituric acid (**2**) (25 g, 0.10 mol) in 100 ml of 32% HBr–HOAc in a stoppered Wheaton glass pressure bottle was stirred overnight and then allowed to stand at 25° for 5 days. Compound **8** was filtered and the filtrate diluted with 200 ml of H_2O and used to wash **8** several times. After drying the yield was 88% (22 g): mp 259–261° (Me_2CO); ir (KBr) 3400 (NH), 1700 (C=O), 1620 cm^{-1} [C=CC(=O)N]; nmr (DMSO-d_6) δ 1.42 (d, 3 H, CH_3), 3.8 (m, 2 H, NCH_2C), 5.1 (m, 1 H, OCH), 11.1 (br s, 1 H, NH).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.10; H, 5.02; N, 11.41.

2,4-Diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (13).—Bromine (25.6 g, 0.16 mol) was added all at once to a stirred solution of *N*-allyl-5-phenylbarbituric acid (**2**) (40 g, 0.16 mol) in 750 ml of ethylene glycol dimethyl ether which was cooled in an ice bath. The suspension was allowed to stir for 30 min and then N_2 was bubbled through the suspension to remove Br_2 vapors. The solvent was removed *in vacuo* and the residue washed with 40 ml of Me_2CO to yield **13** (31.7 g). The Me_2CO was evaporated to leave an oil which was dissolved in EtOAc and decolorized with a solution of Na_2SO_3 in H_2O. The organic layer was dried ($MgSO_4$) and evaporated to leave a solid which was washed with 200 ml of hot C_6H_6 and dried to yield another 9 g of **13** (total yield 40.7 g, 79%): mp 230° (Me_2CO); nmr (DMSO-d_6) δ 4.0 (m, 4 H, CH_2Br, CH_2N), 5.3 (m, 1 H, OCH), 11.2 (br s, 1 H, NH).

Anal. Calcd for $C_{13}H_{11}BrN_2O_3$: C, 48.31; H, 3.43; N, 8.66. Found: C, 48.67; H, 3.34; N, 8.93.

2,4-Diketo-8-acetoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (14).—A stirred suspension of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (2.0 g, 6.2 mmol) and AgOAc (2.0 g, 12 mmol) in 5 ml of DMSO, 5 ml of DMF, and 5 ml of HOAc was heated at 100° for 1 hr. The suspension was filtered and the filtrate diluted with 100 ml of H_2O and made acidic with 10% HCl. The gummy precipitate was filtered and recrystallized twice to yield **14** (1.1 g, 59%): mp 198–200° (EtOAc); nmr (DMSO-d_6) δ 4.0 (m, 2 H, NCH_2), 4.4 (m, 2 H, OCH_2), 5.2 (m, 1 H, OCH), 11.0 (br s, 1 H, NH).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.66; N, 9.26. Found: C, 59.85; H, 4.80; N, 9.05.

2,4-Diketo-8-benzoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (15).—A stirred solution of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (2.0 g, 6.2 mmol) and NaOBz (1.0 g, 7.0 mmol) in 20 ml of DMF was refluxed 4 hr, cooled, and poured into 150 ml of H_2O. The suspension was made acidic (10% HCl) and the gummy precipitate collected to yield **15** (1.0 g, 44.3%): mp 210–212° (EtOAc–petroleum ether 60–70°); nmr (DMSO-d_6) δ 4.2 (m, 2 H, NCH_2), 4.7 (m, 2 H, OCH_2), 5.3 (m, 1 H, OCH), 11.2 (br s, 1 H, NH).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.42; N, 7.68. Found: C, 65.64; H, 4.61; N, 7.77.

2,4-Diketo-8-iodomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (16).—A solution of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (20 g, 0.06 mol) and NaI (45 g, 0.32 mol) in 1500 ml of Me_2CO was refluxed overnight. The solvent was removed *in vacuo* and the black residue decolorized with Na_2SO_3 in H_2O. The solid was collected on a filter to yield **16** (8.3 g), mp 226–228° dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{11}IN_2O_3$: C, 42.08; H, 2.99; N, 7.56. Found: C, 42.00; H, 2.92; N, 7.18.

The above filtrate was made acidic (10% HCl) and the precipitate collected by filtration. The solid was washed with 200 ml of boiling EtOAc and the insoluble material filtered to yield more **16** (4.6 g, total yield 51.6%). Concentration of the filtrate yielded *N*-allyl-5-phenylbarbituric acid (**2**) (6.0 g, 39.8%).

4-Keto-2-thio-8-methyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (17).—A stirred solution of *N*-allyl-5-phenylthiobarbituric acid (**3**) (25 g, 0.09 mol) in 100 ml of 32% HBr–HOAc (Eastman) was refluxed 8 hr in a stoppered Wheaton glass pressure bottle and then allowed to stir overnight at 25°. The solid was collected and washed with 150 ml of Me_2CO to yield **17** (16.6 g, 66.5%), mp 239–242° dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.64; N, 10.76. Found: C, 60.26; H, 4.85; N, 10.56.

4-Keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18).—A solution of Br_2 (24.6 g, 0.154 mol) in 100 ml of CCl_4 was added all at once to a stirred suspension of *N*-allyl-5-phenylthiobarbituric acid (**3**) (40.0 g, 0.154 mol) in 500 ml of ethylene glycol dimethoxy ether cooled in an ice bath. The mixture was stirred 30 min, refluxed 1 hr, and concentrated *in vacuo*. The oily residue was washed with 200 ml of Me_2CO–petroleum ether (60–70°) and the solid collected to yield **18** (44.2 g, 85%), mp 238–239° dec (Me_2CO–petroleum ether 60–70°); the spectral data are consistent with the assigned structure.

(4) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR 10 spectrophotometer and nmr data on Varian Associates A-60, A-60-A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

Anal. Calcd for $C_{13}H_{11}BrN_2O_2S$: C, 46.03; H, 3.26; N, 8.25. Found: C, 46.12; H, 3.9; N, 8.38.

4-Keto-2-thio-8-acetoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (19).—A stirred suspension of 4-keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18) (3.0 g, 8.9 mmol) and AgOAc (1.6 g, 10 mmol) in 30 ml of HOAc was refluxed 1.25 hr and the solid filtered. The filtrate was concentrated *in vacuo* and added to 50 ml of H_2O which was made acidic (10% HCl). The precipitate was collected to yield 19 (1.5 g, 52%), mp 202–204° (EtOAc–Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79. Found: C, 56.35; H, 4.52; N, 8.79.

4-Keto-2-thio-8-methylene-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (20).—A stirred solution of 4-keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18) (4.00 g, 11.8 mmol) and NaOBz (1.87 g, 13.0 mmol) in 10 ml of DMF was refluxed 5 hr, cooled, and poured into 200 g of crushed ice. The suspension was made acidic (10% HCl) and the precipitate collected and decolorized with activated charcoal in Me_2CO. The Me_2CO was removed *in vacuo* to yield 20 (0.5 g, 16.4%), mp 186–187° (Me_2CO); the spectral data were consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84. Found: C, 60.07; H, 3.74; N, 10.54.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).—A stirred solution of *N*-(2-hydroxyethyl)-5-phenylbarbituric acid (4) (10.0 g, 0.04 mol) in 100 ml of 32% HBr–HOAc (Eastman) was refluxed overnight in a stoppered Wheaton glass pressure bottle. The HOAc was removed *in vacuo* and the residue added to 400 ml of crushed ice. The H_2O was decanted and the gummy residue crystallized to yield 21 (4.25 g, 46.2%), mp 267–268° (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.37; N, 12.16. Found: C, 62.46; H, 4.48; N, 12.15.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (22).—A solution of *N*-(3-bromopropyl)-5-phenylbarbituric acid (5) (1.0 g, 3.0 mmol) in 30 ml of C_5H_5N was stirred 3 days and then concentrated *in vacuo*. The residue was dissolved in 10 ml of H_2O and the solution made acidic (10% HCl). The precipitate was collected to yield 22 (400 mg, 54.6%), mp 290.5–291.5 dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.15; H, 5.03; N, 11.57.

α-Phenylacetamide (23). A. Hydrolysis of 4-Keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18).—A solution of 18 (3.0 g, 8.8 mmol) in 10 ml of 58% NH_4OH and 20 ml of 21% $(NH_4)_2S$ was maintained at 150° in a steel reaction vessel for 3 days. The solvent was removed *in vacuo* and the residue dissolved in $CHCl_3$, decolorized (activated charcoal), dried ($MgSO_4$), and evaporated to yield 23 (0.30 g, 26%), mp 154–155° ($CHCl_3$–Et_2O) (lit.[5] mp 154–155°). The spectral data were identical with those for α-phenylacetamide.[6]

B. Hydrolysis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).—The procedure utilized was identical with that in A. Compound 23, mp 151–152° ($CHCl_3$–Et_2O), was obtained.

C. Hydrolysis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]decane (22).—The procedure utilized was identical with that in A and B. Compound 23, mp 154–155 ($CHCl_3$–Et_2O), was obtained.

Registry No.—8, 30345-98-3; 9, 30345-99-4; 14, 30346-00-0; 15, 30346-01-1; 16, 30346-02-2; 17, 30346-03-3; 18, 30409-27-9; 19, 30346-04-4; 20, 30346-05-5; 21, 30346-06-6; 22, 30349-28-0.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants GM-09254 and GM-01341. We appreciate the assistance rendered by Mr. Darrell Abernethy in the preparation of starting materials.

(5) "The Merck Index," 7th ed, Merck and Co., Inc., Rahway, N. J., 1960, p 799.

(6) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1970, Prism No. 2236, nmr no. 6588.

The Synthesis of the Thalictrum Alkaloids, Adiantifoline and Thalicsimidine[1]

RAYMOND W. DOSKOTCH,* J. D. PHILLIPSON,[2] A. B. RAY, AND JACK L. BEAL

Division of Natural Products Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received January 5, 1971

A total synthesis is described for adiantifoline (1) involving, in the final step, the joining by the Ullmann reaction of the two components (+)-(*S*)-6′-bromolaudanosine (12) and (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (4), thus establishing the structure for the alkaloid. The aporphine intermediate 4 was formed by two routes, both leading to the same Pschorr cyclization reactant, 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (8). One pathway started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxyphenylacetamide (5) with the nitro group being introduced to the tetrahydroisoquinoline 7, while the other procedure started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxy-6′-nitrophenylacetamide (9). Only polyphosphoric ester was successful in cyclizing compound 9 in the Bischler–Napieralski reaction. Methylation of compound 4 to (+)-(*S*)-1,2,3,9,10-pentamethoxyaporphine (13) or thalicsimidine constitutes its total synthesis and confirms its structure earlier assigned on the basis of spectroscopic evidence. Four pentaoxygenated benzyltetrahydroisoquinolines, 14–17, were obtained from intermediates in the synthesis.

Adiantifoline, the fourth member of a novel group dimeric benzylisoquinoline–aporphine alkaloids, was isolated from *Thalictrum minus* L. var. *adiantifolium* Hort., and was assigned structure 1 from physical and chemical evidence.[3] A confirmation of this structure was necessary and was obtained by a total synthesis of (+)-adiantifoline,[4] since scarcity of the alkaloid precluded further degradative studies and the evidence at hand was also consistent with structure 2. In addition, a quantity of the alkaloid could now be made available for pharmacological testing,[5] which otherwise would not have been possible.

(1) Alkaloids of Thalictrum. XII. Paper XI: R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Lloydia*, **32**, 29 (1969). This investigation was supported by Public Health Service research grants HE-07502 and FR-00328, the latter for purchase of a Varian A-60A nmr spectrometer with accessories.

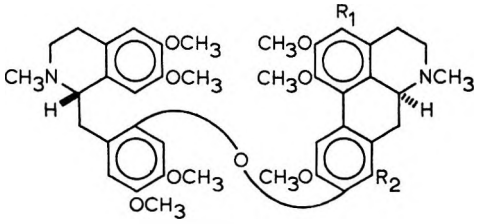
(2) Acknowledges with thanks the receipt of a Wellcome Research Travel Grant. Permanent address: Department of Pharmacy, Chelsea College, University of London, London, United Kingdom.

(3) (a) R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Tetrahedron Lett.*, 4999 (1968). (b) The isolation procedure is found in paper XI.[1]

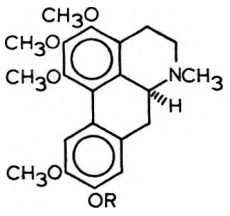
(4) A preliminary report of this work has appeared: R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *Chem. Commun.*, 1083 (1969).

(5) Testing for antitumor activity will be of special interest because of the success thalicarpine (3) has been having in the evaluation program of the Cancer Chemotherapy National Screening Center; see R. E. Perdue and J. L. Hartwell, *Morris Arbor. Bull.*, **20**, 35 (1969).

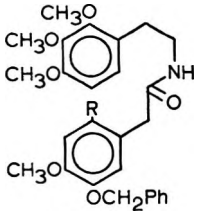
Since the proposed structure for adiantifoline differs from that of thalicarpine (**3**) by the presence of one additional methoxyl group, the general route for its synthesis was patterned after the successful one for thalicarpine,[6] in which the suitable benzyltetrahydroisoquinoline and aporphine portions were in the final step joined *via* the Ullmann reaction. The required aporphine, (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), for adiantifoline was prepared starting with 2,3,4-trimethoxyphenylethylamine[7] and 3-benzyloxy-4-methoxyphenylacetic acid[8] as the acid chloride. The Schotten–Baumann condensation product, *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoyxphenylacetamide (**5**), was cyclized under conditions of the Bischler–Napieralski reaction and the unstable imine product was quickly reduced to 1-(3′-benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and isolated as the hydro-



1, R_1 = OCH_3; R_2 = H
2, R_1 = H; R_2 = OCH_3
3, R_1 = R_2 = H



4, R = H
13, R = CH_3

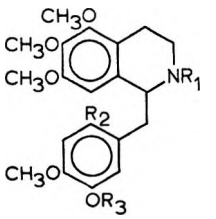


5, R = H
9, R = NO_2

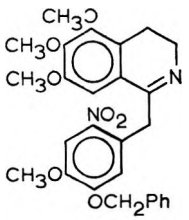
chloride salt. N-Methylation of compound **6** by formaldehyde and sodium borohydride gave 1-(3′-benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**7**) which on nitration according to the conditions of Shamma and Slusarchyk[9] yielded the 6′-nitro compound **8**. The assigned position of nitration was supported: first, by the nmr spectrum of the nitro product, since the aromatic region—excluding the protons of the benzyloxy group—showed three one-proton singlets at δ 6.25, 6.57, and 7.54; second, by the nmr spectrum of the eventual aporphine product (racemic **4**) which exhibited a one-proton singlet downfield at δ 7.96, a position unique for H_{11} protons,[10] and in agreement with the predicted product; and third, by the formation (*vide infra*) of 1-(3′-benzyloxy-4′-methoxybenzyl-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**) *via* an alternate unambiguous route through the nitroamide **9**.

The Pschorr reaction product, 1,2,3,10-tetramethoxy-9-hydroxyaporphine (racemic **4**), was obtained from the nitroamine **8** through the reduction product, 1-(3′-benzyloxy-4′-methoxy-6′-aminobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**), and, under the conditions of cyclization, the benzyloxy group was, in addition, summarily removed. Resolution of the racemic aporphine **4** was accomplished by fractional crystallization of the di-*p*-toluoyl (+)-tartarate salts yielding the diastereoisomer with the (+)-(*S*)-aporphine enantiomer **4** as the least soluble salt, after first removal of part of the (−)-(*R*) enantiomer with di-*p*-toluoyl-(−)-tartaric acid. The Ullmann condensation of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**) with (+)-(*S*)-6′-bromolaudanosine (**12**)[11] afforded adiantifoline (**1**) in a yield of 21% after chromatography of the reaction mixture. Comparison of the synthetic compound with the natural product was made by the examination of the ir, uv, and nmr spectra, CD curves, tlc characteristics, and mixture melting points. No distinguishing characteristics were noted.

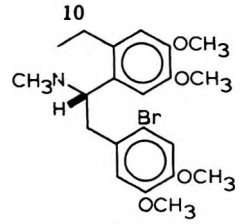
Another synthetic route leading to the aporphine **4** was developed in which the nitro group necessary for the Pschorr cyclization was introduced early in the sequence. The nitroamide **9** was prepared from 3-benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone[12] and 2,3,4-trimethoxyphenylethylamine[7] *via* the Arndt–Eistert method. Cyclization of the nitroamide **9** in the Bischler–Napieralski reaction could not be accomplished by the use of the usual condensation reagents under a variety of conditions,[13] but, with polyphosphoric ester prepared according to Cava, *et al.*,[14] a moderate yield of 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-didhydroisoquinoline (**10**) was realized. Reaction of the cyclization product **10** with methyl iodide gave the quaternary methiodide which on reduction with sodium borohydride formed 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**) identical with the nitration product from 1-(3′-benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**7**). In practice, this



6, R_1 = R_2 = H; R_3 = benzyl
7, R_1 = CH_3; R_2 = H; R_3 = benzyl
8, R_1 = CH_3; R_2 = NO_2; R_3 = benzyl
11, R_1 = CH_3; R_2 = NH_2; R_3 = benzyl
14, R_1 = R_2 = R_3 = H
15, R_1 = CH_3; R_2 = R_3 = H
16, R_1 = R_2 = H; R_3 = CH_3
17, R_1 = R_3 = CH_3; R_2 = H



10



12

(6) M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Chem. Pharm. Bull.* (*Tokyo*), **15**, 959 (1967).
(7) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).
(8) A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Rumuz, *J. Chem. Soc.*, 3600 (1964).
(9) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).
(10) S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.* (*London*), 306 (1958).
(11) M. Tomita and K. Ito, *J. Pharm. Soc. Jap.*, **78**, 103 (1958).
(12) M. Tomita and I. Kikkawa, *Chem. Pharm. Bull.* (*Tokyo*), **4**, 230 (1956).
(13) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).
(14) M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969).

second route results in a higher overall yield of the aporphine **4**, since it eliminates the nitration of the benzyltetrahydroisoquinoline **7**, which was found to give unexplained inconsistent yields.

Thalicsimidine, an alkaloid from *Thalictrum simplex* L., was assigned the structure of (+)-(*S*)-1,2,3,9,-10-pentamethoxyaporphine (**13**) on the basis of physical evidence.[15] Methylation of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**) with diazomethane gave the pentamethoxyaporphine **13** which possessed physical properties (melting point, $[\alpha]_D$, and uv, ir, and nmr spectra) in agreement with those reported for thalicsimidine. This synthesis, therefore, substantiates the suggested structure and, in addition, constitutes the total synthesis of this alkaloid.

Having on hand the pentaoxygenated benzylisoquinolines, 1-(3′-benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and its N-methyl derivative **7**, allowed us to prepare 1-(3′-hydroxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**14**), its N-methyl derivative **15**, and 1-(3′,4′-dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**16**) and its N-methyl derivative **17**. To our knowledge, alkaloids possessing these structures have as yet not been discovered. We record their properties for value in characterization, as it is very likely that they will be discovered in the future.

Experimental Section[16]

***N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxyphenylacetamide (5).**—Thionyl chloride (8 ml) was added to 3-benzyloxy-4-methoxyphenylacetic acid[8] (11 g) in 30 ml of dry benzene and the mixture was heated for 3 hr at 50° under anhydrous conditions. The beige-colored acid chloride remaining, after removal of the volatiles by evaporation of the reaction mixture at reduced pressure, was dissolved in 50 ml of dry ether and added dropwise to a well-stirred mixture of 2,3,4-trimethoxyphenylethylamine[7] hydrochloride (10 g) in 200 ml of 5% aqueous NaOH and 300 ml of ether. After stirring 1 hr at room temperature, the mixture was extracted with $CHCl_3$ and the extract was washed with H_2O, dilute HCl, and H_2O and then dried (Na_2SO_4). The thick oil left after evaporation of the solvent crystallized from ether–chloroform as colorless needles of **5** (18.0 g): mp 104–105°; ir 3410 (NH) and 1655 cm^{-1} (amide C=O).

Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.68; H, 6.67; N, 3.22. Found: C, 69.74; H, 6.77; N, 3.29.

1-(3′-Benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (6).—Amide **5** (5 g) in 50 ml of dry benzene and 5 ml of $POCl_3$ were heated at 80° for 1 hr, under nitrogen. The brown residue left after evaporation of the mixture was triturated twice with petroleum ether, then dissolved in 50 ml of acetone, and diluted with 200 ml of 2% aqueous HCl. The aqueous solution was washed twice with ether, cooled (ice), basified with dilute NH_4OH, and rapidly extracted with ether. The washed (H_2O) and dried (Na_2SO_4) ether solution was evaporated and the residue (imine) was dissolved in 50 ml of CH_3OH, cooled (ice), and treated with 2.2 g of $NaBH_4$ over a 0.5-hr period while stirring. After 2 hr the residue remaining on evaporation of the solvent was treated with H_2O and extracted with ether. The residue from the ether solution gave from ether–95% ethanol the crystalline hydrochloride of **6** as needles (3.6 g): mp 118–119°; uv max 282 mμ (log ε 3.71).

Anal. Calcd for $C_{27}H_{32}NO_5Cl \cdot H_2O$: C, 64.35; H, 6.75; N, 2.78. Found: C, 64.77; H, 6.84; N, 2.95.

1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (7).—The amine **6** (generated from 4.8 g of the HCl salt) in 150 ml of CH_3OH was stirred at room temperature with 40 ml of 37% formalin for 0.5 hr, then cooled (ice), and treated with 7.5 g of $NaBH_4$ over 0.5 hr. After stirring an additional 2 hr, the reaction mixture was evaporated to dryness, treated with H_2O, and extracted with ether. The ether-soluble residue after forming the hydrochloride gave from ether–methanol the crystalline salt of **7** (4.7 g): mp 123–125°; uv max 282 mμ (log ε 3.66).

Anal. Calcd for $C_{28}H_{34}NO_5Cl$: C, 67.34; H, 6.81; N, 2.81; Cl, 7.10. Found: C, 67.22; H, 6.98; N, 2.86; Cl, 7.17.

1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7trimethoxy-1,2,3,4-tetrahydroisoquinoline (8). A. By Nitration of 7.—To compound **7** (liberated from 4.2 g of the HCl salt) frozen in 20 ml of glacial HOAc was added ice-cold concentrated HNO_3 (7.5 ml) in five equal portions. After the first portion was added, the frozen mixture was liquified by crushing and vigorous stirring. The completed reaction mixture was poured onto crushed ice, basified with NH_4OH, and extracted with $CHCl_3$. The red oil remaining after evaporation of the dried (K_2CO_3) $CHCl_3$ solution was treated with 10 ml absolute EtOH followed by an ethereal HCl solution until precipitation was complete. The beige solid was crystallized from ether–methanol to give 3.2 g of the hydrochloride **8**, mp 129–131°.

B. From the Nitroimine 10.—A solution of the nitroimine **10** (492 mg) in 20 ml of CH_3OH, and 2 ml of CH_3I was refluxed for 24 hr. The cooled solution deposited an oil which solidified as pale yellow prisms of the methiodide, mp 159–160°. The reaction mixture was evaporated to dryness at reduced pressure. The crystalline residue was dissolved in 20 ml of CH_3OH and then treated with 0.2 g of $NaBH_4$ in small portions over 0.5 hr and the reaction was allowed to proceed overnight. The residue remaining on removal of the solvent was taken up in water and extracted with ether. The dried (Na_2SO_4) ether extract left a residue (0.41 g) that formed the crystalline hydrochloride of **8**, mp 129–131°.

Anal. Calcd for $C_{28}H_{33}N_2O_7Cl$: C, 61.70; H, 6.06; N, 5.14. Found: C, 61.54; H, 6.11; N, 5.17.

1-(3′-Benzyloxy-4′-methoxy-6′-aminobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (11).—The base **8** (liberated from 5.5 g of the HCl salt) in ice-cold 60% aqueous HOAc (120 ml) was stirred and treated with 10 g of zinc dust over a period of 5 min. Stirring was continued until an almost colorless solution formed and then the zinc was removed by filtration. The ice-cold filtrate was basified with NH_4OH and extracted exhaustively with $CHCl_3$. The chloroform residue, remaining after evaporation of the washed (H_2O) and dried (K_2CO_3) extract, was crystallized from methanol–ether and recrystallized from ether to give rosettes of compound **11** (3.1 g): mp 117–118°; uv max 284 mμ (log ε 3.48), 299 (3.53); ir 3400 cm^{-1} (NH).

Anal. Calcd for $C_{28}H_{34}N_2O_5$: C, 70.27; H, 7.16; N, 5.85. Found: C, 70.17; H, 7.15; N, 5.91.

1,2,3,10-Tetramethoxy-9-hydroxyaporphine (Racemic 4).—The diamine **11** (956 mg) was dissolved at 5° in a solution of 20 ml of glacial HOAc, 20 ml of H_2O, and 2 ml of concentrated H_2SO_4. A solution of $NaNO_2$ (152 mg) in 5 ml of H_2O was added dropwise. After 15 min of stirring the green diazonium salt solution was added dropwise while cold into 100 ml of a boiling 25% (v/v) H_2SO_4 solution. The resulting red solution was treated with 3 g of activated zinc and refluxed 1 hr, then diluted with water, filtered, cooled in ice, made basic with NH_4OH, and then extracted with $CHCl_3$. The extract after drying (K_2CO_3) yielded on evaporation a dark oil which was chromatographed on 30 g of silicic acid (Mallinckrodt) starting with $CHCl_3$ as eluting solvent. The chloroform–methanol (99:1) effluent residue crystallized from CH_3OH as cubes (190 mg) of racemic aporphine **4**: mp 206–207°; uv max 312, 301, 231 mμ (log ε 4.08, 4.13, 4.15); in 0.01 *N* methanolic KOH, uv max 323 mμ (log ε 4.28); nmr δ 2.53 (NCH_3), 3.73 (OCH_3), 3.90 (2 OCH_3), 3.97 (OCH_3), 5.5 (broad OH, lost in D_2O), 6.84 (s, H_8) and 7.96 (s, H_{11}). The compound gave a positive $FeCl_3$ test.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.08; H, 6.88; N, 3.89.

(15) Z. F. Ismailov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, **4**, 136 (1968) Kh. S. Umarov, M. V. Tetezhenetskaya, Z. F. Ismailov, and S. Yu. Yunusov, *ibid.*, **3**, 353 (1967).

(16) Analyses were performed by Dr. Alfred Bernhardt, West Germany. Melting points are uncorrected. Nmr spectra were run in $CDCl_3$ (tetramethylsilane as internal standard) unless stated otherwise, using a Varian A-60 instrument; ultraviolet spectra were taken in CH_3OH on a Cary Model 15 spectrophotometer; infrared spectra were taken in $CHCl_3$ or in KBr windows on a Perkin-Elmer Model 237 or 257 instrument; and ORD, CD curves, and optical rotations were measured in methanol on a Jasco Model ORD/UV-5 spectropolarimeter with a CD attachment.

Resolution of 1,2,3,10-Tetramethoxy-9-hydroxyaporphine to the (+)-(*S*) Enantiomer 4.—The aporphine (racemic **4**, 700 mg) and di-*p*-toluoyl-(−)-tartaric acid (716 mg) were dissolved in 20 ml of EtOH by slight warming. After standing overnight the crude crystalline di-*p*-toluoyl (−)-tartarate [diastereoisomer with (−)-(*R*) enantiomer] was collected by filtration as was a second crop which formed on concentrating the filtrate by one-half. The base liberated from the mother liquor [the (+)-(*S*) enantiomer predominating] was mixed with an equal amount of di-*p*-toluoyl-(+)-tartaric acid and dissolved in the minimum amount of EtOH with warming. The long fibrous needles that formed overnight at room temperature were collected, washed with ether, and recrystallized from EtOH to give flat needles, mp 150–151°. The liberated free base was subjected twice more to the whole operation and finally crystallized from CH_3OH as cubes (180 mg) of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), mp 186–187°, $[\alpha]_D$ +108° (c 0.17, CH_3OH). Additional treatment with the resolving reagent did not affect the specific rotation.[17]

Adiantifoline (1).—A mixture of the (+)-(*S*)-aporphine **4** (350 mg), (+)-(*S*)-6′-bromolaudanosine (250 mg), anhydrous K_2CO_3 (250 mg), CuO (45 mg), KI (5 mg), and pyridine (5 ml) was heated with stirring, under nitrogen, in an oil bath at 138–144° for 9 hr. The cooled reaction mixture was dissolved in 25 ml of $CHCl_3$ and filtered and the filtrate was evaporated to dryness at reduced pressure. The residue was taken up in 10% HCl and washed with ether and the acid phase was basified with NH_4OH and then extracted with ether. The ether solution was washed with 5% NaOH and water, then dried (K_2CO_3), and evaporated to leave a 370 mg of oily residue. Chromatography of the oil on 40 g of silicic acid was started beginning with $CHCl_3$ as eluent. The chlorform–methanol (98:2) eluent gave 40 mg (+)-6′-(*S*)-bromolaudanosine, and adiantifoline mixed in some runs with a trace of (+)-laudanosine was obtained with chloroform–methanol (96:4) as eluent. Removal of this contaminant was by thick layer (0.5 mm) chromatography on silica gel G (Merck) plates (20 cm × 20 cm) with benzene–acetone–diethylamine (32:32:1) as solvent. The adiantifoline band was located at R_f 0.46. Extraction of the band, twice with boiling CH_3OH, left a residue, after evaporation of the solution, that was suspended in $CHCl_3$ and filtered. The filtrate residue crystallized from ethanol–ether to give adiantifoline as fine needles (67 mg, second crop 20 mg; 21% overall based on **12**), mp 142–143°, mmp 142–143° with natural adiantifoline.[18] The uv, ir, and nmr spectra and the CD curves were identical for the two samples.

***N*-(2,3,4-Trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxy-6′-nitrophenylacetamide (9).**—To a stirred solution at 60° of 3-benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone[12] (6.6 g) in 200 ml of dry benzene containing 0.66 g of freshly prepared Ag_2O was added a solution of 2,3,4-trimethoxyphenylethylamine[7] (liberated from 4.95 g of the HCl salt) in 120 ml of dry benzene. After 3 hr, an additional 0.66 g of Ag_2O was added and the reaction mixture was refluxed for 0.5 hr. The mixture was filtered through diatomaceous earth and the insolubles were washed with benzene. The combined filtrate and washings (500 ml) on concentrating deposited 7.83 g of buff-colored crystals. Recrystallization from EtOH furnished compound **9** as fibrous needles: mp 170–171°; ir 3375 (NH) and 1660 cm^{-1} (amide C=O).

Anal. Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92. Found: C, 63.39; H, 5.74.

1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (10).—The amide **9** (2.65 g), 10 ml of $CHCl_3$, and 20 g of polyphosphoric ester[14] were stirred at room temperature under anhydrous conditions for 48 hr. The green reaction mixture was then poured into 200 ml of 5% HCl and nitrogen was bubbled through the stirred solution while the chloroform was evaporated. The filtered solution was basified with NH_4OH and extracted with ether. The dried (Na_2SO_4) ether solution on evaporation left a heavy oil that crystallized from methanol to give 1.2 g of the imine **10**, mp 179–181°.

Anal. Calcd for $C_{27}H_{28}N_2O_7$: C, 65.84; H, 5.73; N, 5.69. Found: C, 65.72; H, 5.72; N, 5.75.

(17) The extent of resolution was also checked by circular dichroism. The maximum values approached were $[\theta]_{312}$ −17,400, $[\theta]_{300}$ −22,000, $[\theta]_{278}$ −26,700, and $[\theta]_{242}$ +225,000.

(18) Adiantifoline as reported in ref 4 is polymorphic. The synthetic product from hexane gave a microcrystalline powder, mp 107–108°. The natural product also furnishes the same low melting solid when crystallized from the same solvent.

(+)-(*S*)-1,2,3,9,10-Pentamethoxyaporphine (Thalicsimidine) (13).—The aporphine **4** (100 mg) dissolved in methanol was mixed with an ethereal solution of diazomethane (300 mg) and the mixture was kept overnight in the refrigerator. After evaporation of the solvent, the residue was first crystallized from EtOH to give pale yellow needles and then from hexane to furnish colorless needles of **13** (89 mg): mp 134–135°; $[\alpha]_D$ +66° (c 2.02, CH_3OH); uv max 224, 282 and 302 mμ (log ε 4.48, 4.17, and 4.14); nmr[19] δ 2.55 (s, 3 H, NCH_3) 3.75 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.94 (s, 6 H, OCH_3), 3.98 (s, 3 H, OCH_3), 6.81 (s, 1 H, Ar H) and 8.00 (s, 1 H, Ar H); picrate mp 141° dec [lit.[15] mp 131–132°; $[\alpha]_D$ +57.85° (c, 0.96 EtOH); uv max 220, 280, and 300 mμ; nmr δ 2.47 (s, 3 H, NCH_3), 3.64 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.70 (s, 1 H, Ar H), 7.89 (s, 1 H, Ar H); picrate mp 141–150°].

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.49; H, 7.13; N, 3.80.

1-(3′-Hydroxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (14).—Compound **6** (500 mg) was heated on the steam bath for 1.5 hr in a solution of 12.5 ml of acetic acid and 12.5 ml of 20% HCl. The reaction solution was diluted with ice, basified with NH_4OH, and extracted with ether. The ether residue crystallized from absolute ethanol–ether as white microcrystals (220 mg) of **14**: mp 121–122°; uv max 282 mμ (log ε 3.89); nmr δ 2.6–3.3 (envelope 6 H, methylene protons), 3.82 (s, 6 H, OCH_3), 3.88 (s, 6 H, OCH_3), 4.10 (m, 1 H, methine), 6.51 (s, 1 H, H_8), 6.77 (m, 3 H, H_2', H_5', H_6'), and a D_2O exchangeable peak at 4.30 (2 H).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.78; H, 6.97; N, 3.77.

1-(3′,4′-Dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (16).—To a solution of 15 mg of compound **14** in 3 ml of CH_3OH was added an ethereal solution of diazomethane (~0.1 g). After the mixture was allowed to stand overnight in the cold, the solvent was removed and the resulting residue which would not crystallize was passed through a column of alumina (1 g). The benzene effluent (15 ml) yielded a homogeneous glass (11 mg) which formed a crystalline hydrochloride (from methanol–ether) of compound **16**: mp 210–212°; nmr (CD_3OD) δ 3.86 (s, 9 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.86 (s, 3 H, Ar H), and 6.95 (s, 1 H, Ar H). Since the salt and base were not very stable, the acetate, mp 100–101°, was prepared for analysis.

Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.56; H, 7.07; N, 3.52.

1-(3′-Hydroxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (15).—Compound **7** hydrochloride (500 mg) in 12.5 ml of glacial acetic acid and 12.5 ml of 20% HCl was heated on the steam bath for 1.5 hr. The reaction mixture was diluted with ice, basified with NH_4OH, and extracted with ether. The ether residue crystallized from ether to give 160 mg of **15**: mp 110–111°; uv max 282 mμ (log ε 3.76); nmr δ 2.51 (s, 3 H, NCH_3), 2.6–3.4 (envelope, 6 H, CH_2 protons), 3.58 (s, 3 H, OCH_3 at C_5), 3.83, 3.85, 3.87 (s, 3 H each, OCH_3 at C_5, C_6, and C_4'), ~3.7 (m, 1 H, methine), 5.6 (broad, 1 H, OH, D_2O exchangeable), 5.97 (s, 1 H, H_8), and 6.4–6.9 (m, 3 H, H_2', H_5', and H_6').

Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.42; H, 7.35; N, 3.75.

1-(3′,4′-Dimethoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (17).—The phenol **15** (50 mg) was dissolved in methanol and treated with an ethereal solution of diazomethane prepared from 1.07 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. The next day the solution was filtered to remove a slight precipitate and evaporated to dryness. The nonphenolic residue yielded the hydrochloride of **17** (40 mg) from methanol–ether: mp 169–170°; uv max 282, 218 mμ (log ε 3.60, 4.12); nmr (free base) δ 2.53 (s, 3 H, NCH_3), 2.5–3.1 (envelope, 6 H, CH_2 protons), 3.59 (s, 3 H, OCH_3 at C_7), 3.79 (s, 3 H, OCH_3), 3.85 (s, 9 H, 3 OCH_3), ~3.7 (m, 1 H, methine), 5.97 (s, 1 H, H_8) and 6.4–6.9 (m, 3 H, H_2', H_5', H_6').

Anal. Calcd for $C_{22}H_{29}NO_5 \cdot HCl$: C, 62.33; H, 7.14; N, 3.31. Found: C, 62.04; H, 7.21; N, 3.40.

(19) All of the peak values differ by δ +0.10 ± 0.01 units from those in the literature. Such a uniform displacement was considered to be due to a variable in the determination of the spectrum and not to signify a compound difference.

Registry No.—**1**, 20823-96-5; (±)-**4**, 24314-85-0; (+)-(*S*)-**4**, 24314-86-1; **5**, 24214-36-6; **6** HCl, 29883-53-2; **7** HCl, 29883-54-3; **8** HCl, 29883-55-4; **9**, 29969-76-4; **10**, 29969-77-5; **11**, 29883-56-5; **13**, 19775-47-4; **14**, 29883-57-6; **15**, 29883-58-7; **16**, 29969-78-6; **16** HCl, 29883-59-8; **17** HCl, 29883-60-1.

Photochemical Synthesis of Aporphines[1]

S. MORRIS KUPCHAN,*[2] JERRY L. MONIOT, RAMESH M. KANOJIA, AND JOHN B. O'BRIEN

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, and Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received January 29, 1971

The photolysis of iodo aromatic compounds has been employed as the key step in new synthetic routes to aporphines. Photocyclization of 1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochlorides (**18**, **19**, **10**, **11**) yielded noraporphines **29** and **30** and aporphines **33** and **34** directly. Photocyclization of *N*-acyl-1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinolines (**14**–**17**) followed by hydrolysis gave noraporphines **25**–**28**. Photolysis of urethanes **12** and **13** afforded substituted dehydronoraporphines **23** and **24**, and two-step reduction gave (±)-aporphine (**33**) and (±)-nuciferine (**34**). Photolysis of *N*-carbophenoxy-1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinolines **20** and **21** followed by one-step reduction afforded good yields of (±)-aporphine (**33**) and (±)-nuciferine (**34**). The routes *via* photocyclization of *N*-acyl iodo aromatic compounds have yielded oxygenated aporphines and noraporphines in the best yields reported to date.

Aporphines, which contain the tetracyclic ring system shown in structure **33**, have been the subject of considerable chemical and pharmacological interest for many years.[3] Nevertheless, all aporphines synthesized up to 1966 were obtained only from the corresponding 1-(2′-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines by way of a Pschorr-type cyclization, usually in quite low yield.[4] In 1966, two mechanistically different photochemical syntheses of aporphines were reported, one involving an oxidative stilbene–phenanthrene photocyclization,[5,6] and the other involving photocyclization of iodostilbenes to phenanthrenes.[1a,7] The present paper gives details of the photocyclization of iodobenzyltetrahydroisoquinolines to noraporphines and aporphines and an improved method for the synthesis of *N*-acyl and *N*-carbamyl noraporphines and aporphines. In addition, we now report a novel modification of the syntheses in which iodobenzylidene tetrahydroisoquinolines are cyclized to substituted dehydronoraporphines. Since the dehydronoraporphines can be readily reduced to aporphines, this method constitutes an efficient aporphine synthesis.[8]

Results

The photolysis of 1-(2′-iodobenzyl)tetrahydroisoquinolines was investigated as the most direct route to the aporphine ring system. Condensation of the appropriately substituted β-phenethylamines **1** and **2** with *o*-iodophenylacetyl chloride (**3**) gave the amides **4** and **5** (Sheme I). Bischler–Napieralski cyclization of **4** and **5** using polyphosphate ester[9] gave the 3,4-dihydroisoquinolines **6** and **7** in 93–98% yields. Direct reduction with sodium borohydride afforded the noraporphine precursors **18** and **19**, respectively. Treatment of **6** and **7** with methyl iodide followed by reduction of the stable quaternary iodides **8** and **9** with sodium borohydride gave the aporphine precursors **10** and **11**, respectively. Photolysis of **18** gave a complex intractable mixture of products which showed negligible uv absorption in the region characteristic of aporphines (270 mμ). Apparently, the presence of the free electron pair on nitrogen was detrimental to the desired photocyclization of **18**, and other reactions predominated. Salt formation was conceived as a potential method to circumvent this effect. Photolyses of the hydrochloride salts of **18**, **19**, **10**, and **11** were carried out in methanol–water mixtures in the presence of sodium bisulfite and afforded the desired noraporphines (**29** and **30**) and aporphines (**33** and **34**) in 13–20% yields (Table I). The low yield of aporphine **33** was found to be attributable to formation during the reaction of a secondary product which had the spectral characteristics of a phenanthrene. The *N*-methyl derivative of this product was shown to be identical with **22**, prepared by Hofmann degradation of aporphine **33**. This product is presumed to have resulted from cleavage of the initially formed aporphine in a manner analogous to the Hofmann reaction.

To avoid this side reaction, the photolysis of the less labile *N*-acyl precursors was investigated, with a view toward subsequent hydrolysis of the cyclization products to noraporphines. The noraporphine precursors **18** and **19** were treated with acetic anhydride–pyridine to obtain the acetamides **14** and **15** and with benzoyl chloride–pyridine to obtain the benzamides **16** and **17**, respectively. Photolysis of the *N*-acyl precursors **14**, **15**, **16**, and **17** in benzene solution in the presence of sodium thiosulfate afforded the substituted noraporphines

(1) (a) A portion of this work was reported in a preliminary communication: S. M. Kupchan and R. M. Kanojia, *Tetrahedron Lett.*, 5353 (1966). (b) This work was supported by grants from the National Institutes of Health (HE-13184 and CA-12059).

(2) Department of Chemistry, University of Virginia.

(3) For recent reviews of aporphine alkaloids, see (a) M. Shamma, *Alkaloids*, **9**, 1 (1967); (b) M. P. Cava and A. Venkateswarlu, *Annu. Rep. Med. Chem.*, 231 (1968).

(4) For a brief review of the synthesis of aporphines up to 1960, see A. R. Pinder in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1960, Chapter 25.

(5) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

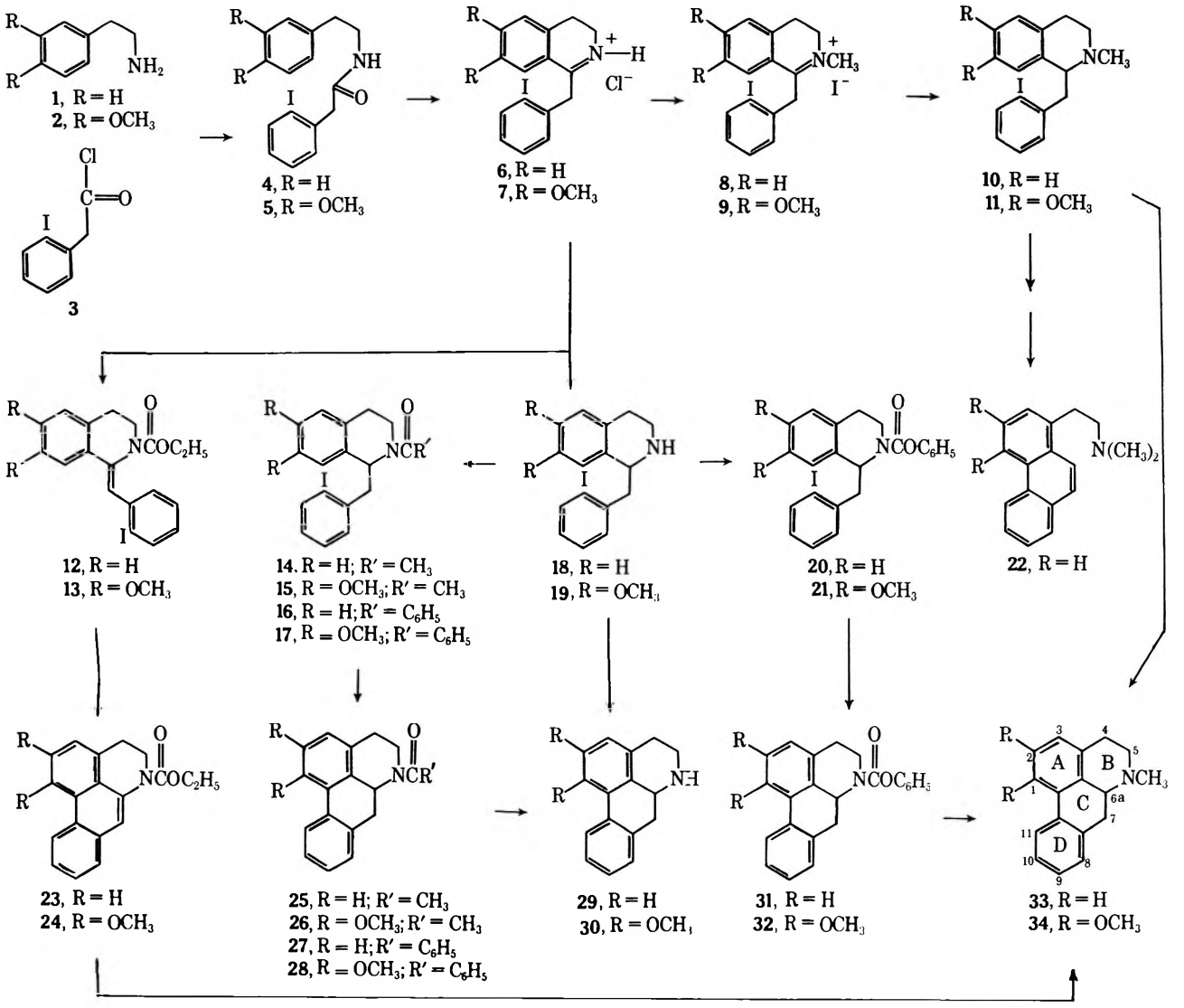
(6) N. C. Yang, G. R. Lenz, and A. Shani, *ibid.*, 2941 (1966).

(7) S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).

(8) After completion of this work, the nonoxidative photocyclization of chloro- and bromostilbene noraporphine precursors was reported: M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *ibid.*, **35**, 175 (1970). The authors proposed, however, that their photocyclizations proceeded principally *via* closure to dihydrophenanthrene intermediates rather than by photochemical homolysis of the aryl halide bond involved in the photocyclization of iodostilbenes[7] [*cf.* R. K. Sharma and N. Kharasch, *Angew. Chem. Int. Ed. Engl.*, **7**, 36 (1968)].

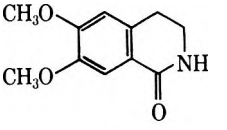
(9) Y. Kamaoka E. Sato, O. Yonematsu, and Y. Ban, *Tetrahedron Lett.*, 2419 (1964).

SCHEME I



25, 26, 27, and 28 in 30–45% yields. Sodium thiosulfate was used to trap liberated iodine, which slowed the reaction appreciably if allowed to accumulate. Despite the possibility of solvent capture of the radical generated, high yields of intramolecular reaction products were obtained. Treatment of acetamide **25** or benzamide **27** with freshly prepared triethyloxonium fluoroborate,[10-12] followed by aqueous acid hydrolysis, gave (±)-noraporphine (**29**) in *ca.* 75% yield. Analogous treatment of the acetamide **26** and of the benzamide **28** afforded (±)-nornuciferine (**30**) in 72 and 76% yields, respectively.

In order to combine the potentially advantageous effects of intramolecular photocyclization of aryl iodides, N-acylation, and the stilbene–phenanthrene entropy factor,[7] the 1-(2′-iodobenzylidene)-2-carbethoxy-1,2,3,4-tetrahydroisoquinolines **12** and **13** were prepared for photolysis. Previous methods[13] for the preparation of this type of compound involved treating 3,4-dihydroisoquinolines with ethyl chloroformate under Schotten–Baumann conditions and gave yields of 65–75%, presumably accompanied by partially hydrolyzed starting materials. The use of an aprotic solvent with an organic base circumvented this problem. Treatment of the 3,4-dihydroisoquinolines **6** and **7** with ethyl chloroformate in pyridine gave **12** and **13** in 90% yields. These were assigned the trans configuration of the aromatic substituents about the double bond on the basis of the deshielded methyl signal at τ 9.2 in their nmr spectra.[6] Irradiation of **12** and **13** in benzene solution in the presence of sodium thiosulfate gave the desired dehydronoraporphine carbamides **23** and **24** in 41 and 67% yields (based on unrecovered starting material), respectively. The two-step conversions of **23** and **24** to (±)-aporphine[14] and (±)-nuciferine[3,15] have been reported. When urethane **13** was irradiated in methanol solution in the presence of sodium thiosulfate, 3,4-dihydro-6,7-dimethoxyisocarbostyryl (**35**) was obtained



35

(10) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).
(11) H. Muxfeldt and W. Rogalski, *J. Amer. Chem. Soc.*, **87**, 933 (1965).
(12) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(13) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **289**, 479 (1956).
(14) B. Franck and G. Schlingloff, *Justus Liebigs Ann. Chem.*, **659**, 123 (1962); B. Franck and G. Blaschke, *ibid.*, **695**, 144 (1936).
(15) M. Shamma and W. A. Slusarchyk, *Chem. Commun.*, 528 (1965).

TABLE I
PHOTOCYCLIZATION YIELDS OF APORPHINE DERIVATIVES

Precursor	Overall yield of precursor	Photocyclization medium	Product	Yield, %
18	79	H_2O, $NaHSO_3$	(±)-Noraporphine (29)	13
19	82	H_2O, $NaHSO_3$	(±)-Nornuciferine (30)	16
10	74	H_2O, $NaHSO_3$	(±)-Aporphine (33)	18
11	73	H_2O, $NaHSO_3$	(±)-Nuciferine (34)	21
14	74	Benzene, $Na_2S_2O_3$	(±)-*N*-Acetylnoraporphine (25)	30
15	80	Benzene, $Na_2S_2O_3$	(±)-*N*-Acetylnornuciferine (26)	45
16	71	Benzene, $Na_2S_2O_3$	(±)-*N*-Benzoylnoraporphine (27)	36
17	71	Benzene, $Na_2S_2O_3$	(±)-*N*-Benzoylnornuciferine (28)	38
20	70	Benzene, $Na_2S_2O_3$	(±)-*N*-Carbophenoxynoraporphine (31)	45
21	70	Benzene, $Na_2S_2O_3$	(±)-*N*-Carbophenoxynornuciferine (32)	31
12	75	Benzene, $Na_2S_2O_3$	(±)-*N*-Carbethoxy-6*a*,7-dehydronoraporphine (23)	67
13	77	Benzene, $Na_2S_2O_3$	(±)-*N*-Carbethoxy-6*a*,7-dehydronornuciferine (24)	41

in addition to the desired dehydronoraporphine **24**. Attempts to minimize oxidative side reactions by irradiation in a nitrogen atmosphere led to drastically reduced yields of cyclized products. To circumvent the oxidative cleavage problem, the photolysis of 1-(2′-iodobenzyl)-2′-carbophenoxy-1,2,3,4-tetrahydroisoquinolines was investigated. Treatment of **18** and **19** with phenyl chloroformate in pyridine gave the urethanes **20** and **21** in 88% yield. Irradiation of **20** and **21** in benzene solution in the presence of sodium thiosulfate afforded the desired carbophenoxy noraporphines **31** and **32** in 45 and 31% yields, respectively. Since lithium aluminum hydride reductions of urethane derivatives were known to give mixtures of N–H and *N*-methyl products, Meerwein's reagent was used. The urethane **32** was treated with triethyloxonium fluoroborate in dichloromethane followed by sodium borohydride in ethanol to give (±)-nuciferine (**34**) in 75% yield. Analogous treatment of urethane **31** afforded (±)-aporphine (**33**) in 72% yield.

Discussion

While the nature of the *N*-acyl group had little effect on the extent of cyclization, solvents and trapping agents had profound effects. In order of decreasing efficiency for use in benzene, the trapping agents were thiosulfate, bisulfite, cupric acetate, and silver trifluoroacetate. In general reaction mixtures from photolyses in benzene were much cleaner than those from photolyses in methanol.

The Bischler–Napieralski route was chosen because of the high synthetic utility of the 3,4-dihydroisoquinolines. All of the precursors (**10**–**21**) were prepared by this route in yields from 88 to 98% for each step.

The aporphines were prepared in 19–23% overall yields *via* the urethane route. In the synthesis of (±)-nuciferine, the cyclization yield for the saturated urethane **21** (31%) is comparable to that recently obtained by nonoxidative photocyclization of a chlorostilbene analog of **13** (35%).[8] However, the latter route requires two postcyclization reduction steps of about 70% yield each, whereas the former procedure requires only one. The yields of aporphines from the Reissert synthesis and Pschorr cyclization route[16] suffer from several 70% yield reactions prior to cyclization. In general, the yield of the Pschorr reaction decreases as the oxygenation level of the precursor increases, limiting its applicability.[17,18]

The route *N*-acyl precursor → *N*-acyl noraporphine → noraporphine gave 28–33% yields of noraporphines; this appears to constitute the highest yield synthesis to date of noraporphine and nornuciferine.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Ultraviolet spectra were determined in methanol solution on a Beckman Model DK-2A recording spectrophotometer. Nmr spectra were recorded on Varian Models A-60A and HA-100 spectrometers, in deuteriochloroform solution containing tetramethylsilane as internal standard. Infrared spectra were determined on Beckman Model IR-9 and Perkin-Elmer Models 257 and 337 recording spectrophotometers. Mass spectra were determined on Hitachi Model RMU-6E and Atlas AEI MS-902 spectrometers. Photolyses were carried out using low-pressure mercury arc lamps (2537 Å). Thin layer chromatography was carried out using silica gel F-254 and aluminum oxide F-254 (type T) analytical layer plates (Brinkman) and spots were visualized by ultraviolet light or Dragendorf spray reagent or both. Skellysolve B refers to the petroleum ether fraction of bp 60–68°. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

***N*-(β-Phenethyl)-2′-iodophenylacetamide (4).**—A solution of *o*-iodophenylacetyl chloride (**3**, 11.3 g) in chloroform (40 ml) was added dropwise to a stirred solution of β-phenylethylamine (1, 4.84 g) and triethylamine (4.04 g) in chloroform (40 ml) at 0°. The chloroform solution was stirred for 2 hr at room temperature, washed successively with 100-ml portions of water, hydrochloric acid (2.5%), and sodium bicarbonate (2.5%), dried over sodium sulfate, and evaporated. Recrystallization of the solid residue from acetone–hexane afforded 13.3 g (92%) of 4 as fine needles: mp 122–123°; λ_{max}^{KBr} 3.01, 6.10, 6.46 μ.

Anal. Calcd for $C_{16}H_{16}INO$: C, 52.81; H, 4.38; N, 3.84. Found: C, 52.91; H, 4.52; N, 3.77.

***N*-(3,4-Dimethoxyphenethyl)-2′-iodophenylacetamide (5).**—A solution of homoveratrylamine (**2**, 3.2 g) and triethylamine (2.2 g) in chloroform (50 ml) at 0° was treated with *o*-iodophenylacetyl chloride (**3**, 5.0 g) and the mixture was stirred for 2 hr at room temperature. The mixture was diluted with chloroform (50 ml), washed successively with 100-ml portions of water, hydrochloric acid (2.5%), and sodium bicarbonate (2.5%), dried over sodium sulfate, and evaporated. The residue was recrystallized from acetone–hexane to give 6.4 g (90%) of 5 as rosettes: mp 137–138.5°; $\lambda_{max}^{CHCl_3}$ 6.12 (NCO) μ.

Anal. Calcd for $C_{18}H_{20}INO_3$: C, 50.82; H, 4.71; N, 3.29. Found: C, 50.89; H, 4.68; N, 3.24.

1-(2′-Iodobenzyl)-3,4-dihydroisoquinoline.—A mixture of the amide **4** (2.0 g) and polyphosphate ester (10.0 g) was heated at 130° for 3 hr. The reaction was cooled, dissolved in water

(16) J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.*, **34**, 3786 (1969).

(17) D. F. DeTar, *Org. React.*, **9**, 409 (1957).

(18) J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963).

(50 ml), and extracted with ether (three 30-ml portions), and the aqueous layer was basified with 5 *N* NaOH and rapidly extracted with ether. The ether layer was washed with water, dried over K_2CO_3, and evaporated under a stream of nitrogen. Recrystallization from hexane gave 1.8 g (93%) of the base: mp 87–89°; HCl salt (6, from EtOH), mp 202–203°; nmr (DMSO-d_6) τ 6.82 (t, 2 H) and 6.10 (t, 2 H, isoquinoline CH_2), 5.22 (t, 2 H, benzylic CH_2), 3.2–2.0 (m, 8 H, aromatic).

Anal. Calcd for $C_{16}H_{15}ClIN$: C, 50.06; H, 3.93; N, 3.67. Found: C, 50.16; H, 3.98; N, 3.68.

1-(2′-Iodobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline.—The amide **5** (2.0 g) was treated with polyphosphate ester (12.0 g) in chloroform (30 ml), and the mixture was heated to 90° for 1.5 hr, cooled, evaporated, dissolved in water, and extracted with ether. The aqueous layer was made basic with ammonium hydroxide (5 *N*) and was extracted with ether. The ether layer was dried over sodium sulfate and treated with hydrogen chloride gas. The precipitate was collected and recrystallized from methanol–ether to give **7** (2.0 g, 99%) as needles: mp 211.5–212.5°; λ_{max}^{EtOH} 227 mμ (ε 16,900), 241 (12,010), 309 (6800). Recrystallization from ethanol–isopropyl ether gave needles, mp 222–223°.

Anal. Calcd for $C_{18}H_{19}ClINO_2$: C, 48.72; H, 4.29; N, 3.16. Found: C, 48.87; H, 4.55; N, 3.09.

1-(2′-Iodobenzyl)-2-methyl-3,4-dihydroisoquinolinium Iodide (8).—A mixture of the free base of **6** (1.0 g) and methyl iodide (5 ml) was heated on a steam bath for 1 hr. The yellow precipitate was filtered and recrystallized from ethanol to give **8** (1.3 g, 92%): mp 205–207°; λ_{max}^{EtOH} 220 mμ (ε 30,000), 284 (11,700).

Anal. Calcd for $C_{17}H_{17}I_2N$: C, 41.75; H, 3.69; N, 2.86; I, 51.89. Found: C, 41.66; H, 3.64; N, 2.82; I, 51.79.

1-(2′-Iodobenzyl)-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Iodide (9).—The free base of **7** was treated as above to give a product which, upon recrystallization from ethanol, yielded **9**: mp 189–191°; λ_{max}^{EtOH} 250 mμ (ε 11,400), 311 (8000), 374 (8400).

Anal. Calcd for $C_{19}H_{21}I_2NO_2$: C, 40.21; H, 4.06; N, 2.47; I, 44.79. Found: C, 40.63; H, 4.32; N, 2.61; I, 44.51.

1-(2′-Iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (10).—A solution of iodide **8** (0.4 g) in ethanol (10 ml) was stirred with sodium borohydride (0.7 g) for 1.5 hr at 25°, the solvent evaporated, and the residue extracted with ether. The ether layer was washed with water, dried over potassium carbonate, and treated with hydrogen chloride gas to give a precipitate. Recrystallization from methanol–ether gave the hydrochloride of **10** (0.316 g, 93%) as fine needles: mp 201–202°; λ_{max}^{EtOH} 226 mμ (ε 10,300).

Anal. Calcd for $C_{17}H_{19}ClIN$: C, 51.07; H, 4.76; Cl, 8.79; I, 31.78. Found: C, 50.96; H, 4.94; Cl, 8.66; I, 31.68.

1-(2′-Iodobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (11).—A methanolic solution of **9** (0.7 g) was treated as above to yield the hydrochloride salt of **11** (0.456 g, 85%). Recrystallization from methanol–acetone gave fine needles: mp 185–187°; λ_{max}^{EtOH} 227 mμ (ε 27,800), 281 (3700), 284 (3800), 289 sh (3400).

Anal. Calcd for $C_{19}H_{23}ClINO_2$: C, 49.62; H, 5.00; N, 3.05. Found: C, 49.80; H, 5.12; N, 3.04.

1-(2′-Iodobenzyl)-1,2,3,4-tetrahydroisoquinoline (18).—A solution of the free base of **6** (1.6 g) in ethanol was stirred with sodium borohydride (2.4 g) for 1.5 hr at 25°, the solvent evaporated, and the residue dissolved in water and extracted with ether. The ether layer was washed with water, dried over potassium carbonate, and treated with hydrogen chloride gas to give a precipitate. Recrystallization from methanol–ether gave 1.536 g (93%) of **18** HCl as needles: mp 249–251°; λ_{max}^{EtOH} 226 mμ (ε 10,850), 257 (922), 264 (922), 271 (800).

Anal. Calcd for $C_{16}H_{17}ClIN$: C, 49.79, H, 4.41; N, 3.63. Found: C, 49.82; H, 4.47; N, 3.72.

1-(2′-Iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19).—Sodium borohydride reduction of the free base of **7** (0.85 g) in methanol by the above procedure gave 0.704 g (85%) of **19** HCl as fine needles from methanol–ether: mp 248–250°; λ_{max}^{EtOH} 226 mμ (ε 17,200), 281 (4800), 284 (4800).

Anal. Calcd for $C_{18}H_{21}ClINO_2$: C, 48.51; H, 4.72; Cl, 7.95; I, 28.36; N, 3.14. Found: C, 48.54; H, 4.90; Cl, 7.91; I, 28.44; N, 3.19.

1-(2′-Iodobenzyl)-2-acetyl-1,2,3,4-tetrahydroisoquinoline (14).—A mixture of **18** (0.41 g), acetic anhydride (1 ml), and pyridine (1.5 ml) was allowed to stand at room temperature overnight. The solution was poured over ice and sodium carbonate, extracted with chloroform (50 ml), washed with 40-ml portions of sodium hydroxide (2%), hydrochloric acid (2.5%), and water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel plates (preparative) to give **14** as a homogeneous oil (0.45 g, 90%): $\lambda_{max}^{CHCl_3}$ 6.10 μ (NC=O); nmr τ 7.94 and 8.58 (*N*-acetyl methyl, two conformations); mass spectrum *m/e* 396 (M^+), 353 (M − acetyl).

1-(2′-Iodobenzyl)-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15).—A solution of **19** (1.0 g) in pyridine (25 ml) and acetic anhydride (0.29 ml) was allowed to stand at 25° for 18 hr and was then poured onto ice and hydrochloric acid and extracted with chloroform. The chloroform extract was washed with 2 *N* sodium hydroxide, 2 *N* hydrochloric acid, and water, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene–hexane to give **15** (1.08 g, 98%) as needles: mp 101–102°; $\lambda_{max}^{CHCl_3}$ 6.19 μ (NC=O); mass spectrum *m/e* 234, 192; nmr τ 8.5 (s, 3 H, acetate methyl), 6.08 (s, 6 H, 2 OCH_3).

Anal. Calcd for $C_{20}H_{22}INO_3$: C, 53.21; H, 4.87; N, 3.10. Found: C, 53.39; H, 5.03; N, 3.20.

1-(2′-Iodobenzyl)-2-benzoyl-1,2,3,4-tetrahydroisoquinoline (16).—A solution of **18** hydrochloride (0.7 g) and benzoyl chloride (1.0 g) in pyridine (4.5 ml) was treated as above to yield an oil which was crystallized from benzene–Skellysolve B to give **16** (0.8 g, 89%) as needles: mp 140–141°; λ_{max}^{KBr} 6.18 μ (NC=O); λ_{max}^{EtOH} 263 mμ (ε 2050), 272 (1500); mass spectrum *m/e* 453 (M^+), 348, 236, 131.

Anal. Calcd for $C_{23}H_{20}INO$: C, 60.94; H, 4.42; N, 3.09. Found: C, 61.07; H, 3.93; N, 2.77.

1-(2′-Iodobenzyl)-2-benzoyl-6,7-dimethoxy-3,4-dihydroisoquinoline (17).—A mixture of **19** (0.46 g), pyridine (2.5 ml), and benzoyl chloride (0.34 ml) was treated as above and the residue on recrystallization from benzene–hexane gave **17** (0.48 g, 80%) as prisms: mp 133–134°; mass spectrum *m/e* 408, 296, 105; nmr τ 6.18 (s) and 6.08 (s) (2 × 3 H, OCH_3), 2.0–3.2 (9 H, aromatic); λ_{max}^{KBr} 6.19 μ (NC=O); λ_{max}^{EtOH} 263 mμ (ε 1930), 272 (1400).

Anal. Calcd for $C_{25}H_{24}INO_3$: C, 58.48; H, 4.68; N, 2.73. Found: C, 58.49; H, 4.72; N, 2.66.

1-(2′-Iodobenzyl)-2-carbophenoxy-1,2,3,4-tetrahydroisoquinoline (20).—A solution of **18** (0.2 g) and triethylamine (1 ml) in chloroform (25 ml) was cooled to 0° and phenyl chloroformate (0.85 ml) was added. The mixture was allowed to warm to room temperature and was then heated to 40° for 2 hr. The solution was diluted with chloroform (50 ml) and washed with 3% hydrochloric acid, 3% sodium bicarbonate, and water, dried over sodium sulfate, and evaporated to dryness. Chromatography on alumina afforded a residue which was recrystallized from benzene–hexane to give **20** (0.218 g, 88%) as fine needles: mp 151–152°; λ_{max}^{KBr} 5.86 μ (NCOOR); mass spectrum *m/e* 348, 252, 131; nmr τ 2.0–3.5 (m, 13 H, aromatic).

Anal. Calcd for $C_{23}H_{20}INO_2$: C, 58.84; H, 4.26; N, 3.00. Found: C, 59.03; H, 4.37; N, 2.99.

1-(2′-Iodobenzyl)-2-carbophenoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21).—A solution of **19** (0.19 g) and triethylamine (0.85 ml) in chloroform (25 ml) was cooled to 0° and phenyl chloroformate (0.7 ml) was added. The mixture was treated as above to yield a residue which, after alumina chromatography and recrystallization from benzene–hexane, afforded **21** (0.196 g, 87%) as needles: mp 160–161°; λ_{max}^{KBr} 5.83 μ (NCOOR); mass spectrum *m/e* 408, 312, 191; nmr τ 6.15 (s) and 6.10 (s) (2 × 3 H, OCH_3), 3.3 (s, 1 H), 3.1 (s, 1 H), 2.8 (m, 8 H), 2.1 (m, 1 H, aromatic).

Anal. Calcd for $C_{25}H_{24}INO_4$: C, 56.71; H, 4.53; N, 2.64. Found: C, 56.78; H, 4.64; N, 2.71.

1-(2′-Iodobenzylidene)-2-carbethoxy-1,2,3,4-tetrahydroisoquinoline (12).—A solution of the 3,4-dihydroisoquinoline hydrochloride **6** (2.43 g) in chloroform (40 ml) and pyridine (8 ml) was cooled to −10°, and ethyl chloroformate (12 ml) was added dropwise. The mixture was allowed to warm to room temperature slowly and was stirred at 40° for 2 hr. The solution was cooled, diluted with chloroform (50 ml), extracted with 100-ml portions of hydrochloric acid (2.5%), aqueous sodium bicarbonate (2.5%), and water, and dried over sodium sulfate. Chromatography on a silica gel column yielded **12** (2.34 g, 89%) as light yellow plates: mp 92–93°; λ_{max}^{KBr} 5.83 μ (NCOOR); λ_{max}^{EtOH} 293 mμ (ε 26,600); nmr τ 9.20 (t, 3 H, CH_3CH_2), 6.35 (q, 2 H, J = 7 Hz, CH_3CH_2–), 3.2–2.0 (9 H, aromatic); mass spectrum *m/e* 419 (M^+), 346 ($M^+ - CO_2Et$).

Anal. Calcd for $C_{19}H_{18}INO_2$: C, 54.41, H, 4.29; N, 3.35. Found: C, 54.35; H, 4.33; N, 3.30.

1-(2′-Iodobenzylidene)-2-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13).—A solution of the 3,4-dihydroisoquinoline hydrochloride **7** (2.32 g) in chloroform (40 ml) and pyridine (7 ml) was cooled to −20° and ethyl chloroformate (10.85 g) was added dropwise. The mixture was stirred for 2 hr at 25° and for 1 hr at 40°, diluted with chloroform (50 ml), extracted with 100 ml each of 2.5% hydrochloric acid, 2.5% aqueous sodium bicarbonate, and water, dried over sodium sulfate, and evaporated. Chromatography on alumina (neutral) gave a residue which on recrystallization from benzene–Skellysolve B afforded **13** (2.25 g, 90%) as platelets: mp 135–136°; λ_{max}^{KBr} 5.93 μ (NCOOR); λ_{max}^{EtOH} 221 mμ (ε 32,900), 298 (15,750), 322 (18,100); nmr τ 9.18 (t, 3 H, CH_3CH_2), 6.03 (s), 6.10 (s) (2 × 3 H, OCH_3).

Anal. Calcd for $C_{21}H_{22}INO_4$: C, 52.61; H, 4.59; N, 2.90. Found: C, 52.76; H, 4.74; N, 3.05.

Noraporphine (29). A. From Photolysis.—A solution of the hydrochloride salt of **18** (0.5 g) and sodium bisulfite (0.15 g) in water (1.0 l.) was irradiated for 18 hr and evaporated. The residue was made basic with ammonium hydroxide and extracted with chloroform. The chloroform extract was chromatographed on silica gel using chloroform–methanol mixtures to yield a homogeneous oily fraction (0.15 g). Conversion to the hydrochloride salt and recrystallization from acetone–methanol gave **29** HCl (0.14 g, 33%): mp 275–280° dec; λ_{max}^{EtOH} 270 mμ (ε 19,300) [lit.[19] mp 284° dec; λ_{max}^{EtOH} 270 mμ (ε 18,200)].

B. From Hydrolysis of 25.—A solution of the acetamide **25** (50 mg) in dichloromethane (5 ml) was treated with freshly prepared triethyloxonium fluoroborate (0.12 g) and the mixture was stirred for 42 hr. The solution was evaporated and 3% acetic acid in dioxane (6 ml) was added. The mixture was warmed to 40° for 12 hr, diluted with aqueous sodium hydroxide (2%), and extracted with ether. The ether layer was dried over sodium sulfate and treated with hydrogen chloride gas. The resulting precipitate was collected and recrystallized from methanol–acetone to give **29** HCl (31 mg, 74%), mp 282–284° dec, identical in all respects (ir, uv, nmr, tlc, mass spectrum, mixture melting point) with a sample of (±)-noraporphine prepared by the above method.

C. From Hydrolysis of 27.—A solution of the benzamide **27** (50 mg) in dichloromethane (2 ml) was treated with triethyloxonium fluoroborate (0.05 g) for 36 hr. The mixture was worked up as above to give, after acidification and recrystallization, **29** HCl (29.8 mg, 75%), mp 282–285°, identical with that obtained above by ir, mass spectral, and mixture melting point determinations.

Nornuciferine (30). A. From Photolysis.—A solution of the hydrochloride salt of **19** (0.4 g) and sodium bisulfite (0.13 g) in water (1.0 l.) was irradiated for 12 hr, the solvent removed, and the residue purified as above. Recrystallization of the hydrochloride salt from methanol–ether gave **30** (0.058 g, 21%), mp 260–262° dec (lit.[20] mp 261–262° dec). The infrared spectra of **30** and of an authentic sample of nornuciferine (from *Nelumbo lutea*) in chloroform solution were identical.

B. From Hydrolysis of 28.—A solution of the benzamide **28** (60 mg) in dichloromethane (5 ml) was treated with triethyloxonium fluoroborate (0.1 g) and the mixture was stirred under nitrogen for 36 hr. The solution was evaporated and the residue was dissolved in 3% acetic acid in dioxane, stirred for 18 hr at 40°, diluted with aqueous sodium hydroxide (2%), and extracted with ether. The ether solution was dried over sodium sulfate and treated with hydrogen chloride gas. The precipitate was collected and recrystallized from methanol–ether to give **30** HCl (38 mg, 76%): mp 230–262° dec, mass spectrum *m/e* 281 (M^+). Infrared spectra of samples of **30** and an authentic specimen of (−)-nornuciferine from *Nelumbo lutea*, measured in chloroform, were superimposable.

C. From Hydrolysis of 26.—A solution of the acetamide **26** (50 mg) in dichloromethane (5 ml) was treated with triethyloxonium fluoroborate (0.1 g) and treated as above to yield **30** HCl (35.2 mg, 72%) as needles, mp 260–262°, identical (ir, tlc, mass spectrum, mixture melting point) with that obtained above.

Aporphine (33). A. From Photolysis.—A solution of the hydrochloride salt of **10** (0.2 g) and sodium bisulfite (0.052 g) in water (20 ml) and methanol (180 ml) was irradiated for 12 hr and the solvent evaporated; the residue was made basic with ammonium hydroxide (5%) and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), evaporated, and chromatographed on silica gel plates using 12% methanol in chloroform, to give two materials. The higher R_f material showed the characteristic aporphine uv spectrum and was rechromatographed, converted to the hydrochloride salt, and recrystallized from methanol–acetone to give **33** (0.018 g, 13%): mp 253–255°; λ_{max}^{EtOH} 270 mμ (ε 18,520), 282 (15,400) [lit.[18] mp 255°; λ_{max}^{EtOH} 270 mμ (ε 18,600), 282 (15,490)].

B. From Reduction of 31.—A solution of carbamate **31** (0.05 g) in dichloromethane (6 ml) was treated with freshly prepared triethyloxonium fluoroborate (0.12 g) and was stirred for 38 hr at 25°. The solvent was removed *in vacuo*, ethanol (6 ml) was added, and the solution was cooled to 0°. Sodium borohydride (0.2 g) was added in portions and the mixture was stirred overnight, evaporated, dissolved in water, and extracted with ether (three 50-ml portions). The ether extract was dried over sodium sulfate, concentrated to 25 ml, and treated with hydrogen chloride gas. The resulting precipitate was filtered and recrystallized from methanol–acetone to give **33** HCl (38 mg, 72%), mp 253–255°, indistinguishable from that obtained above by ir, nmr, mass spectrum, and mixture melting point.

***N,N*-Dimethyl-β-(1-phenanthryl)ethylamine Hydrochloride (22). A. From the Photolysis of 10.**—A second product of the mixture from the photolysis of **10** was obtained by silica gel chromatography as an oil and was converted to its hydrochloride salt. This material had a diffuse melting point and showed λ_{max}^{EtOH} 296 mμ (ε 15,000), 255 (60,900), 248 (45,000). The hydrochloride salt was dissolved in methanol (15 ml) and stirred with 37% formalin (0.5 ml) at 25° for 30 min. Sodium borohydride (0.1 g) was added and stirring was continued for 1 hr. The solvent was evaporated, and the residue was made basic and extracted with chloroform. The chloroform layer was evaporated, the residue dissolved in ether, and hydrogen chloride gas added. The precipitate was recrystallized from methanol–acetone to give the hydrochloride of **22**: mp 237° (sealed tube); λ_{max}^{EtOH} 298 mμ (ε 16,100), 286 (12,400), 276 (13,000), 255 (62,000), 248 (48,400), 221 (20,000).

B. By Hofmann Degradation of 33.—A mixture of methyl iodide (0.3 ml) and aporphine **33** (0.04 g) was heated under reflux on a steam bath for 3 hr, the excess methyl iodide was evaporated under N_2, methanol (10 ml) and potassium hydroxide (2 g) were added, and the mixture was again heated under reflux for 3 hr. The solvent was evaporated and the residue partitioned between water and chloroform. The chloroform layer was washed with water, dried over sodium sulfate, treated with hydrogen chloride gas, and evaporated; the residue recrystallized from methanol–acetone to give the hydrochloride of **22** (0.02 g), mp 239° (sealed tube). The infrared spectra in chloroform solution of the salts derived from both routes were superimposable. The nmr spectrum showed τ 7.67 [s, 6 H, $N(CH_3)_2$], 6.72 (t, 2 H, NCH_2), 7.40 (t, 2 H, benzylic CH_2), 1.43 (m, 2 H, C-4, C-5), 2.0–3.6 (m, 7 H, aromatic).

Anal. Calcd for $C_{18}H_{20}ClN$: C, 75.62; H, 6.70; N, 4.90. Found: C, 75.52; H, 6.75; N, 4.84.

(±)-Nuciferine (34). A. From Photolysis.—A solution of the hydrochloride salt of **11** (0.2 g) in water (0.5 l.) containing sodium bisulfite (0.052 g) was irradiated for 10 hr, and the solvent was removed under reduced pressure, made basic with ammonium hydroxide (5%), and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, evaporated, and chromatographed on silica gel using chloroform–methanol (0–12%) mixtures to give **34** HCl (0.024 g, 16%), mp 257° dec. The infrared spectrum of **22** was superimposable on that of an authentic sample of nuciferine.

B. From Reduction of 32.—A solution of the carbamate **32** (50 mg) and triethyloxonium fluoroborate (0.2 g) in dichloromethane (2 ml) was stirred at room temperature overnight, evaporated under a stream of nitrogen, and treated with ethanol (15 ml) and sodium borohydride (0.2 g). The mixture was stirred at room temperature for 12 hr, heated to 40° for 2 hr, evaporated, dissolved in water (30 ml), and extracted with ether (three 30-ml portions). The ether extract was dried over potassium carbonate, concentrated to 25 ml, and treated with hydrogen chloride. The resulting precipitate was collected and recrystallized from chloroform–methanol to give **34** HCl (30 mg, 75%), mp 256–257°. The infrared spectra of **34** and an authentic sample of nuciferine from *Nelumbo lutea*, measured in chloroform, were superimposable.

(19) E. Ochiai and J. Kuriyoshi, *Pharm. Bull.*, **5**, 292 (1967).

(20) J. A. Weisbach and B. Douglas, *J. Org. Chem.*, **27**, 3738 (1962).

C. From Reduction of 24.—A solution of the dehydroaporphine **24** (0.2 g) in ether–THF (1:1) was added dropwise to a stirred slurry of lithium aluminum hydride (86 mg) in dry ether at room temperature. The mixture was stirred for 8 hr, the excess reagent decomposed with wet ether, and the solution dried over sodium sulfate. Hydrogen chloride gas was added and the solvent was removed *in vacuo*. The residue (0.188 g) was dissolved in 80% acetic acid (30 ml) and stirred with platinum oxide catalyst (120 mg) in a hydrogenator at 1 atm pressure for 18 hr. The filtrate from the hydrogenation was basified and extracted with ether. The ether was evaporated and the residue was chromatographed on silica gel preparative layer plates to give **34** (73 mg, 51%) as needles from chloroform–hexane: mp 141°; λ_{max}^{MeOH} 230 mμ (ε 18,000), 272 (14,500), 310 (2000). The infrared spectra of a sample of **34** and authentic nuciferine in chloroform solution were superimposable.

***N*-Acetylnoraporphine (25).**—Irradiation of a solution of **14** (0.19 g) and sodium thiosulfate (0.19 g) in benzene (100 ml) and water (1 ml) for 12 hr, followed by evaporation and silica gel chromatography using chloroform, afforded a solid which was recrystallized from chloroform–methanol to yield **25** (0.04 g, 31%), mp 214°. Recrystallization from benzene–Skellysolve B gave needles: mp 215°; λ_{max}^{EtOH} 271 mμ (ε 18,600); λ_{max}^{KBr} 6.12 μ (*N*-acetyl); nmr τ 7.79 (s, 3 H, acetyl methyl), 6.5–7.5 (m, 7 H, CH_2), 2.0–3.0 (m, 7 H, aromatic); mass spectrum *m/e* 263 (M^+), 220 (M^+ − acetyl).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.32; H, 6.61; N, 5.65. Found: C, 82.13; H, 6.46; N, 5.32.

***N*-Acetylnornuciferine (26).**—A solution of **15** (70 mg) and sodium thiosulfate (70 mg) in benzene (75 ml) and water (1 ml) was irradiated for 12 hr and worked up as above. Chromatography and recrystallization from benzene–hexane gave **26** (23 mg, 44%) as rosettes: mp 232–233°; λ_{max}^{KBr} 6.17 μ (NCO); mass spectrum *m/e* 291 (M^+), 248 (M^+ − acetyl); λ_{max}^{EtOH} 274 mμ (ε 32,100); nmr τ 7.81 (s, 3 H, $NCOCH_3$), 6.33 (s) and 6.12 (s) (2 × 3 H, OCH_3), 3.32 (s, 1 H, C-5), 1.57 (m, 1 H, C-11), 2.69 (m, 4 H, aromatic). These data were in good agreement with those previously reported.[21,22]

***N*-Benzoylnoraporphine (27).**—Irradiation of a solution of **16** (0.14 g) and sodium thiosulfate (0.14 g) in benzene (100 ml) and water (1 ml) and purification as above gave **27** (0.032 g, 36%) from methanol as needles: mp 201–202°; λ_{max}^{KBr} 6.19 μ (NCO); λ_{max}^{EtOH} 269 mμ (ε 19,550); mass spectrum *m/e* 325 (M^+), 220.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.67; H, 6.28; N, 4.29. Found: C, 84.80; H, 6.32; N, 4.24.

***N*-Benzoylnornuciferine (28).**—A solution of **17** (0.4 g) and sodium thiosulfate (0.15 g) in benzene (100 ml) and water (2 ml) was irradiated for 12 hr. The benzene layer was washed with water, evaporated, and chromatographed on silica gel plates to afford a solid residue. Recrystallization from acetone–Skellysolve B gave **28** (0.116 g, 38%) as prisms: mp 193–194°; λ_{max}^{KBr} 6.19 μ (amide CO); λ_{max}^{EtOH} 271 mμ (ε 21,800); mass spectrum *m/e* 385 (M^+), 280 (M^+ − benzoyl).

Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.74; H, 6.02; N, 3.52.

***N*-Carbophenoxynoraporphine (31).**—A solution of **20** (0.1 g) and sodium thiosulfate (0.1 g) in benzene (100 ml) and water (1 ml) was irradiated for 9 hr. Evaporation and chromatography on silica gel using chloroform as eluent gave a light yellow oil which was crystallized from methanol. Recrystallization from chloroform–methanol gave **31** (0.032 g, 45%) as rosettes: mp 212–213°; λ_{max}^{KBr} 5.83 μ (NCOOR); nmr τ 7.01 (t, 2 H, *J* = 6 Hz), 6.8 (t, 2 H, *J* = 6 Hz), 2.7 (m, 11 H, aromatic), 1.7 (m, 1 H, C-11 proton); mass spectrum *m/e* 341 (M^+), 264, 220.

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 80.76; H, 5.64; N, 3.99.

***N*-Carbophenoxynornuciferine (32).**—A solution of **21** (0.096 g) and sodium thiosulfate (0.100 g) in benzene (100 ml) and water (1 ml) was irradiated for 10 hr. The reaction mixture was evaporated and chromatographed in silica gel using chloroform as eluent; the light tan residue obtained was recrystallized from methanol to yield **32** (0.025 g, 31%) as rosettes: mp 205–206°; λ_{max}^{KBr} 5.83 μ (NCOOR); nmr τ 6.10 (s) and 6.32 (s) (2 × 3 H, OCH_3), 3.30 (s, 1 H, C-5), 2.5–3.0 (m, 9 H, aromatic), 1.5 (m, 1 H, C-11); mass spectrum *m/e* 401 (M^+), 263, 249, 235 amu.

Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.49, H, 5.78; N, 3.49. Found: C, 74.54; H, 5.83; N, 3.36.

***N*-Carbethoxy-6a,7-dehydronoraporphine (23).**—A mixture of the stilbene **12** (0.158 g) and sodium thiosulfate (0.158 g) in benzene (75 ml) and water (3 ml) was irradiated for 11 hr. The benzene layer was evaporated and chromatographed on silica gel (preparative) layer plates to give two fractions, A and B. Fraction A was crystallized from benzene–Skellysolve B to give **23** (0.056 g): mp 92–93°; mass spectrum *m/e* 291 (M^+), 263, 218; λ_{max}^{KBr} 5.93 μ (carbamate ester); λ_{max}^{MeOH} 254 mμ (ε 8000), 261 (9300), 304 (3000); nmr τ 8.66 (t, 3 H, *J* = 7 Hz), 1.90–2.80 (m, 6 H, aromatic), 1.4 (d, 2 H, C-1 and C-11).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.38; H, 5.74; N, 4.78.

Fraction B was crystallized from benzene–Skellysolve B to give 36 mg of the unreacted starting material **12**, mp 91–92°. The yield of **23** (calculated on the basis of unrecovered starting material) was 67%.

***N*-Carbethoxy-6a,7-dehydronornuciferine (24).**—A solution of the stilbene **13** (0.25 g) and sodium thiosulfate (0.25 g) in benzene (100 ml) and water (2.5 ml) was irradiated for 14 hr. The benzene solution was evaporated and the residue chromatographed on a silica gel column using chloroform containing 1.5% methanol to give **24** (0.068 g, 36.5%) as prisms: mp 129–130°; λ_{max}^{KBr} 5.92 μ (carbamate ester); λ_{max}^{MeOH} 254 mμ (ε 44,200), 260 (44,700), 310 (8150), 321 (8250), 353 (950); nmr τ 8.72 (t, 3 H, *J* = 7 Hz), 6.82 (t, 2 H, *J* = 6 Hz), 5.92 (t, 2 H, *J* = 6 Hz), 5.68 (q, 2 H, *J* = 7 Hz), 6.0 (s, 3 H), 6.08 (s, 3 H), 2.92 (s, 1 H), 2.1–2.5 (m, 4 H), 0.41 (m, 1 H).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.98. Found: C, 71.82; H, 6.01; N, 3.95.

Later fractions eluted from this column yielded a residue which was recrystallized from benzene–Skellysolve B to give 0.026 g (10%) of unreacted starting material, mp 135–136°. The yield of **24** calculated on the basis of unrecovered **13** was 41%.

Portionwise photolysis of the stilbene **13** (7.2 g) in methanol (5.5 l.) solution containing water (60 ml) and sodium thiosulfate (2.4 g) for 16 hr and work-up as above gave 1.82 g of crude product. This residue was chromatographed on silicic acid and neutral alumina columns using 1% methanol in chloroform as eluent to afford the desired dehydronoraporphine **24** (0.36 g), identical with that obtained above. A second product (0.075 g), after recrystallization from ethyl acetate, showed mp 172–173°, and was identified as 3,4-dihydro-6,7-dimethoxyisocarbostyryl (**35**) by its melting point (lit.[23] 175°) and ir, uv, and nmr characteristics.

Registry No.—**4**, 14528-35-9; **5**, 30237-85-5; **6**, 14528-36-0; **6** HCl, 14528-37-1; **7** HCl, 30237-88-8; **8**, 14645-27-3; **9**, 30237-90-2; **10** HCl, 30256-05-4; **11** HCl, 30256-06-5; **12**, 30237-91-3; **13**, 30237-92-4; **14**, 30256-07-6; **15**, 30256-08-7; **16**, 30256-09-8; **17**, 30256-10-1; **18** HCl, 30256-11-2; **19** HCl, 30256-12-3; **20**, 30256-13-4; **21**, 30256-14-5; **22** HCl, 30237-93-5; **23**, 7630-70-8; **24**, 13555-30-1; **25**, 30256-36-1; **26**, 29424-85-9; **27**, 30256-37-2; **28**, 30256-38-3; **31**, 30256-39-4; **32**, 30256-40-7; **34** HCl, 5868-18-8.

(21) I. Baxter and G. Swan, *J. Chem. Soc.*, 4014 (1965).

(22) D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Lett.*, 2687 (1965).

(23) K. Wiesner, Z. Valenta, A. J. Manson, and F. W. Stonner, *J. Amer. Chem. Soc.*, **77**, 675 (1955).

Human Pituitary Growth Hormone. XXXI. The Synthesis of Two Protected Peptide Fragments Occurring in the Region of Residues 53–67

KUNG-TSUNG WANG AND CHOH HAO LI*

The Hormone Research Laboratory, University of California, San Francisco, California 94122

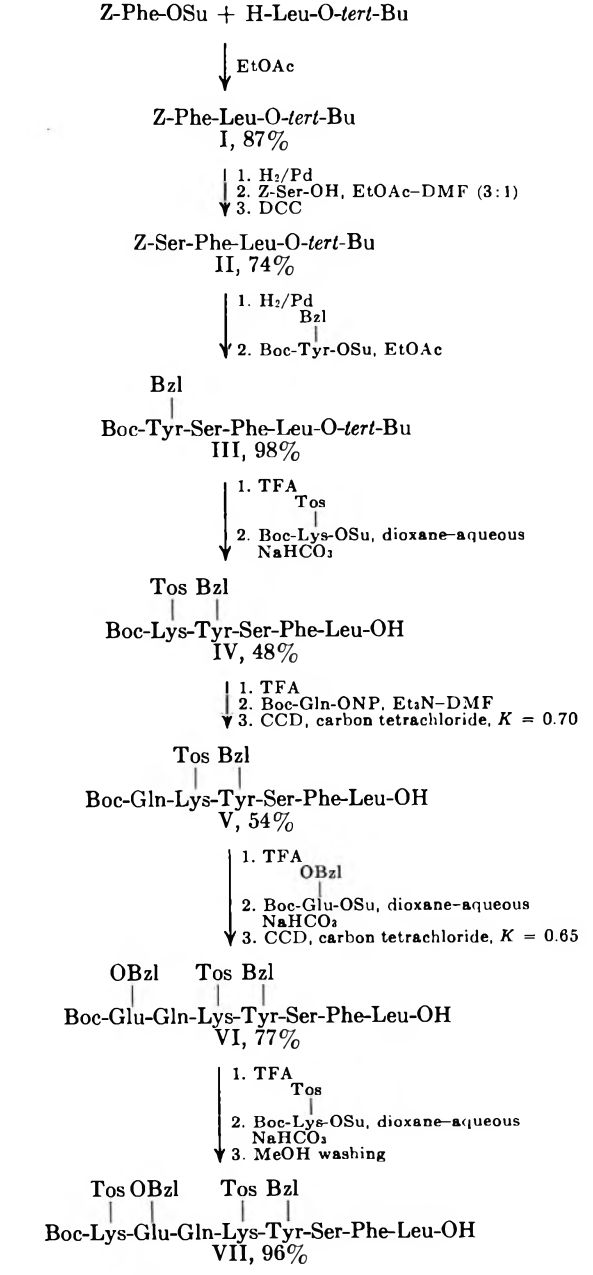
Received December 28, 1970

Two protected peptide fragments occurring in the region of residues 53–67 in the HGH molecule have been synthesized. These peptides are Boc-Lys(Tos)-Glu(OBzl)-Gln-Lys(Tos)-Tyr(Bzl)-Ser-Phe-Leu-OH and Boc-Gln-Asp(OBzl)-Pro-Glu(OBzl)-Thr-Ser-Leu-OH.

In a previous report,[1] we described the synthesis of three protected peptides occurring in the region of residues 53–67 in the amino acid sequence[2,3] of the HGH molecule.[4] This paper presents an alternative synthesis of this pentadecapeptide as two fragments, an octa- and a heptapeptide, in highly purified form and in excellent yields. They are, respectively, N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysyl-γ-benzylglutamylglutaminyl-N^{ϵ}-tosyllysyl-*O*-benzyltyrosylserylphenylalanylleucine[5] (VII) and *tert*-butyloxycarbonylglutaminyl-β-benzylaspartylprolyl-γ-benzylglutamylthreonylserylleucine (XIII).

Scheme I illustrates the synthesis steps for the octapeptide corresponding to residues 53–60 of HGH and Scheme II for the heptapeptide corresponding to residues 61–67. Leucine *tert*-butyl ester[6] was coupled with benzyloxycarbonylphenylalanine *N*-hydroxysuccinimide ester[7] in ethyl acetate to obtain crystalline benzyloxycarbonylphenylalanylleucine *tert*-butyl ester (I). After catalytic hydrogenolysis, the free base dipeptide ester was coupled with benzyloxycarbonylserine using dicyclohexylcarbodiimide[8] (DCC) to obtain the crystalline protected benzyloxycarbonylserylphenylalanylleucine *tert*-butyl ester (II). The tripeptide II was catalytically hydrogenolyzed to remove the benzyloxycarbonyl group and then coupled with *tert*-butyloxycarbonyl-*O*-benzyltyrosine *N*-hydroxysuccinimide ester[9] to yield the crystalline protected tetrapeptide *tert*-butyloxycarbonyl-*O*-benzyltyrosylserylphenylalanylleucine *tert*-butyl ester (III) in high yield. Peptide III was then treated with trifluoroacetic acid to remove both N- and C-protecting groups. Reaction of the deblocked tetrapeptide with the *p*-nitrophenyl ester of N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysine gave a low yield (10%) of pentapeptide N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysyl-*O*-benzyltyrosylserylphenylalanylleucine (IV). However, when the *N*-hydroxysuccinimide ester of N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysine was used for coupling, the yield of pentapeptide IV was up to 48%. Peptide IV was treated with trifluoroacetic acid to remove the *tert*-butyloxycarbonyl group and then reacted with *tert*-butyloxycarbonylglutamine *p*-nitrophenyl ester[10] to yield the hexapeptide *tert*-butyloxycarbonylglutaminyl-N^{ϵ}-tosyllysyl-*O*-benzyltyrosylserylphenylalanylleucine (V). In attempts to syn-

SCHEME I
SYNTHESIS OF THE PROTECTED OCTAPEPTIDE VII



(1) K. Kovacs, Y. Kovacs-Petres, and C. H. Li, *Int. J. Protein Res.*, **3**, 93 (1971).

(2) C. H. Li, W.-K. Liu, and J. S. Dixon, *J. Amer. Chem. Soc.*, **88**, 2050 (1966).

(3) C. H. Li, J. S. Dixon, and W.-K. Liu, *Arch. Biochem. Biophys.*, **133**, 70 (1969).

(4) Abbreviations: HGH, human pituitary growth hormone; DCC, dicyclohexylcarbodiimide; Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; *tert*-Bu, *tert*-butyl; OSu, *N*-hydroxysuccinimide ester; Bzl, benzyl; Tos, tosyl; ONP, *p*-nitrophenyl ester; tlc, thin layer chromatography; CCD, countercurrent distribution; TFA, trifluoroacetic acid; DMF, dimethylformamide; NMM, *N*-methylmorpholine.

(5) All the amino acids occurring in the peptides mentioned in this paper are of the L configuration.

(6) R. Roeske, *J. Org. Chem.*, **28**, 1251 (1963).

(7) G. W. Anderson, J. E. Zimmerman, and F. Callahan, *J. Amer. Chem. Soc.*, **85**, 3039 (1963); *ibid.*, **86**, 1839 (1964).

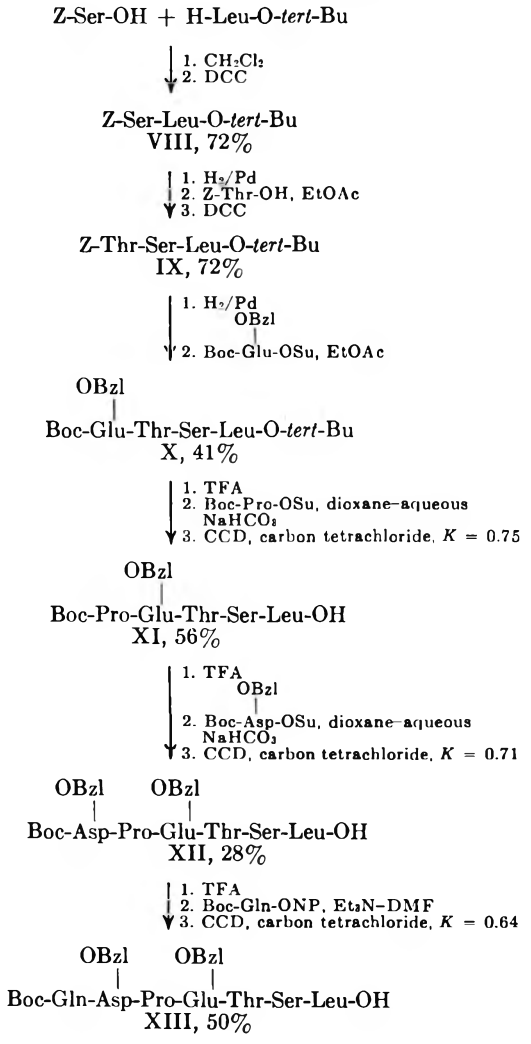
(8) J. C. Sheehan and G. P. Hess, *ibid.*, **77**, 1067 (1955).

(9) M. Low and L. Kisfaludy, *Acta Chim. Acad. Sci. Hung.*, **44**, 61 (1965).

(10) H. Zahn, W. Danho, and B. Gutte, *Z. Naturforsch., B*, **21**, 763 (1966).

SCHEME II

SYNTHESIS OF THE PROTECTED HEPTAPEPTIDE XIII



thesize V *via* the *N*-hydroxysuccinimide ester of *tert*-butyloxycarbonylglutamine[11] very low yields (5%) were obtained, caused perhaps by the rapid intramolecular cyclization of the activated ester.[12] The protected hexapeptide V was treated with trifluoroacetic acid and then coupled with *tert*-butyloxycarbonyl-γ-benzylglutamic acid *N*-hydroxysuccinimide ester[13] to produce the protected heptapeptide *tert*-butyloxycarbonyl-γ-benzylglutamylglutaminyl-N^{ϵ}-tosyllysyl-*O*-benzyltyrosylserylphenylalanylleucine (VI). Peptide VI was deblocked with trifluoroacetic acid and coupled with N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysine *N*-hydroxysuccinimide ester to yield N^{ϵ}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysyl-γ-benzylglutamylglutaminyl-N^{ϵ}-tosyllysyl-*O*-benzyltyrosylserylphenylalanylleucine (VII).

The heptapeptide corresponding to residues 61–67 of HGH was synthesized by first coupling benzyloxycarbonylserine to leucine *tert*-butyl ester using DCC to form benzyloxycarbonylserylleucine *tert*-butyl ester (VIII). The protected dipeptide was subjected to catalytic hydrogenolysis to remove the benzyloxycarbonyl group and then coupled with benzyloxycarbonylthreonine using DCC to yield benzyloxycarbonylthreonylserylleucine *tert*-butyl ester (IX). Peptide IX was freed from the protecting group by catalytic hydrogenolysis and the resulting free tripeptide ester was allowed to react with the *N*-hydroxysuccinimide ester of *tert*-butyloxycarbonyl-γ-benzylglutamic acid to yield *tert*-butyloxycarbonyl-γ-benzylglutamylthreonylserylleucine *tert*-butyl ester (X). Tetrapeptide X was treated with trifluoroacetic acid to remove the *tert*-butyloxycarbonyl and *tert*-butyl ester groups, and subsequent condensation with *tert*-butyloxycarbonylproline *N*-hydroxysuccinimide ester[7] yielded *tert*-butyloxycarbonylprolyl-γ-benzylglutamylthreonylserylleucine (XI). This pentapeptide derivative was deprotected by treatment with trifluoroacetic acid and then coupled with *tert*-butyloxycarbonyl-β-benzylaspartic acid *N*-hydroxysuccinimide ester[14] to form *tert*-butyloxycarbonyl-β-benzylaspartylprolyl-γ-benzylglutamylthreonylserylleucine (XII). Finally, the protected hexapeptide was deprotected with trifluoroacetic acid and coupled with *tert*-butyloxycarbonylglutamine *p*-nitrophenyl ester to yield *tert*-butyloxycarbonylglutaminyl-β-benzylaspartylprolyl-γ-benzylglutamylthreonylserylleucine (XIII). Peptide XIII was purified by countercurrent distribution and found to be homogeneous in thin layer chromatography in several systems.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. All samples for microanalysis[15] were dried in an Abderhalden pistol over phosphorus anhydride at 77° for 16 hr at 0.3 mm. Thin layer chromatography on silica gel was carried out with the following solvent systems: methanol–chloroform (1:1), acetone–chloroform (1:1), and 1-butanol–acetic acid–water (4:1:1). Peptide spots were located by the ninhydrin reagent and by the chlorine method.[16] Countercurrent distribution was performed on a 100-tube, all-glass apparatus with a capacity of 50 cc for each phase. Analysis of the material was by weight determination after removal of an aliquot and subsequent evaporation and drying. The solvent systems used were toluene, toluene–chloroform–methanol–water (5:5:8:2), and carbon tetrachloride, carbon tetrachloride–chloroform–methanol–water (1:3:3:1). Catalytic hydrogenolysis was performed in the presence of palladium (6–10 mmol of peptide per 50 ml of methanol), freshly prepared[17] from palladium chloride, by means of a Vibro-Mixer[18] in the apparatus described by Meienhofer.[19] Acidolytic cleavage of *tert*-butyloxycarbonyl groups was done as follows. The peptide is dissolved in trifluoroacetic acid (1 mmol per 15 ml of acid). After being stirred at room temperature for 20 min, the trifluoroacetic acid was removed *in vacuo* and the residue was triturated repeatedly with absolute methanol followed by evaporation *in vacuo* to remove traces of trifluoroacetic acid.

Schemes I and II describe in detail the conditions used in the synthesis of the octa- and heptapeptides. Concentrations for the coupling reactions were as follows. The DCC couplings, 12–20 mmol per 100 ml of solvent, and equimolar quantities of each reactant were used. The *p*-nitrophenyl and *N*-hydroxysuccinimde ester reactions, 6–10 mmol per 100 ml of solvent with a 10% excess of the active ester, were used. Purification of the various peptides followed procedures described previously,[20] *i.e.*, the filtration, evaporation, and washings normally utilized in peptide synthesis. The physical properties and analytical description of each peptide fragment are presented in Tables I and II.

(11) P Lefrancier and E Bricas, *Bull Soc. Chim. Biol.*, **49**, 1257 (1967).
(12) H. Zahn and E. Folsche, *Chem. Ber.*, **102**, 2158 (1969).
(13) W. O. Danho and C. H. Li, *Int J. Protein Res.*, **3**, 99 (1971).
(14) See ref 13.
(15) Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.
(16) H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).
(17) R. Willstätter and E. Waldschmidt-Leitz, *Ber.*, **54**, 128 (1921).
(18) Vibro-Mixer, A. G. Feuer Chemie-Apparatebau, Zurich, Model E1.
(19) J. Meienhofer, *Chimia*, **16**, 385 (1962).
(20) C. H Li, B. Gorup, D. Chung, and J. Ramachandran, *J. Org. Chem.*, **28**, 178 (1963).

TABLE I

PHYSICAL DATA OF SYNTHETIC FRAGMENTS FOR THE SYNTHESIS OF PROTECTED OCTAPEPTIDE VII[a]

Compd	State (solvent, mp, °C)	R_f[b] A	B	C	$[\alpha]^{25}D$, deg
Z-Phe-Leu-O-*tert*-Bu (I)	Crystalline (petroleum ether, 94∼95)	0.85	0.75	0.64	−27.0 (*c* 1, methanol)
Z-Ser-Phe-Leu-O-*tert*-Bu (II)	Crystalline (EtOAc, 160–161)	0.86	0.77	0.56	−39.2 (*c* 1, methanol)
Bzl Boc-Tyr-Ser-Phe-Leu-O-*tert*-Bu (III)	Crystalline (EtOAc–petroleum ether, 99∼100)	0.87	0.71	0.52	−24.6 (c 1, methanol)
Tos Bzl Boc-Lys-Tyr-Ser-Phe-Leu-OH (IV)	Crystalline (EtOAc, 148–150)	0.86	0.62	0	−33.9 (*c* 1, methanol)
Tos Bzl Boc-Gln-Lys-Tyr-Ser-Phe-Leu-OH (V)	Amorphous (196–198)	0.82	0.60	0	−23.0 (*c* 1, methanol)
OBzl Tos Bzl Boc-Glu-Gln-Lys-Tyr-Ser-Phe-Leu-OH (VI)	Amorphous (195–197)	0.80	0.58	0	−26.2 (*c* 1, methanol)
Tos OBzl Tos Bzl Boc-Lys-Glu-Gln-Lys-Tyr-Ser-Phe-Leu-OH (VII)[c]	Amorphous (205–209)	0.75	0.55	0	−30.1 (*c* 1, DMF)

[a] Elementary analyses (C, H, N) for all compounds in the table were within ±0.3% of calculated values. [b] Solvent systems: A, 1-butanol–acetic acid–water (4:1:1); B, chloroform–methanol (1:1); C, chloroform–acetone (1:1). [c] Amino acid analysis of VII (theoretical, found) by acid hydrolysis: Lys (2.00, 1.81); Ser (1.00, 0.91); Glu (2.00, 2.06); Leu (1.00, 1.04); Tyr (1.00, 0.48); Phe (1.00, 1.02).

TABLE II

PHYSICAL DATA OF SYNTHETIC FRAGEMNTS FOR THE SYNTHESIS OF PROTECTED HEPTAPEPTIDE XIII[a]

Compd	State (solvent, mp, °C)	R_f[b] A	B	C	$[\alpha]^{25}D$, deg
Z-Ser-Leu-O-*tert*-Bu (VIII)	Crystalline (EtOAc–ether, 91–93)	0.87	0.74	0.63	−41.5 (*c* 1, methanol)
Z-Thr-Ser-Leu-O-*tert*-Bu (IX)	Crystalline (chloroform–ether, 120–121)	0.85	0.75	0.50	−36.5 (*c* 1, methanol)
OBzl Boc-Glu-Thr-Ser-Leu-O-*tert*-Bu (X)	Crystalline EtOAc, 117–119)	0.86	0.70	0.52	−32.4 (*c* 1, methanol)
OBzl Boc-Pro-Glu-Thr-Ser-Leu-OH (XI)	Amorphous (95–100)	0.71	0.69	0.49	−43.2 (*c* 1, methanol)
OBzl OBzl Boc-Asp-Pro-Glu-Thr-Ser-Leu-OH (XII)	Amorphous (100–102)	0.80	0.65	0.20	−35.1 (*c* 1, methanol)
OBzl OBzl Boc-Gln-Asp-Pro-Glu-Thr-Ser-Leu-OH (XIII)[c]	Amorphous (115–118)	0.75	0.57	0.10	−56.2 (*c* 1, methanol)

[a] Elementary analyses (C, H, N) for all compounds in the table were within ±0.3% of calculated values except as follows: VIII, N within 0.35%; X, C within 0.4%; XII, C within 0.6%; XIII, N within 0.45%. [b] Solvent systems: A, 1-butanol–acetic acid–water (4:1:1); B, chloroform–methanol (1:1); C, chloroform–acetone (1:1). [c] Amino acid analysis of XIII (theoretical, found) by acid hydrolysis: Asp (1.00, 0.98); Thr (1.00, 0.96); Ser (1.00, 0.93); Glu (2.00, 2.05); Pro (1.00, 1.06); Leu (1.00, 1.02).

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-tosyllysine *N*-Hydroxysuccinimide Ester.—N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-tosyllysine cyclohexylamine salt (4.99 g, 10 mmol) and *N*-hydroxysuccinimide (1.15 g, 10 mmol) were dissolved in 45 ml of dioxane–ethyl acetate (3 l., v/v) with stirring and cooled to 3∼5°. Dicyclohexylcarbodiimide (2.06 g, 10 mmol) was added and the mixture was stirred overnight at 3∼5°. Filtration to remove dicyclohexylurea was followed by evaporation to dryness. The residue was dissolved in 2-propanol (50 ml) and kept in the refrigerator for 1 week. It crystallized out slowly. Filtration yielded the

activated ester (3.13 g, yield 62.8%), mp 114–117°, $[\alpha]^{25}D$ −19.1° (c 1, methanol).

Anal. Calcd for $C_{22}H_{31}N_3O_8S$ (497.6): C, 53.10; H, 6.28; N, 8.45. Found: C, 53.74; H, 6.48; N, 8.43.

Registry No.—I, 29842-94-2; II, 29842-95-3; III, 29842-96-4; IV, 29842-97-5; V, 29842-98-6; VI, 29842-99-7; VII, 29843-00-3; VIII, 28252-48-4; IX, 29843-02-5; X, 29843-03-6; XI, 29843-04-7; XII, 29843-05-8; XIII, 29843-06-9; N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-tosyllysine *N*-hydroxysuccinimide ester, 29843-07-0.

Acknowledgments.—This work was supported in part by the American Cancer Society, The Allen Foundation, and The Geffen Foundation. One of us (K.-T. W.) is a Fulbright Scholar for 1969–1971 and on leave from the Department of Chemistry, National Taiwan University, Taiwan. We wish to thank D. Chung and J. Ramachandran for helpful suggestions during the course of this work.

The Structure of Paradisiol, a New Sesquiterpene Alcohol from Grapefruit Oil

H. SULSER, J. R. SCHERER, AND K. L. STEVENS*

Western Regional Research Laboratory, Agricultural Research Service, U. S. Department of Agriculture, Albany, California 94710

Received December 4, 1970

Paradisiol, a new sesquiterpene alcohol isolated from grapefruit peel oil, was shown to be 5β*H*,7β,10α-selin-11-en-4α-ol (**8**).

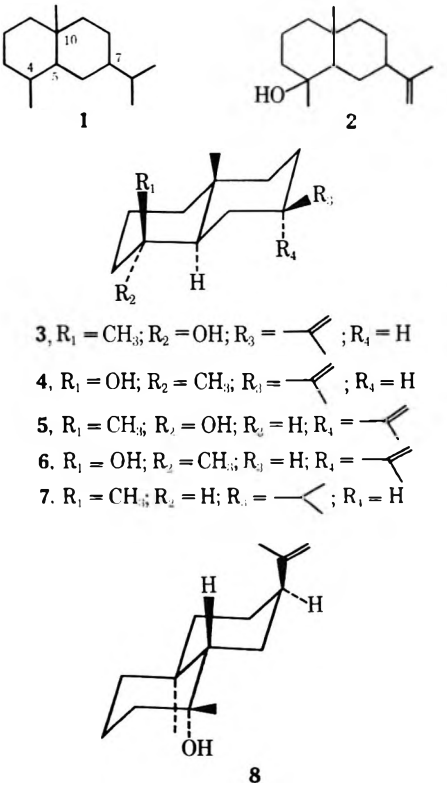
Previous investigations of grapefruit oil (*Citrus paradisi* Swingle) led to the detection of a bicyclic sesquiterpene ketone, nootkatone, which is considered to be the principal flavoring constituent.[1,2] Although it is the major oxygenated sesquiterpene (0.3%) in the oil, it occurs with a number of other compounds of which no detailed information is yet available.[3] Since further flavor contributors may be expected in this group, we started a composition study of a grapefruit oil fraction which was rich in nootkatone and contained a multitude of other components. In this paper we report the isolation and chemical structure of a new sesquiterpenic alcohol, named paradisiol (**8**).

Paradisiol (**8**), mp 85–86°, $C_{15}H_{26}O$, shows tertiary hydroxyl bands at 3612 and 3480 cm^{-1} and terminal methylene bands at 3090, 1635, and 890 cm^{-1}. The proton resonance spectrum shows two tertiary methyl groups at δ 0.93 (s, 3 H) and 1.04 (s, 3 H), one vinylic methyl at δ 1.74 (s, 3 H), and one methylene group at δ 4.84 (s, 2 H). On catalytic hydrogenation with palladium/C in acetic acid or with platinum/C in ethanol, 1 mol of hydrogen was consumed.

Paradisiol was readily dehydrated with phosphorus oxychloride in pyridine to give a mixture of two isomeric olefins (**9**, **10**) which could be separated by gas chromatography. Both the major (**9**) and the minor (**10**) dehydration products show bands in the infrared for terminal methylene (3080, 1642, 888 and 3090, 1640, 890 cm^{-1}, respectively). The nmr spectrum of **9** contains signals for a tertiary methyl group at δ 0.73 (s, 3 H) and a vinylic methyl group at δ 1.70 (s, 3 H). In addition, two terminal methylene groups at δ 4.37 (s, 1 H), 4.63 (s, 1 H), 4.77 (s, 1 H), and 4.85 (s, 1 H) are shown. The nmr spectrum of **10** shows a tertiary methyl group at δ 0.83 (s, 3 H) and two vinylic methyl groups at δ 1.56 (s, 3 H) and 1.71 (s, 3 H). It further shows a total of three olefinic protons at δ 4.80 (s, 2 H) and 5.22 (s, 1 H), the latter one being attached to a trisubstituted double bond.

(1) W. D. MacLeod, Jr., and N. M. Buigues, *J. Food Sci.*, **29**, 565 (1964).
(2) W. D. MacLeod, Jr., *Tetrahedron Lett.*, 4779 (1965).
(3) H. E. Nursten and A. A. Williams, *Chem. Ind.* (*London*), 486 (1967).

Paradisiol is thus a bicyclic tertiary alcohol, bearing an isopropenyl group. Hydrogenation of either **9** or **10**, Pd/C in acetic acid, was shown by gas chromatography to yield an identical tetrahydro derivative. This hydrocarbon was shown to be identical with selinane (eudesmane) (**1**), prepared from β-selinene. The gross structure of paradisiol can therefore be written as selin-



11-en-4-ol (**2**). In analogy with β- and α-selinene, "β" and "α" are used to designate the position of the double bond in **9** and **10**, respectively.

All naturally occurring compounds of the selinane family hitherto reported are *trans*-decalin derivatives. Assuming paradisiol to be trans also (*vide infra*), the discussion on the relative configuration can be confined

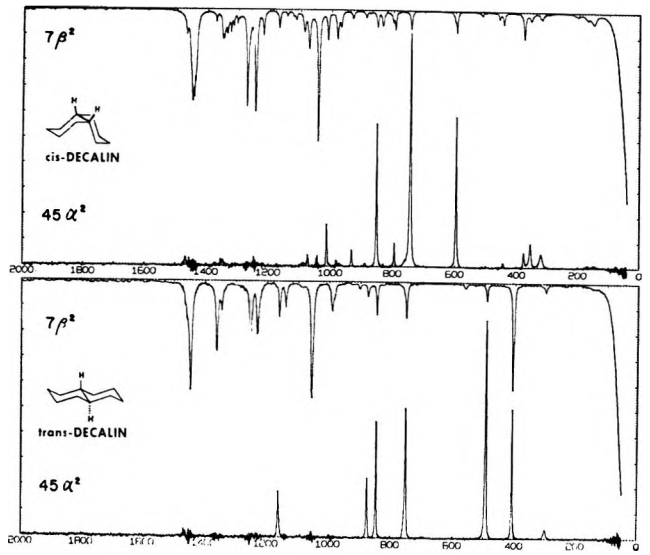


Figure 1.—Raman spectra of *cis*- and *trans*-decalin: slit 1 cm^{-1}, time constant 0.3 sec, scan rate 0.8 cm^{-1}/sec, laser power 50 mW.

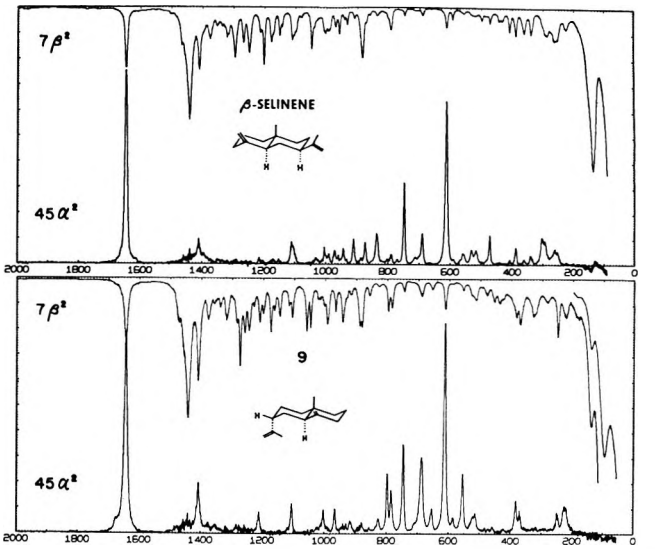


Figure 2.—Raman spectra of β-selinene and 9: slit 2 cm^{-1}, time constant 0.3 sec, scan rate 0.8 cm^{-1}/sec, laser power 50 mW.

to the possible trans isomers of selin-11-en-4-ol. In the *trans*-decalin form, the angular substituents at C-5 and C-10 are fixed in an axial conformation; hence the structure for paradisiol is reduced to structures **3**–**6** (or their enantiomers).

Compounds **3** and **4**, bearing an equatorial isopropenyl group (as does α- and β-selinene) are both reported in the literature.[4,5] Clearly, the spectral and physical data of paradisiol do not match these data.[6] Consequently paradisiol must be either compound **5** or **6** (or their enantiomers) with an axial isopropenyl group. Since paradisiol was converted to selinane (equatorial isopropyl), isomerization at C-7 must have occurred. This is underlined by the fact that a hydrocarbon, not identical with selinane, was obtained by hydrogenation in the presence of platinum/C in ethanol. Similarly, hydrogenation of paradisiol over palladium/C (acetic acid) and over platinum/C (ethanol) gave different dihydro alcohols. These findings are readily explained by the fact that inversion of the isopropenyl group at C-7 occurred with palladium/C. Catalyst-induced inversion involves migration of the double bond which takes place only when the allylic hydrogen to be removed is sterically accessible to the catalyst and the resulting isopropylidene group can consume the incoming hydrogen from the less hindered side. This phenomenon of isomerization of axial isopropenyl groups is well documented both in the steroid field and in a structure similar to paradisiol.[7]

Until now a cis-fused ring system has not been excluded. A *cis*-decalin structure would be isomerized to a *trans*-decalin if inversion at C-5 took place. This is very unlikely to occur upon catalytic reduction of paradisiol since it would involve a shift of the double bond along three carbon atoms, for which no precedent is known.[8] In contrast, the dehydro compounds derived from paradisiol, both possessing and allylic hydrogen at C-5, might have been isomerized when reduced with palladium/C. Hydrogenation of paradisiol over palladium/C (inversion of C-7), followed by dehydration and hydrogenation over platinum/C (no isomerization), again gave selinane. Thus, inversion has only occurred at C-7 and paradisiol must be a *trans*-selin-11-en-4-ol with an axial isopropenyl group.

In accordance with the above findings, the Raman spectra give evidence for the *trans*-decalin ring structure. The stretching of C–C bonds of cyclic hydrocarbons gives rise to large contributions to the isotropic part of Raman scattering (α), and it has been found that the intensity of a polarized line is dependent on the in-phase additivity of the C–C stretching coordinates.[9] Consequently, the "isotropic Raman scattering" is quite characteristic of the C–C skeletal structure. *cis*- and *trans*-decalin are shown in Figure 1. The anisotropic part of the scattering ($7\beta^2$) is plotted downward and the isotropic part ($45\alpha^2$) in the normal upward manner. We note that, while many of the spectral lines show similarities in their anisotropic spectra (principally due to C–H deformations and antisymmetric C–C stretches), the isotropic spectra are very different, particularly in the region below 700 cm^{-1}. We should expect similar differences between the cis and trans isomers of substituted decalins.

In Figure 2 we show the isotropic and anisotropic Raman spectra of β-selinene and **9**, and, in Figure 3 (+)-selinane and **11**. It is clear from these spectra that the isotropic spectral components of each molecule in both figures are quite similar. We therefore rule out the possibility of a *cis*-decalin structure for **9** and **11**. The only remaining conclusion is that the axial orientation of the isopropenyl group is responsible for the minor deviations from the isotropic spectra exhibited by β-selinene and (+)-selinane.

In considering compounds **5** and **6**, intermedeol, the enantiomer of **5**, has been reported.[10,11] The comparison of paradisiol with intermedeol on the base of spec-

(4) R. E. Corbett and R. A. J. Smith, *Tetrahedron Lett.*, 1009 (1967).

(5) V. B. Zalkow, A. M. Shaligram, and L. H. Zalkow, *Chem. Ind. (London)*, 194 (1964).

(6) The nmr data are often given without an indication of the solvent used; hence, conclusions based on nmr data alone may not be reliable.

(7) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

(8) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6087 (1960).

(9) R. G. Snyder, private communication.

(10) L. H. Zalkow, V. B. Zalkow, and D. R. Brannon, *Chem. Ind. (London)*, 38 (1963).

(11) G. L. Chetty, V. B. Zalkow, and L. H. Zalkow, *Tetrahedron Lett.*, 3223 (1968).

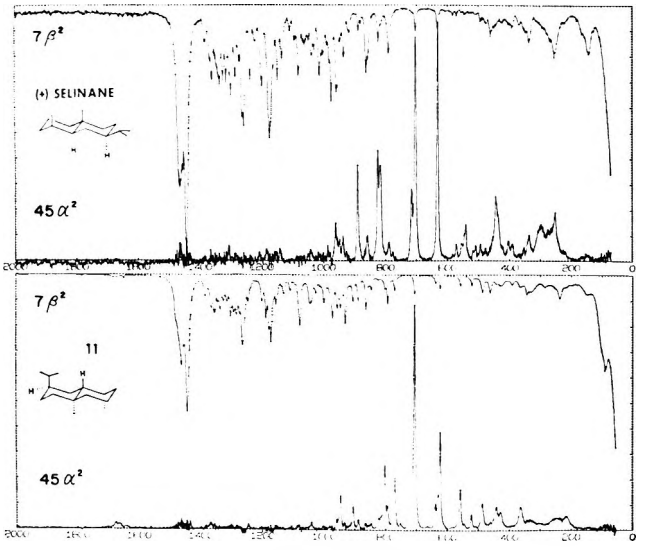
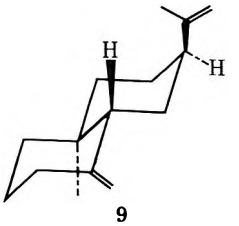


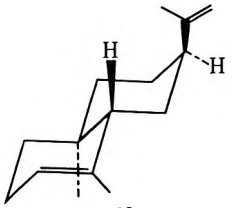
Figure 3.—Raman spectrum of (+)-selinane: slit 1 cm^{-1}, time constant 1 sec, scan rate 0.46 cm^{-1}/sec, laser power 50 mW. Raman spectrum of compound 11: slit 2 cm^{-1}, time constant 0.3 sec, scan rate 0.8 cm^{-1}/sec, laser power 50 mW.

tral data was not satisfactory, as little information on the latter compound is available. However, the melting points are different, and hydrogenation of paradisiol over palladium/C yielded a dihydro alcohol which was not the enantiomer of platinum-hydrogenated **3**, the spectral data of which are reported,[4] thus showing that paradisiol and intermedeol are not identical. Hence, paradisiol must be **6** or its enantiomer.

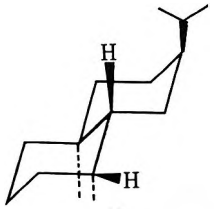
Compound **6**, bearing an axial hydroxyl group, is the C-4 epimer of intermedeol. Dehydration of paradisiol (**8**) (phosphorus oxychloride, pyridine) furnished, as stated earlier, a mixture of dienes **9** and **10**. Gas



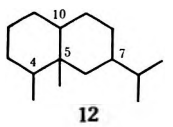
9



10



11



12

chromatography indicated about 67% of the β isomer and 28% of the α isomer. This distribution of products is diagnostic for a hydroxyl group in an equatorial position.[12] However, normal elimination toward C-5 may be rendered difficult by the axial isopropenyl group which shields the axial C-5 hydrogen, thus making it inaccessible to the base. This may explain the relatively high amount of β isomer in the olefin mixture. This is partially substantiated by thermal dehydration of paradisiol (**8**) which gave three dehydro derivatives in about equal amounts as shown by gas chromatography.

Measurement of the pyridine-induced shifts (relative to chloroform) in the nmr spectrum often gives information on the sterical vicinity of hydroxyl groups in saturated cyclic systems.[13] In platinum-hydrogenated paradisiol a paramagnetic shift of the methyl group at C-10 of δ 0.28 was observed. Such a deshielding effect is consistent with the fact that the hydroxyl function at C-4 occupies a position 1,3 diaxial to the methyl group, thus confirming the axial conformation of the hydroxyl substituent in paradisiol.

The absolute configuration of paradisiol may be readily established. Reactions leading to selinane, including inversion of C-7, gave in all cases (−)-selinane, whereas selinane observed from β-selinene was (+)-selinane. The absolute configuration of (+)-selinane (**7**) is well established;[4,14] hence the absolute configuration of paradisiol is 5βH,7β,10α-selin-11-en-4α-ol (**8**). Correspondingly, the β dehydration product is 5βH,-7β,10α-selina-4(14),11-diene (**9**), the α isomer is 5βH,-7β,10α-selina-3,11-diene (**10**),[15] and the parent hydrocarbon is 4α,5βH,7β,10α-selinane (**11**).

Paradisiol is the first compound of the selinane group found in grapefruit. Nootkatone and valencene,[2,16] the latter one occurring in grapefruit juice, are usually looked upon as members of the same family, in which the isoprene rule is not obeyed. Biosynthetic studies on the formation of eremophilane sesquiterpenes (**12**) have not been described yet, but it was suggested long ago that the methyl group at C-10 might experience migration to C-5 by a Wagner rearrangement.[17] Thus, if a normal isoprenoid structure is assumed to be an intermediate in the biogenetic pathway, paradisiol would fit the stereochemical requirements to lead to valencene by a series of 1,2 shifts of substituents (Scheme I).[18]

It is interesting to note that compound **9** and valencene give virtually the same mass spectral pattern. This would suggest that these two compounds, upon ionization, have a common intermediate, thus lending support to the above hypothesis.

Experimental Section

Gas Chromatography.—A Perkin-Elmer[19] 226 gas chromatograph, fitted with a 75 ft × 0.01 in. Carbowax 20M column was used for all analytical runs. Temperature was programmed from 75 to 150° (2°/min) and helium gas flow held at 10-psi pressure.

For preparative purposes a 30 ft × 0.5 in. column packed with 4% SF-96 (50) silicone oil and 0.2% Carbowax 20M on 60–70 mesh Chromosorb G, and a 300 ft × 0.03 in. large-bore open

(12) D. H. R. Barton, A. S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(13) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(14) W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

(15) This compound has been reported by E. Klein and W. Rojahn, *Tetrahedron Lett.*, 279 (1970); however, the nmr data does not exactly match our data. This may possibly be due to instabilities in the 60-MHz instrument.

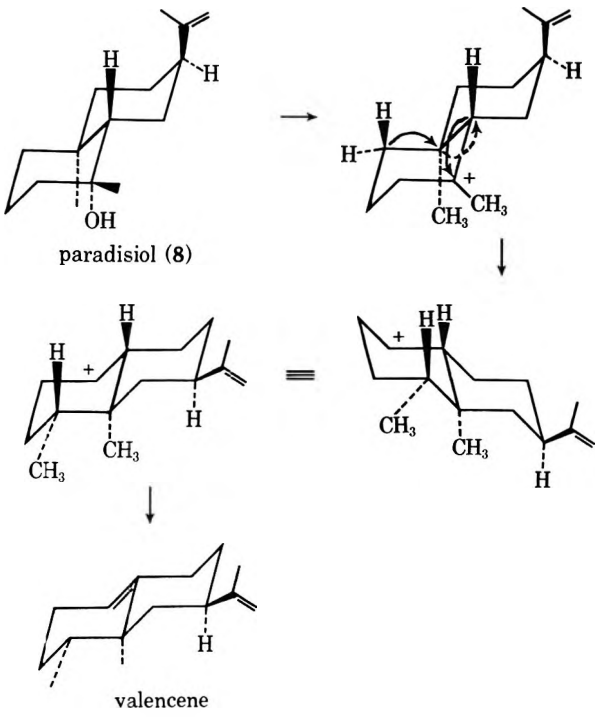
(16) G. L. K. Hunter and W. B. Brogden, Jr., *J. Food Sci.*, **30**, 383 (1965).

(17) Sir R. Robinson, cited by A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 87 (1939).

(18) A similar scheme has been proposed by N. H. Andersen, *Phytochemistry*, **9**, 145 (1970), in the conversion of a 2-keto-4,10-*epi*-eudesmane to α-vetivone. See also, N. H. Andersen, M. S. Falcone, and D. D. Syrdal, *Tetrahedron Lett.*, 1759 (1970).

(19) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

SCHEME I



tubular column coated with OV-101 dimethylsilicone oil (Ohio Valley Specialty Chemical Co.) were used.

Infrared Spectra.—A Perkin-Elmer Model 237 infrared spectrophotometer was used. All samples were run in carbon tetrachloride.

Raman Spectra.—Spectra were obtained on submilligram quantities of material using an axial (illumination)/transverse (90° scattering) sampling technique.[20] The exciting source is a 50 mW He/Ne 6328-Å Spectra Physics laser equipped with a polarization rotator. The monochromator is a Spex 1401 with slit-shaped FW-130 photomultiplier detector and photon counting electronics. The instrumental conditions for the scans are given with each figure. The spectra shown here are not ordinary Raman scans but are scans representing "isotropic" and "anisotropic" Raman scattering. The Raman scattering experiment is described in a right-handed coordinate system in which the incident laser beam is on the z axis, the direction of observation in the y axis and the sample at the origin. The scan measuring the total scattered light intensity as a function of wavelength when the incident radiation is polarized perpendicular to the direction of observation (x) is proportional to $45\alpha^2 + 7\beta^2$ where α is the mean polarizability and β the anisotropy.[21] A second scan with the direction of laser polarization along the y axis measures $6\beta^2$. The Raman spectrometer system is on-line to a digital computer[22] which is used to calculate the scattering from the $45\alpha^2$ term. All intensities have been corrected for photomultiplier and general instrument intensity nonlinearity.[22]

Nuclear Magnetic Resonance Spectra.—A Varian HR-100 modified with an internal field frequency designed at WRRL was used. All samples were run in carbon tetrachloride (unless otherwise stated) with tetramethylsilane as an internal standard, using a microcell technique.[23]

Mass Spectra.—An EAI Model 300 quadrupole mass spectrometer and a CEC Model 110 high-resolution mass spectrometer were used.

Optical Rotation.—An NPL automatic polarimeter (Bendix Scientific Instruments), was used.

Isolation of Paradisiol (8).—Fivefold grapefruit oil was distilled at 23° and 10-μ pressure low-boiling constituents. The temperature was then raised to 55° and an intermediate fraction distilled off. The residue remaining was then distilled through a falling-film molecular still in which the pressure was held at 1 μ and the temperature of the outer jacket kept at 70°. The distillate was cooled, and crystalline nootkatone separated and filtered off. The resulting mother liquor was shown by gas chromatography to contain 30–40% nootkatone and about 5% paradisiol, and was redistilled at 3-mm pressure. The fraction boiling between 110 and 115° contained about 30% paradisiol. Further enrichment was achieved by liquid–solid chromatography on a 1 ft × 1 in. alumina (80–200 mesh) column which was charged with 1 g of distillate and developed with benzene. Elution of nootkatone was accomplished with 900 ml of benzene and paradisiol with 250 ml of benzene–ether (1:1). The latter fraction (275 mg), after evaporation of solvent, was further purified by gas chromatography on the 30-ft column. Pure paradisiol emerged in 44 min, crystallizing with mp 85–86°, optical rotation (95% EtOH) $[\alpha]^{25}D$ +14°. Spectral data:[24] ir 3612, 3480 (broad), 3090, 2940, 1635, 1452, 1383, 1261, 1168, 1090, 1063, 1053, 1038, 1022, 960, 932, 909, 890 cm^{-1}; mass spectrum m/e (rel intensity) 43 (100), 41 (54), 55 (29), 81 (26), 67 (25), 71 (25), 28 (22), 39 (18), 53 (16), 26 (15), 95 (15); mol wt molecular ion peak (determined by high-resolution mass spectrum) m/e 222.2001 (calcd for $C_{15}H_{26}O$, 222.1984).

Dihydroparadisiol, Palladium Catalyzed.—Paradisiol (58 mg, 0.26 mmol) dissolved in glacial acetic acid (20 ml) was hydrogenated at room temperature and 1 atm in the presence of 5% palladium/charcoal (45 mg) as a catalyst. The uptake of hydrogen was completed in 15 min with 1.15 equiv of hydrogen being consumed. The hydrogenation mixture was worked up in the usual manner leaving an oil which was purified by gas chromatography, using an OV-101 large-bore open tubular column and operated at 156° and 25-psi carrier gas pressure. Lack of material did not allow recrystallization of the gas chromatographically pure sample, mp 65–70°, mol wt (mass spectrum) 224. Spectral data: ir 3600, 3450 (broad), 2930, 1460, 1382, 1362, 1336, 1160, 1085, 1038, 918, 908 cm^{-1}; nmr δ 0.80 (s, 3 H), 1.13 (s, 3 H), 1.01 (d, 6 H, J = 7 Hz); mass spectrum m/e (rel intensity) 43 (100), 81 (69), 41 (54), 71 (40), 93 (40), 55 (34), 91 (33), 105 (32), 95 (31), 67 (29), 79 (29).

Dihydroparadisiol, Platinum Catalyzed.—Paradisiol (85 mg, 0.38 mmol) dissolved in 95% EtOH (35 ml) was hydrogenated after addition of 5% platinum/charcoal (55 mg) as a catalyst. After consumption of hydrogen (1.12 equiv), the dihydro derivative was purified by gas chromatography using an OV-101 silicone oil open tubular column. Lack of material did not allow recrystallization of the gas chromatographically pure sample, mp 48–55°, mol wt (mass spectrum) 224. Spectral data: ir 3615, 3480 (broad), 2930, 1460, 1386, 1366, 1336, 1178, 1166, 1092, 1063, 1044, 917, 906 cm^{-1}; nmr δ 0.92 (s, 3 H), 0.91 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz); nmr ($CDCl_3$) δ 0.94 (s, 3 H), 1.10 (s, 3 H); nmr (pyridine-d_5) δ 1.20 (s, 3 H), 1.22 (s, 3 H); mass spectrum m/e (rel intensity) 43 (100), 71 (70), 41 (56), 83 (47), 81 (46), 55 (43), 69 (40), 95 (34), 85 (32), 67 (31).

Dehydroparadisiol (9, 10).—Paradisiol (100 mg, 0.45 mmol) was dissolved in pyridine (2 ml) and phosphorous oxychloride (250 mg, 1.63 mmol) was slowly added. The mixture was held at room temperature for 16 hr, filtered, and, after addition of water, extracted with ether. The oily residue (87 mg) remaining, after drying and evaporation of the ether, was separated by gas chromatography on an OV-101 silicone oil column at 148° and 25-psi gas pressure, yielding two dehydration products emerging in 8 and 9.5 min, respectively.

β Isomer (9): mol wt (mass spectrum) 204; ir 3080, 2935, 1642, 1442, 1408, 1378, 1245, 1230, 1173, 1148, 1057, 1045, 989, 964, 942, 888, 858 cm^{-1}; mass spectrum m/e (rel intensity) 41 (100), 105 (48), 91 (46), 39 (45), 29 (43), 79 (40), 27 (38), 55 (37), 107 (34), 93 (32); mass spectrum of valencene 41 (100), 91 (45), 79 (43), 39 (42), 55 (41), 105 (41), 93 (39), 107 (38), 29 (36), 161 (35).

α Isomer (10): mol wt (mass spectrum) 204; ir 3090, 2915, 1640, 1456, 1376, 1237, 1218, 1176, 1128, 1071, 1017, 1002, 926, 890, 846 cm^{-1}; mass spectrum m/e (rel intensity) 41 (100), 122 (93), 161 (76), 107 (68), 39 (51), 29 (50), 28 (47), 91 (46), 105 (41), 55 (40).

The distribution of products obtained from thermal dehydration was determined by injecting paradisiol on a gas chromatography column at an injector temperature of 280°.

(20) G. F. Bailey, S. Kint, and J. R. Scherer, *Anal. Chem.*, **39**, 1040 (1967).

(21) E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill, New York, N. Y., 1955, p 43.

(22) J. R. Scherer and S. Kint, *Appl. Opt.*, **9**, 1615 (1970).

(23) R. A. Flath, N. Henderson, R. E. Lundin, and R. Teranishi, *Appl. Spectrosc.*, **21**, 183 (1967).

(24) Nmr data which were used for discussion are given there.

(+)-**Selinane (7) from β-Selinene.**—β-Selinene (131 mg, 0.64 mmol) was hydrogenated in the presence of platinum/charcoal (100 mg) in 95% EtOH (50 ml) as described above, 2.14 equiv of hydrogen being consumed. Purification by gas chromatography on the OV-101 column at 148° afforded (+)-selinane, mol wt (mass spectrum) 208, optical rotation (95% EtOH) $[\alpha]^{25}D$ +10°. Spectral data: ir 2930, 1468, 1386, 1370, 1326, 1236, 1206, 1170, 1030, 974, 934, 918, 854 cm^{-1}; nmr δ 0.88 (s, 3 H), 0.88 (d, 6 H, *J* 6 Hz), 0.87 (d, 3 H, *J* = 6 Hz); mass spectrum *m/e* (rel intensity) 43 (100), 95 (65), 109 (60), 83 (54), 81 (52), 41 (47), 55 (43), 69 (40), 67 (37), 58 (25).

(−)-**Selinane from Paradisiol. A.**—A mixture of **9** and **10** (140 mg 0.63 mmol) was hydrogenated in the presence of 5% palladium/charcoal (100 mg) in acetic acid (40 ml) with 2.20 equiv of hydrogen being consumed. Work-up of the product in the usual manner gave a saturated hydrocarbon having identical ir, nmr, and mass spectra with (+)-selinane, optical rotation (95% EtOH), $[\alpha]^{25}D$ −16°.

B.—Dihydroparadisiol (palladium-catalyzed) (45 mg, 0.20 mmol) was dehydrated as described above. The resulting mixture of olefins (36 mg) was hydrogenated over 5% platinum/charcoal (25 mg) in 95% ethanol (30 ml) with 1.09 equiv of hydrogen being consumed. Work-up in the usual manner gave a compound identical with that made by method A.

Hydrocarbon 11 from Paradisiol.—A mixture of **9** and **10** (67 mg, 0.33 mmol) was reduced catalytically with 5% platinum/charcoal (44 mg) in 95% ethanol (20 ml), 2.31 equiv of hydrogen being consumed. The crude hydrogenation mixture was purified by gas chromatography as described above, giving **11** with the following spectral data: mol wt (mass spectrum) 208; ir 2930, 1460, 1386, 1366, 1282, 1170, 1108, 1080, 1038, 998, 976, 938, 904, 854 cm^{-1}; nmr δ 0.89 (s, 3 H), 0.91 (d, 3 H = 6 Hz), 0.88 (d, 3 H, *J* = 6 Hz), 0.85 (d, 3 H, *J* = 6 Hz); mass spectrum *m/e* (rel intensity) 93 (100), 107 (98), 41 (89), 79 (85), 55 (78), 67 (69), 82 (63), 69 (61), 81 (57), 43 (47).

Registry No.—**8**, 29969-75-3; **9**, 29868-52-8; **10**, 28290-23-5; **11**, 28290-24-6; dihydroparadisiol, 29868-51-7.

Acknowledgment.—The authors wish to thank Nancy Bennett for the nmr data and W. F. Haddon for the high-resolution mass spectral data.

Conformation of Valerane

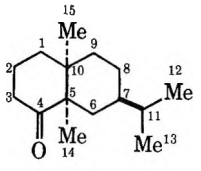
P. NARASIMHA RAO

Department of Organic Chemistry, Division of Biological Growth and Development, Southwest Foundation for Research and Education, San Antonio, Texas 78228

Received December 31, 1970

5β-Hydroxy-*cis*-9,10-dimethyl-2-decalone (2) which was shown to exist in the steroid cis conformation C was converted to 2α-acetyl-5β-hydroxy-*cis*-9,10-dimethyldecalin (6) and 2β-acetyl-5β-hydroxy-*cis*-9,10-dimethyldecalin (7). Through nmr spectral data and base equilibration, compounds 6 and 7 were assigned steroid cis conformations E and F, respectively. Through a sequence of reactions, decalin 6 was transformed to *dl*-valerane (13) and *dl*-7-isovalerane (15). The stereochemistry and conformation of the key intermediates were established by nmr studies. This investigation lends additional support for the conformation of the carbon skeleton of valeranone.

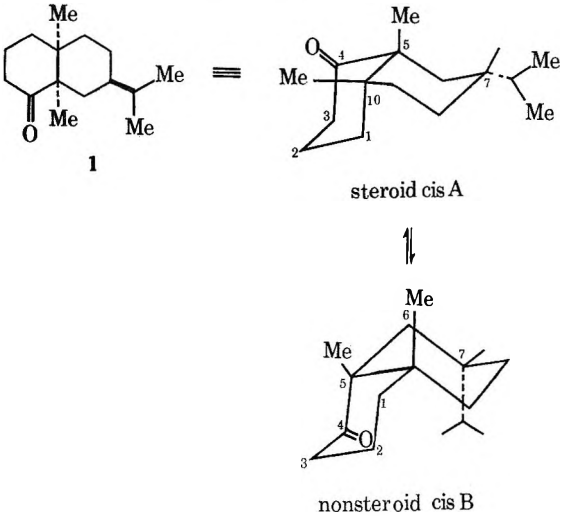
The natural product *l*-valeranone is one of the few known nonisoprenoid sesquiterpene ketones. After a great deal of experimentation by several groups of investigators its structure and absolute stereochemistry were finally established as shown in formula **1**.[1] It



1

possesses an unusual carbon skeleton having two angular methyl groups in a cis-fused decalin ring system. The C-14 and C-15 methyl groups are α-oriented whereas the C-7 isopropyl group is β-oriented. The correctness of the proposed structure was substantiated by two different syntheses of *d*- and *l*-valeranones.[2,3] Subsequently other naturally occurring sesquiterpenoids structurally related to valeranone have been isolated from Japanese valerians.[1f] In view of the flexible nature of the cis decalin, valeranone could exist in at least two interchangeable all-chair conformations such as the "steroid" cis conformation A or the "nonsteroid" cis conformation B.

Hartshorn, *et al.*,[4] compared the optical rotatory dispersion curve of valeranone (*a*, −166) with those of 5β-



1 steroid cis A ⇌ nonsteroid cis B

methylcholestan-4-one (*a*, −75) and methyl 1-oxo-5β-etianate (*a*, −136) and suggested that the carbonyl group of valeranone is situated in the same relative en-

(1) (a) J. Kripinsky, M. Romanuk, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 3122 (1963); (b) E. Hohne, *ibid.*, **28**, 3128 (1963); (c) W. Klyne, S. C. Bhattacharyya, S. K. Paknikar, C. S. Narayanan, K. S. Kulkarni, J. Krepinsky, M. Romanuk, V. Herout, and F. Šorm, *Tetrahedron Lett.*, 1443 (1964); (d) K. S. Kulkarni, S. K. Paknikar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 1289 (1964); (e) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.*, **11**, 1207 (1963); (f) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *ibid.*, **13**, 1408 (1965).

(2) J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Lett.*, 4807 (1965).

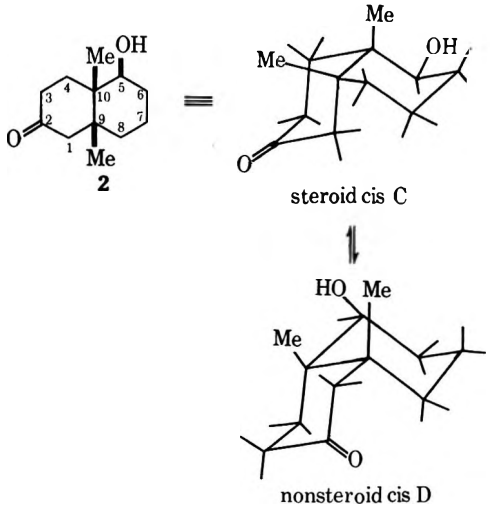
(3) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(4) M. P. Hartshorn, D. N. Kirk, and W. Klyne, *Tetrahedron Lett.*, 89 (1965).

vironment as in the steroid compounds and hence proposed the steroid cis conformation A. Hikino, *et al.*,[5] from a similar study of the optical rotatory dispersion data of valeranone and its monobromo derivative, also arrived at the conclusion that valeranone exists in conformation A.

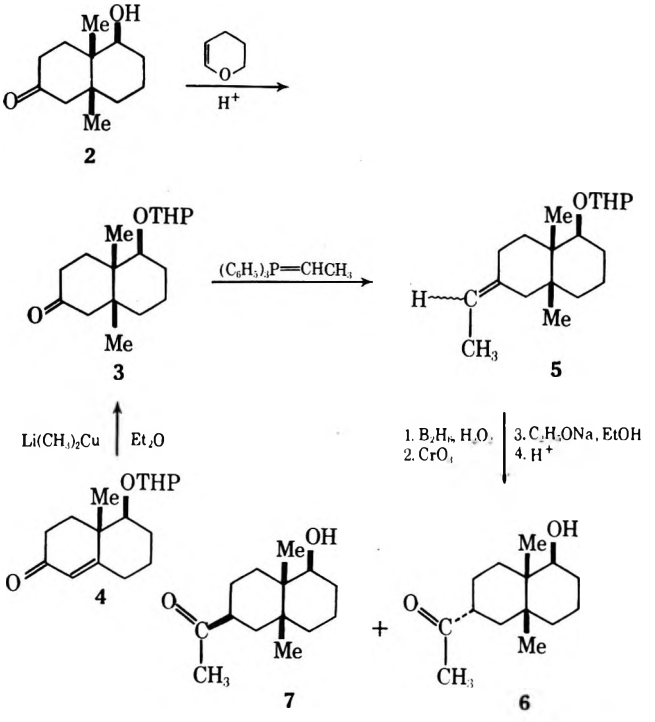
However, the above investigations failed to provide conclusive evidence about the conformation of the nonoxygenated ring, and it was assumed that this ring was in the chair form so as to keep the C-7 isopropyl group equatorial. Although this assumption was reasonable, we felt it desirable to provide unequivocal evidence for its conformation. In this study we have provided additional evidence for the conformation of valerane by unambiguous chemical methods and through nmr spectral data.

Recently we described the synthesis of 5β-hydroxy-*cis*-9,10-dimethyl-2-decalone (2).[6,7] From a detailed



nmr study we have demonstrated that decalone **2** was locked in the steroid cis conformation C.[6] The 5β-hydroxyl group in **2** exerts a strong 1,3-diaxial interaction with the C-9 methyl group in the nonsteroid conformation D and therefore it could conveniently assume the conformation C. Well-established procedures are available for stereospecific introduction of an equatorial substituent such as an isopropyl group through the carbonyl function in decalone **2**, and the 5β-hydroxyl group (or the bulky THP ether function) might greatly help to induce the molecule to adopt the steroid cis conformation. It was anticipated that in the nmr spectrum analysis of the resonance signal due to the methine proton adjacent to the C-5 hydroxyl might yield valuable information about the conformation of the products derived from ketone **2**. After having established that an equatorial isopropyl group had been introduced through the carbonyl function in decalone **2** and the steroid cis conformation validated, subsequent removal of the hydroxyl function should give *dl*-valerane. To avoid the 1,3-diaxial interaction with the angular methyl group at C-9 in the nonsteroid conformation, the equatorial isopropyl substituent will induce *dl*-valerane to assume the steroid cis conformation. The comparison of the nmr data of this racemic product with *l*-valerane, which was prepared earlier by Hikino, *et al.*,[1f] from natural *l*-valeranone, should provide conclusive evidence for the conformation of the ring containing the isopropyl group. The synthetic sequence employed is outlined in Scheme I. The 5β-hydroxyl group in decalone **2** was

SCHEME I



protected as a tetrahydropyranyl ether by reacting with dihydropyran in the presence of a catalytic amount of toluene-*p*-sulfonic acid to give **3**. Alternatively, by reacting the known tetrahydropyranyl ether derivative **4**[8] with lithium dimethylcopper[9] in ether, compound **3** was obtained in 75% yield. The decalone **3** was subjected to a Wittig reaction with ethylidenetriphenylphosphorane in dimethyl sulfoxide[10] at 50–60° to afford in high yield the 2-ethylidene compound **5** as a mixof the two geometrical isomers. Hydroboration of **5** with diborane in tetrahydrofuran solution followed by oxidation of the resulting organoborane with alkaline hydrogen peroxide[11] gave a mixture of two epimeric secondary alcohols, which without further purification were oxidized with 8 *N* chromic acid[12] to give a mixture of 2ξ-acetyl-9,10-*cis*-dimethyldecalin derivatives. Equilibration of this mixture with sodium ethoxide in ethanol and subsequent removal of the tetrahydropyranyl protecting group afforded two crystalline compounds **6** and **7** in 78% overall yield.[13] The equilibrated mixture consisted of 97.4% of compound **6** and 2.6% of compound **7** and they could be readily separated by column chromatography on alumina. The nmr spectra data of each of these isomeric products shed

(5) H. Hikino, Y. Takeshita, Y. Hikino, and Y. Takemoto, *Chem. Pharm. Bull.*, **13**, 626 (1965).

(6) P. N. Rao and J. E. Burdett, Jr., *J. Org. Chem.*, **34**, 1090 (1969).

(7) All structural formulas except **1**, **16**, and **17** designate only one enantiomorph of a racemic mixture.

(8) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(9) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966); (b) J. A. Marshall and H. Roebke, *ibid.*, **33**, 840 (1968); (c) E. Piers and R. J. Keziere, *Can. J. Chem.*, **47**, 137 (1969).

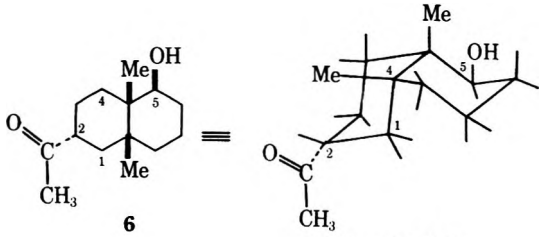
(10) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(11) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

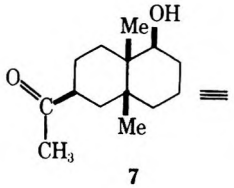
(13) The yield was based on the amount of pure material actually isolated.

considerable light on their conformation. In the spectrum of compound **6** the C-5 methine proton gave rise to an unresolved broad band centered at 4.03 ppm whose width at half-height (19 Hz) suggested the axial orientation.[14] Consequently, the hydroxyl group in this compound should be equatorially disposed. On the other hand, in the nmr spectrum of the isomeric compound **7**, the C-5 methine proton displayed a poorly resolved triplet centered at 3.38 ppm whose width at half-height (8 Hz) clearly indicated the equatorial orientation. As a result the hydroxyl group in compound **7** must have an axial configuration. An additional interesting feature of the nmr spectra of compounds **6** and **7** is that they both displayed one-proton signals as complex broad bands centered at 2.6 ($W_{1/2}$ = 23 Hz) and 2.5 ($W_{1/2}$ = 22 Hz) ppm, respectively. This may be attributed to the C-2 methine proton in **6** and **7** adjacent to the acetyl function. The large width at half-height in both these compounds again suggested the axial orientation of these protons, and hence the acetyl group in both **6** and **7** may be assigned equatorial orientation. Under the basic equilibration conditions the bulky acetyl group assumed the stable equatorial conformation in both compounds **6** and **7**. In view of the above evidence compounds **6** and **7** were assigned steroidal cis conformation E and nonsteroidal cis conformation F, respectively. In the two conformations E and F the 2-acetyl group has equatorial orientation, whereas the C-5 hydroxyl group in **6** is equatorial and the one in **7** is axial.

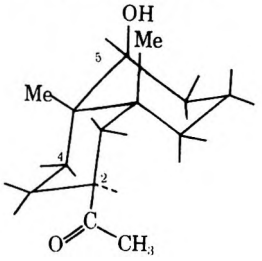


6 ≡

steroid cis E
C-2 H $W_{1/2}$ = 23 Hz
C-5 H $W_{1/2}$ = 19 Hz



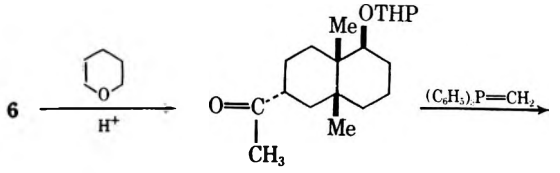
7 ≡



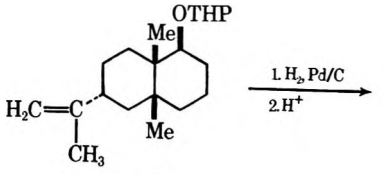
nonsteroid cis F
C-2 H $W_{1/2}$ = 22 Hz
C-5 H $W_{1/2}$ = 8 Hz

To gain additional information as to the ratio of the two isomers E and F at equilibrium, compounds **6** and **7** were separately equilibrated with ethanolic sodium ethoxide. Under these conditions compound **6** was epimerized to **7** *only in 3% yield, and 97% of the material was recovered unchanged, whereas compound* **7** *was epimerized to* **6** *in 97% yield and only 3% remained unchanged.* An examination of the Dreiding models revealed that the hydroxyl group in compound **7** exerts a strong 1,3-diaxial interaction with the C-9 methyl group in the nonsteroid conformation F and hence exists in low concentration at equilibrium. In the steroid conformation E, such interaction is minimal when both C-2 acetyl and C-5 hydroxyl groups assume the more stable equatorial orientation. These studies clearly support the stereochemistry assigned to compounds **6** and **7**.

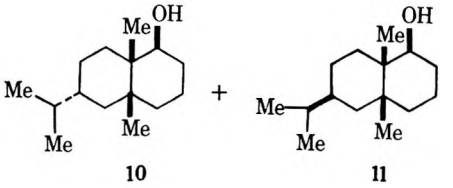
Subsequent synthetic operations were carried out with **6**. Protection of the 5β-hydroxyl group in **6** was readily accomplished by reacting **6** with dihydropyran in the presence of a catalytic amount of toluene-*p*-sulfonic acid to give the tetrahydropyranyl ether **8**. Treatment of ketone **8** with methylenetriphenylphosphorane in dimethyl sulfoxide[10] gave the isopropenyl compound **9** in excellent yield. Catalytic hydrogenation of **9** in the presence of 5% palladium on carbon in ethyl acetate solution and then removal of the tetrahydropyranyl protecting group with ethanolic hydrochloric acid gave two crystalline compounds, **10** and **11**, in the approximate ratio of 24:1, which were separated on a column of alumina.



8



9

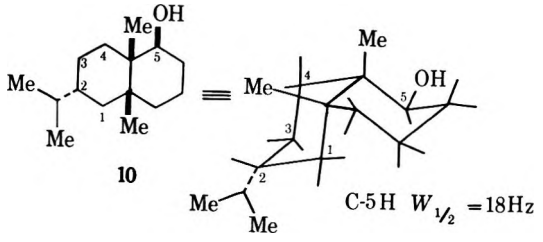


10 **11**

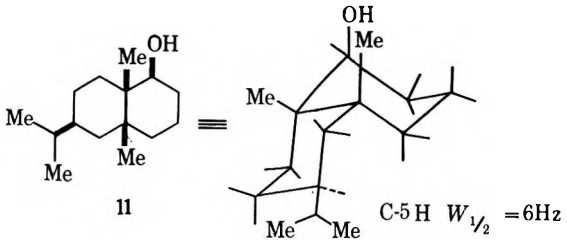
In the nmr spectrum of the major compound **10** the C-5 methine proton appeared as a broad multiplet at 3.91 ppm whose width at half-height (18 Hz) indicated the axial orientation, and therefore the 5β-hydroxyl group must be equatorially disposed. In the isomeric minor product **11** the corresponding hydrogen was seen as a poorly resolved triplet centered at 3.28 ppm whose width at half-height (6 Hz) suggested an equatorial conformation, and consequently the 5β-hydroxy group in this compound must be axially oriented. We have therefore assigned the steroid cis conformation G for the major product **10** and the nonsteroid cis conformation H for the minor product **11** as shown.

Although we have employed the stereochemically homogeneous compound **6**, the fact that we obtained a mixture of the two isomeric compounds **10** and **11** in the ratio of 24:1 after the Wittig reaction and catalytic hydrogenation needs some explanation. We have demonstrated (*vide supra*) that compound **6** under alkaline

(14) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 78–81.



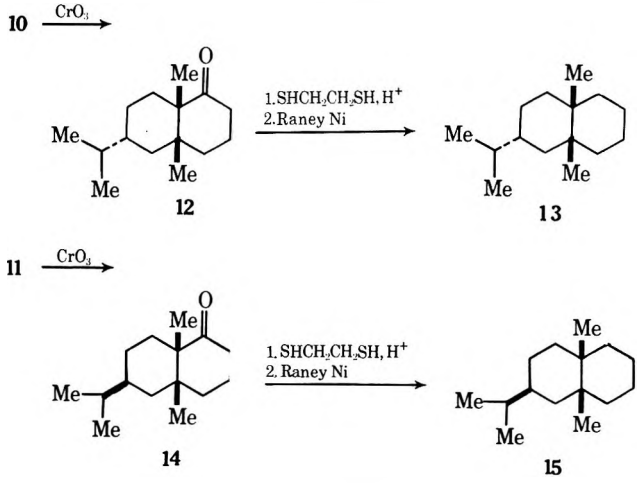
steroid cis G



nonsteroid cis H

conditions can equilibrate, and a very small amount (3%) of compound **7**, with nonsteroid cis conformation, can be obtained. Apparently under the alkaline Wittig reaction conditions the tetrahydropyranyl ether derivative **8** must have similarly epimerized to a small extent, resulting in formation of **11** with nonsteroid cis conformation. It was also possible that some inversion of the acetyl side chain of ketone **6** took place during the preparation of the tetrahydropyranyl ether.

Oxidation of the major alcohol **10** with Jones reagent[12] gave the ketone **12** in almost quantitative yield. The oxygen function in ketone **12** was removed by first reacting it with ethanedithiol in the presence of boron fluoride etherate to give the 5-ethylene thioketal, which, without further purification, was desulfurized in acetone solution using deactivated Raney nickel[15] to give racemic valerane **13** in excellent yield. The natural *l*-valerane was prepared for comparison from *l*-valeranone[16]



as described by Hikino, *et al.*[1f] The infrared and nmr spectra of the synthetic material **13** were found to be identical with those of the authentic natural *l*-valerane.

Similarly, oxidation of the minor isomeric alcohol **11** with Jones' reagent gave the ketone **14** which was distinctly different from **12**. The infrared, nmr and gas chromatographic retention times of **14** were found to be different from those of the ketone **12**. Furthermore, ketone **12** gave a 2,4-dinitrophenylhydrazone, mp 177–179°, whereas the 2,4-dinitrophenylhydrazone obtained from **14** melted at 154–156°. Removal of the keto group in **14** through ethylene thioketal formation followed by Raney nickel reduction yielded the racemic hydrocarbon **15**. The infrared and nmr spectra of **15** differed considerably from those of compound **13**. The methyl and isopropyl peaks in the nmr spectra (Figures 1 and 2) are particularly helpful in establishing the identity of **13** with the natural product. Accordingly, **15** was designated as *dl*-7-isovalerane.[17]

These studies provide conclusive evidence that valerane exists in a steroid cis conformation with an equatorial isopropyl group and suggest conformation A for valeranone, in agreement with earlier assumptions.

In the nmr spectra of the epimeric pairs of 5β-hydroxy compounds **6** and **7** and **10** and **11**, we noted some interesting features. It has been stated that axial protons attached to hydroxyl-substituted carbon atoms resonate at higher field than the corresponding equatorial protons in the epimeric alcohol.[14] However, the characteristic chemical shifts of the epimeric alcohols, as summarized in Table I, show a reversal of the usual

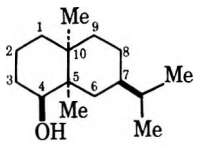
TABLE I

CHEMICAL SHIFTS AND LINE WIDTHS AT HALF-HEIGHT FOR C-5 PROTON ADJACENT TO OXYGEN FUNCTION IN *cis*-9,10-DIMETHYLDECALIN COMPOUNDS

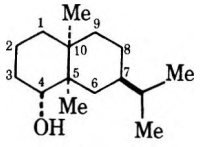
Compd	Chemical shift (δ), ppm	Line width at half-height ($W_{1/2}$), Hz	Conformation of C-5 proton
6	4.03	19	Axial
7	3.38	8	Equatorial
10	3.91	18	Axial
11	3.28	6	Equatorial
16	3.59[a]	16[a]	Axial
17	3.25[a]	6[a]	Equatorial

[a] Data from Hikino, *et al.*[1f]

axial–equatorial relationship and present an exception to the rule. The epimeric alcohols **16** and **17** prepared



16
C-4 H = axial
C-4 OH = equatorial



17
C-4 H = equatorial
C-4 OH = axial

from natural *l*-valeranone by Hikino, *et al.*,[1f] also exhibit a similar reversal of axial–equatorial relationship. Similar exceptions have been reported earlier in the literature.[18] Although one could speculate that this anomaly may be due to long-range shielding effects associated with diamagnetic anisotropy, a clear understanding of this phenomenon is not possible at this time without further detailed study of other model compounds.

(15) (a) G. B. Spero and A. V. McIntosh, Jr., *J. Amer. Chem. Soc.*, **70**, 1907 (1948); (b) G. Rosenkranz, S. F. Kaufman, and J. Romo, *ibid.*, **71**, 3689 (1949); (c) P. N. Rao and H. R. Gollberg, *Tetrahedron*, **18**, 1251 (1962).

(16) The natural *l*-valeranone was kindly supplied by Dr. Hikino. The infrared and nmr spectra of *l*-valerane prepared in Japan were also kindly supplied by Dr. Hikino for our comparison of the product prepared in our laboratories.

(17) Valeranone skeleton numbering.

(18) (a) A. Nickon, M. A. Castle, R. Harada, C. E. Birkoff, and R. O. Williams, *J. Amer. Chem. Soc.*, **85**, 2185 (1963). (b) K. M. Wellman and F. G. Bordwell, *Tetrahedron Lett.*, 1703 (1963).

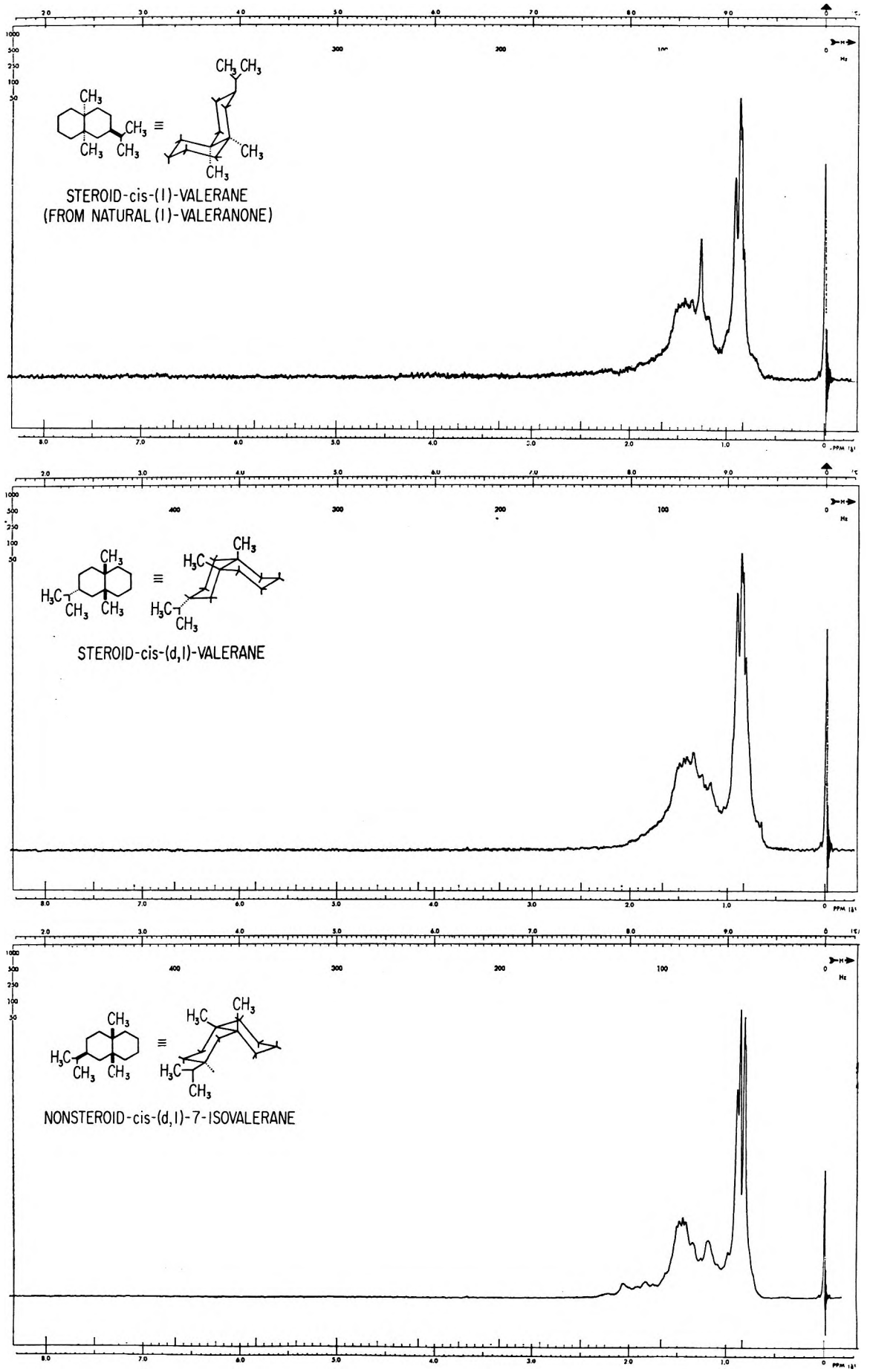


Figure 1.—Nmr spectra of **13**, **15**, and natural valerane in CCl_4.

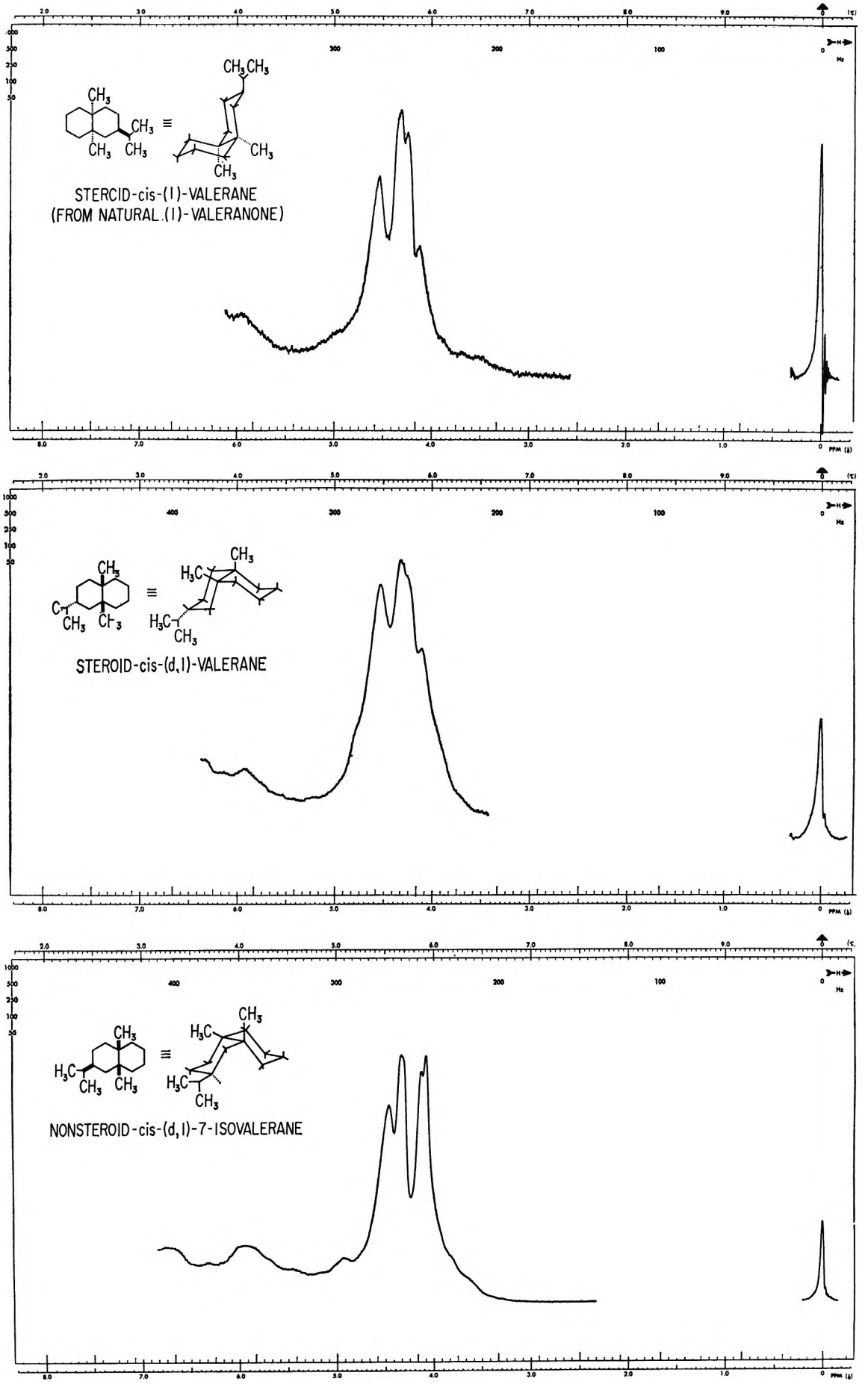


Figure 2.—Nmr spectra of isopropyl and methyl peaks of **13**, **15**, and natural valerane (0.1-Hz sweep time, 100-Hz sweep width).

Experimental Section[19]

5β-Tetrahydropyranyloxy-*cis*-9β,10β-dimethyl-2-decalone (3).[19]—To a solution of 5β-hydroxy-*cis*-9β,10β-dimethyl-2-decalone (2)[6] (2.87 g) in ether (50 ml), dihydropyran (2.5 ml) and toluene-*p*-sulfonic acid (50 mg) were added and the contents were stirred at room temperature for 4 hr. The reaction mixture was then washed with saturated sodium bicarbonate solution and saturated brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was then crystallized from petroleum ether to give **3** (3.8 g, 92%): mp 83–85°, $\nu_{max}^{CHCl_3}$ 2950, 2880, and 1710 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.92 (s, CH_3) and 1.0 (s, CH_3) ppm.

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.80; H, 10.21.

Preparation of 3 from 5β-Tetrahydropyranyloxy-10β-methyl-1(9)-octal-2-one (4) by Conjugate Addition of Lithium Dimethylcopper.—A stirred suspension of cuprous iodide (68.7 g, 0.36 mol) in anhydrous ether (1000 ml) under an atmosphere of dry nitrogen was cooled to −25° by means of an external CCl_4–Dry Ice bath. To this mixture was added an ether solution of methyllithium until the yellow precipitate just disappeared (360 ml of 2 *M* concentration, 0.72 mol). A small amount of cuprous iodide was then added to bring back the yellow precipitate, thus ensuring that no excess methyllithium was present. A solution of ketone 4[8] (35 g, 0.132 mol) in dry ether (360 ml) was slowly added over a period of 20 min and the contents was stirred for 1 hr at −25°. The reaction mixture was then decomposed by pouring it into a rapidly stirred mixture of concentrated ammonium hydroxide (2 l.) and ice. The residue in the reaction flask was also treated with ice-cold ammonium hydroxide and ether and stirred until dissolved. The total combined aqueous-ether mixtures were transferred to a separatory funnel and the ether extract was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was then diluted with petroleum ether and stored at −20° to give compound **3** (27.9 g), mp 83–85°. The mother liquor was passed through a column of alumina (365 g) and eluted with petroleum ether–benzene (8:2) to give an additional amount of **3** (3.4 g), mp 82–84°. The total yield of **3** amounted to approximately 75%. The product prepared by this method was found to be identical in all respects with that of the authentic sample described above.

2-Ethylidene-5β-tetrahydropyranyloxy-*cis*-9β,10β-dimethyldecalin (5).[19c]—The procedure of Corey, *et al.*,[10] was employed. A solution of sodium methylsulfinyl carbanion was prepared under nitrogen from sodium hydride (0.43 g, 0.018 mol) and dimethyl sulfoxide (12 ml). The solution was cooled in a cold water bath and stirred during the addition of ethyl triphenylphosphonium bromide (6.7 g, 0.018 mol) in dimethyl sulfoxide (30 ml), whereupon the characteristic color of the ethylidenephosphorane was produced. After the mixture was stirred at room temperature for 15 min, a solution of the ketone **3** (3.92 g, 0.014 mol) in dimethyl sulfoxide (10 ml) was added and stirring was continued at room temperature for 2 hr and then at 60–65° for an additional hour. The reaction mixture was cooled and poured into cold water (100 ml) and the product was isolated with hexane.[19b] The crude mixture was chromatographed on alumina (130 g) to remove the triphenylphosphine oxide. Elution with petroleum ether gave **5** (3.5 g, 86.5%). An analytical sample was prepared by short-path distillation at 10^{-4} mm, bath temperature 120°: $\nu_{max}^{CHCl_3}$ 2940, 2860, 1620, 1480, 1450, and 1390 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.83 (s, CH_3) and 0.88 (s, CH_3) ppm.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.02; H, 11.03. Found: C, 77.84; H, 11.20.

2α-Acetyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (6) and 2β-Acetyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (7).[19c] (i) **Hydroboration.**—A solution of tetrahydropyranyl ether **5** (24.4 g) in tetrahydrofuran (150 ml) was cooled to 0° and kept under nitrogen atmosphere. A solution of diborane in tetrahydrofuran[20] (164 ml, 1 *M* BH_3–THF complex) was added and the contents stirred at room temperature for 1 hr. Sodium hydroxide solution (235 ml, 10% solution) was added dropwise and the alkaline reaction mixture was brought to 0° once again. Hydrogen peroxide (164 ml, 30% solution) was then slowly added over a period of 20 min and the contents stirred for an additional hour; the reaction product was isolated with ethyl acetate.[19b] The crude product (24 g) exhibited hydroxyl absorption in the infrared spectrum and without further purification was oxidized with 8 *N* chromic acid.

(ii) **Oxidation of the Above Mixture of Alcohols with 8 *N* Chromic Acid.**[12]—The crude reaction product (24 g) from the above hydroboration experiment was dissolved in acetone (250 ml) and the contents was cooled to −5°. A solution of 8 *N* chromic acid[12] was added with stirring until the orange color persisted. The excess reagent was destroyed by the addition of a few drops of methanol and solid sodium bicarbonate was added to neutralize any excess acid. The mixture was filtered through Celite, the residual gummy solid was triturated with ethyl acetate, and the combined filtrates were concentrated under reduced pressure. The oxidation product was isolated with ethyl acetate[19b] to give a mixture of 2ξ-acetyl-*cis*-9β,10β-dimethyldecalin derivative (23.4 g). This crude product exhibited a strong carbonyl absorption at 1700 cm^{-1} in the infrared spectrum.

(iii) **Base-Catalyzed Equilibration of the Above 2ξ-Acetyl Compound.**—A solution of the above ketone (23.4 g) in ethanol (100 ml) was added to a solution of 1 *N* ethanolic sodium ethoxide (100 ml) and the contents was stirred at 60° for 18 hr under nitrogen atmosphere. The excess alkali was carefully neutralized with acetic acid and most of the ethanol was removed under reduced pressure. The product was isolated with ethyl acetate[19b] to yield an oil (23 g).

(iv) **Removal of the Tetrahydropyranyl Protecting Group and Separation of Ketones 6 and 7.**—The product from the above reaction was dissolved in ethanol (250 ml), and concentrated hydrochloric acid (5 ml) and water (2 ml) were added and stirred at room temperature overnight. Most of the ethanol was removed under reduced pressure and the product was isolated with ethyl acetate[19b] to give a thick gummy product (17.8 g) which, on crystallization from ether–petroleum ether, gave 2α-acetyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (**6**) (9.1 g), mp 77–78°. The analytical sample crystallized from ether–hexane: mp 79–81°; $\nu_{max}^{CHCl_3}$ 3600, 2940, 2880, and 1700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.03 (–CHOH, broad multiplet, $W_{1/2}$ = 19 Hz), 2.6 (>CHCOCH$_3$, broad multiplet, $W_{1/2}$ = 23 Hz), 2.13 (s, –COCH$_3$), 0.93 (s, CH_3), and 0.83 (s, CH_3) ppm.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.95.

The mother liquors were combined and chromatographed on alumina (270 g). Elution of the column with petroleum ether–benzene (1:1) gave 2β-acetyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (**7**) (0.377 g) which crystallized from ether–hexane: mp 72–74°; $\nu_{max}^{CHCl_3}$ 3610, 2960, 2875, and 1705 cm^{-1}, $\delta_{TMS}^{CDCl_3}$ 3.38 (CHOH, poorly resolved triplet, $W_{1/2}$ = 8 Hz) 2.5 (>CHCOCH$_3$, broad multiplet, $W_{1/2}$ = 22 Hz), 2.05 (s, –COCH$_3$), 1.05 (s, CH_3), and 1.0 (s, CH_3) ppm.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.74; H, 10.86.

Further elution of the column with benzene and benzene–ether (8:2) gave an additional amount of **6** (5.23 g). The total amount of 2α-acetyl product **6** obtained was 14.33 g. The 2β-acetyl product isolated amounted to 0.377 g. The overall yield of the combined 2ξ-acetyl product was 78.7%, of which 97.4% comprises **6** and 2.6% is compound **7**.

Base-Catalyzed Equilibration of 2α-Acetyl Product 6.—To a solution of 1 *N* ethanolic sodium ethoxide (25 ml) a solution of **6** (150 mg) in ethanol (5 ml) was added and the contents was stirred at 60° for 20 hr. The reaction mixture was neutralized with acetic acid and the alcohol was evaporated under reduced pressure. The equilibrated product was isolated with ethyl acetate.[19b] Thin-layer chromatographic examination (benzene–ether 1:1 solvent system) of a small sample from the total reaction product revealed the presence of a small amount of com-

(19) (a) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer (Model 257) spectrometer. Nmr spectra were run in the specified solution using 2% TMS as internal standard on a Varian A-60A nmr spectrometer. Woelm neutral aluminum oxide activity III was employed for chromatography. Reagent grade silica gel G for tlc prepared by E. Merck was used for thin-layer chromatography in the specified solvent system. Petroleum ether employed was that of Mallinckrodt reagent grade, bp 30–60°. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. (b) The following sequence describes a typical isolation procedure. The reaction mixture was treated with water and extracted with specified organic solvent. The solvent extract was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the solvent was evaporated under reduced pressure on a Büchi rotary evaporator at 60–65°. The residue left in the flask was then purified as described. (c) The prefix *dl* is omitted from the names of racemic substances. The prefixes α and β are used to denote relative stereochemistry.

(20) Available from Ventron Corp., Beverly, Mass.

pound **7**. The total product (150 mg) was then subjected to column chromatography on alumina (5 g). Elution of the column with petroleum ether–benzene (8:2) and (1:1) gave compound **7** (5 mg, 3.3%), mp 72–74°. A mixture melting point with authentic sample did not show depression and the infrared spectrum was found to be identical.

Further elution of the column with benzene and benzene–ether (8:2) gave unchanged **6** (43 mg), mp 79–81°, whose identity was established by comparing the infrared spectrum and mixture melting point determination.

Base-Catalyzed Equilibration of 2β-Acetyl Product 7.—A similar equilibration employing **7** (200 mg) and 1 *N* ethanolic sodium ethoxide (40 ml), after work-up and chromatographic separation as described above, gave **6** (193 mg, 97%), mp 78–80° and unchanged **7** (6 mg), mp 72–73°. The identity of these products was established through mixture melting point determination and by comparison of the infrared spectra.

2α-Acetyl-5β-tetrahydropyranyloxy-*cis*-9β,10β-dimethyldecalin (8).[19c]—To a solution of 2α-acetyl compound (12.1 g) in ether (250 ml), dihydropyran (5.2 ml) and toluene-*p*-sulfonic acid (300 mg) were added and the contents was stirred at room temperature for 18 hr. The ether solution was then washed with saturated sodium bicarbonate and brine and dried (Na_2SO_4), and the solvent was evaporated to give a viscous oil (16 g). The analytical sample was prepared by short-path distillation at 10^{-4} mm, bath temperature 125°: $\nu_{max}^{CHCl_3}$ 2940, 2880, and 1705 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.88 (s, CH_3), 0,95 (s, CH_3), and 2.15 (s, $-COCH_3$) ppm.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.72; H, 10.22.

2α-Isopropenyl-5β-tetrahydropyranyloxy-*cis*-9β,10β-dimethyldecalin (9).[19c]—A solution of methyltriphenylphosphonium bromide (5.36 g, 0.015 mol) in dimethyl sulfoxide (25 ml) was added under nitrogen atmosphere to a solution of dimethylsulfinylsodium[10] prepared from sodium hydride (0.36 g, 0.015 mol) and dimethyl sulfoxide (7.5 ml). The resulting yellow solution was stirred at room temperature for 0.5 hr and then a solution of ketone **8** (3.7 g, 0.012 mol) in dimethyl sulfoxide was added. The reaction mixture was stirred at 55° for 18 hr, cooled, diluted with water, and extracted with hexane. The combined hexane extracts were washed with aqueous dimethyl sulfoxide (50% solution) and water, dried (Na_2SO_4), and filtered, and the solvent was evaporated. The crude residue was then passed through a column of alumina (100 g) and eluted with petroleum ether to give **9** (2.94 g, 73%) as colorless mobile oil. The analytical sample was prepared by short-path distillation at 10^{-4} mm, bath temperature 130°: $\nu_{max}^{CHCl_3}$ 2940, 2860, and 1642 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.66 (d, J = 5 Hz, $C{=}CH_2$), 1.7 (s, $C{=}CCH_3$), 0.92 (s, CH_3), and 0.83 (s, CH_3) ppm.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.34; H, 11.43.

2α-Isopropyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (10) and 2β-Isopropyl-5β-hydroxy-*cis*-9β,10β-dimethyldecalin (11).[19c] (i) **Hydrogenation**—A solution of **9** (15.9 g) in ethyl acetate (150 ml) was hydrogenated in the presence of 5% palladium on charcoal (1 g). The solution was filtered from the catalyst and the solvent was evaporated to give colorless viscous oil (15.9 g). The infrared and nmr spectra of this material indicated complete saturation.

(ii) **Removal of the Tetrahydropyranyl Protecting Group and Separation of Alcohols 10 and 11**—The hydrogenated product (15.9 g) was dissolved in 95% ethanol (150 ml), and concentrated hydrochloric acid (5 ml) was added; the mixture was stirred under nitrogen for 5 hr. The hydrochloric acid was neutralized with sodium hydroxide (5% solution) and most of the solvent was evaporated under reduced pressure; the product was isolated with ethyl acetate[19b] to give a mixture of **10** and **11** as a solid (10.6 g, 91%). Thin layer chromatographic examination (benzene–ether 8:2 solvent system) of a small sample revealed one major product with a small amount of another compound moving slightly ahead of it. The total solid was then crystallized from acetone–hexane to give pure **10** (4.2 g): mp 74–75°; $\nu_{max}^{CHCl_3}$ 3600, 2940, 2870, 1472, 1460, and 1018 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 3.91 (CHOH, broad multiplet, $W_{1/2}$ = 18 Hz), 0.9 (s, CH_3), 0.87 (d, J = 5 Hz, isopropyl), and 0.78 (s, CH_3) ppm.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.32; H, 12.56.

The residue (6.3 g) from the above mother liquor was subjected to very careful chromatography on alumina (190 g). Elution of the column with petroleum ether–benzene (8:2) gave pure **11** (0.39 g) which was crystallized from acetone: mp 75–77°; $\nu_{max}^{CHCl_3}$ 3618, 2980, 2880, 1470, and 980 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 3.28 (CHOH, poorly resolved triplet; $W_{1/2}$ = 6 Hz), 1.03 (s, CH_3), 0.98 (s, CH_3), and 0.87 (d, J = 5 Hz, isopropyl) ppm.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.44; H, 12.59.

Further elution of the column with petroleum ether containing gradual increments of benzene up to 1:1 gave an inseparable mixture of **10** and **11** (0.91 g). Finally, eluting the column with petroleum ether–benzene (1:1) and benzene gave an additional amount of pure **10** (5 g). The total amount of 2α-isopropyl compound **10** isolated from direct crystallization and chromatographic separation amounted to 9.2 g and the 2β-isopropyl compound **11** amounted to 0.39 g.

2α-Isopropyl-*cis*-9β,10β-dimethyl-5-decalone (12).[19c]—To a solution of **10** (1.34 g) in acetone (40 ml) 8 *N* chromic acid[12] was added with stirring until the orange color persisted. The excess reagent was destroyed by the addition of a few drops of methanol and solid sodium bicarbonate was added to neutralize any excess acid. The mixture was then filtered through Celite and the gummy residue was thoroughly washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure and the oxidation product was isolated with ether.[19b] The crude product was purified by distillation at 0.35 mm, bath temperature 100°, to give **12** (1.28 g): $\nu_{max}^{CHCl_3}$ 2940, 2880, and 1700 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 1.03 (s, CH_3), 1.0 (s, CH_3), and 0.83 (d, J = 5 Hz, isopropyl) ppm.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.12; H, 11.59.

The 2,4-dinitrophenylhydrazone derivative of **12** was prepared by the standard procedure and was crystallized from ethyl acetate: mp 177–179°; ν_{max}^{KBr} 3320, 2940, 2880, 1630, 1600, 1530, and 1510 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_4N_4$: C, 62.67; H, 7.51. Found: C, 62.71; H, 7.52.

2β-Isopropyl-*cis*-9β,10β-dimethyl-5-decalone (14).[19c]—2β-Isopropyl compound **11** (450 mg) in acetone solution (10 ml) was oxidized with 8 *N* chromic acid[12] as described above, and the product was purified by distillation at 0.7 mm, bath temperature 110°, to give **14** (410 mg): $\nu_{max}^{CHCl_3}$ 2980, 2880, and 1700 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 0.97 (s, CH_3), 0.89 (d, J = 5 Hz, isopropyl), and 0.80 (s, CH_3) ppm.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.25; H, 11.57.

The 2,4-dinitrophenylhydrazone derivative of **14** was crystallized from ethyl acetate: mp 154–156°; ν_{max}^{KBr} 3220, 2960, 2880, 1628, 1600, 1530, and 1512 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_4N_4$: C, 62.67; H, 7.51. Found: C, 62.70; H, 7.55.

Gas chromatographic analysis[21] indicated that ketone **12** was less polar compared to **14** and the retention times were 8.2 and 10.3 min, respectively.

2α-Isopropyl-*cis*-9β,10β-dimethyldecalin (Racemic Valerane) (13).[19c]—To a solution of the decalone **12** (230 mg) in ethanedithiol (0.5 ml), boron trifluoride etherate (0.5 ml) was added and the contents was stirred at room temperature overnight and then warmed for 4 hr at 70–75°. The crude ethylenethioketal derivative was isolated with ether[19b] and the infrared spectrum indicated the absence of carbonyl group. Without further purification the ethylene thioketal derivative was subjected to desulfurization with deactivated Raney nickel catalyst (W-2, two level teaspoonfuls)[15] in acetone solution (100 ml). After 4.5 hr of refluxing, the acetone solution was filtered from the catalyst, the solvent was evaporated, and the residue (202 mg) was purified by short-path distillation at 2 mm, bath temperature 105°, to give analytically pure compound **13** (127 mg): $\nu_{max}^{CHCl_3}$ 2940, 2880, 1530, 1510, 1400, and 1382 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 0.87 (s, CH_3), 0.86 (d, J = 5 Hz, isopropyl), and 0.85 (s, CH_3) ppm.

Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.37; H, 13.37.

2β-Isopropyl-*cis*-9β,10β-dimethyldecalin (Racemic 7-Isovalerane[17]) (15).[19c]—To a solution of the decalone **14** (375 mg) in ethanedithiol (1 ml), boron trifluoride etherate (1 ml) was added and the contents was stirred at room temperature overnight. The ethylene thioketal derivative was isolated with ether[19b] and

(21) Aerograph Model (90 P3) with a 0.25-in. × 10-ft column of 10% UCON 75H 90,000 polar on 60–80 Gas Pack W was employed at 192° with a helium flow rate of 52 cc/min.

subjected to desulfurization with deactivated Raney nickel (two level teaspoonfuls)[15] in acetone solution (100 ml) as described above. Purification of **15** through short-path distillation at 2.5 mm, bath temperature 105°, gave analytically pure product (187 mg): $\nu_{max}^{CHCl_3}$ 2940, 2880, 1520, 1500, 1400, and 1380 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 0.87 (s, CH_3), 0.85 (d, J = 5 Hz, isopropyl), and 0.82 (s, CH_3) ppm.

Natural Valerane from *l*-Valeranone.—This product was prepared from natural valeranone (120 mg) essentially as described by Hikino, *et al.*,[1f] and the identity of the product prepared in our laboratories was established by comparison of infrared and nmr spectra of material prepared in Japan.[16]

Registry No.—**3,** 29969-74-2; **5,** 29863-73-8; **6,** 29863-74-9; **7,** 29863-75-0; **8,** 29862-76-1; **9,** 29863-77-2; **10,** 29863-78-3; **11,** 29863-79-4; **12,** 29863-80-7; **12** 2,4-DNP, 29863-81-8; **13,** 29863-82-9; **14,** 30008-94-7; **14** 2,4-DNP, 29863-83-0; **15,** 29863-84-1.

Acknowledgment.—We sincerely thank Dr. H. Hikino for helping us with natural valeranone and for providing us with the copies of his infrared and nmr spectra of valerane, Professor Edward Piers for providing us with his experimental details for the preparation of **3** from **4**, Dr. David H. Buss for gas chromatograms, Mr. Melvin C. Seffel for infrared spectra, and Mr. David B. Holland for technical assistance. The interest and encouragement of Dr. Leonard R. Axelrod are gratefully acknowledged. This investigation was supported in part by a research grant from the Southwest Foundation for Research and Education for preparing compounds of medicinal value, and Grant A-03270-12 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Acetylation of Pinane

ROBERT F. TAVARES,* JULIAN DORSKY, AND WILLIAM M. EASTER

Givaudan Corporation, Clifton, New Jersey 07014

Received September 11, 1969

When pinane was treated with acetyl chloride and aluminum chloride under Friedel–Crafts conditions, an unstable product, 2-acetyl-1-chloro-4-isopropyl-1-methylcyclohexane, was formed. This product was transformed to a mixture of acetyl-4-isopropyl-1-methylcyclohexenes by loss of HCl. The stereochemistry of the products and its bearing on the mechanism of the Kondakov reaction is discussed.

Although the chemistry of the pinenes has been extensively studied,[1] relatively little has been learned about the saturated hydrocarbon, pinane. The pinane molecule is quite stable and its potentially labile cyclobutane ring is resistant to most oxidizing agents and mineral acids. It reacts only slowly with hydrogen bromide at 230°.[2]

Whereas free-radical type reactions of pinane have been reported,[3-8] reactions of pinane by ionic mechanisms have not. However, the acetylation of saturated hydrocarbons with acetyl chloride in the presence of aluminum chloride is known[9-11] and offers a feasible route toward functionalizing pinane. We have investigated this reaction and present here the results of our work.

When an ethylene dichloride solution of the complex formed between acetyl chloride and aluminum chloride was added to pinane (**1**), a mixture of chloro ketones **5** was produced. The chloro ketones lost HCl slowly on standing. Upon heating, HCl was evolved more rapidly and the product formed was the α,β-unsaturated ketone **8**. When submitted to glc analysis, HCl was again lost but the products eluted were the β,γ-unsaturated ketones **6** and **7** plus a small amount of **8**.

That the chloro ketones formed are 2-acetyl-1-chloro-4-isopropyl-1-methylcyclohexanes (**5**) was supported by the fact that the same products were formed by adding acetyl chloride to 1-*p*-menthene. Also, the unsaturated ketones eluted from the glc were identical with those prepared by the acetylation of 1-*p*-menthene with acetic anhydride.

The nmr spectra of crude and distilled fractions of the β-chloro ketone **5** revealed that it was a mixture of at least two principal isomers **5a** and **5b**. One isomer (which dominated the earlier fractions of the distilled crude) showed a broad multiplet at τ 6.83 (*ca.* 12-Hz wide, $>CHCOCH_3$), sharp singlets at τ 7.82 (CH_3CO) and 8.35 [$>C(Cl)CH_3$], and a doublet at τ 9.22 (J = 5.5 Hz, $-<\begin{matrix}CH_3\\CH_3\end{matrix}$). The nmr of later fractions showed additional peaks at τ 7.30 (*ca.* 17-Hz wide, $>CHCOCH_3$), a sharp singlet at τ 7.77 (CH_3CO), and a doublet at τ 9.26 (J = 5.5 Hz, $-<\begin{matrix}CH_3\\CH_3\end{matrix}$) assigned to a second isomer. The signals for the methine protons α to the carbonyl indicated that this proton was equatorial in the lower boiling isomer **5a** (less broad and further downfield from TMS) and was axial in the higher boiling isomer **5b** (signal at higher field and broader due to diaxial coupling).[12]

In accord with the above, it was found that **5a** decomposed on glc to a β,γ-unsaturated ketone **6** in which the acetyl group is quasiaxial while isomer **5b** decomposed to a β,γ-unsaturated ketone **7** in which the acetyl

(1) (a) B. D. Sully, *Chem. Ind. (London)*, 263 (1964). (b) D. V. Banthorpe and D. Whittaker, *Chem. Rev.*, **66**, 643 (1966); *Quart. Rev. Chem. Soc.*, 373 (1966). (c) C. Bordenca, *Amer. Perfum. Cosmet.*, **80**, (7), 19 (1965).

(2) B. T. Brooks, "The Chemistry of the Nonbenzenoid Hydrocarbons," 2nd ed, Reinhold, New York, N. Y., 1950, p 533.

(3) (a) G. Bonnet, *Bull. Inst. Pin.*, 217, 241 (1938); 1 (1939). (b) A. Gandini, *Gazz. Chim. Ital.*, **70**, 254 (1940); **71**, 722 (1941).

(4) (a) C. Fillatre and R. Lalande, *Bull. Soc. Chim. Fr.*, 4141 (1968); (b) G. S. Fisher, J. S. Stinson, and L. A. Goldblatt, *J. Amer. Chem. Soc.*, **75**, 3675 (1953).

(5) E. Muller and G. Fiedler, *Chem. Ber.*, **98**, 3493 (1965).

(6) G. A. Schmidt and G. S. Fisher, *J. Amer. Chem. Soc.*, **76**, 5426 (1954).

(7) G. A. Schmidt and G. S. Fisher, *ibid.*, **81**, 445 (1959).

(8) C. Fillatre and R. Lalande, *Bull. Soc. Chim. Fr.*, 1575 (1966).

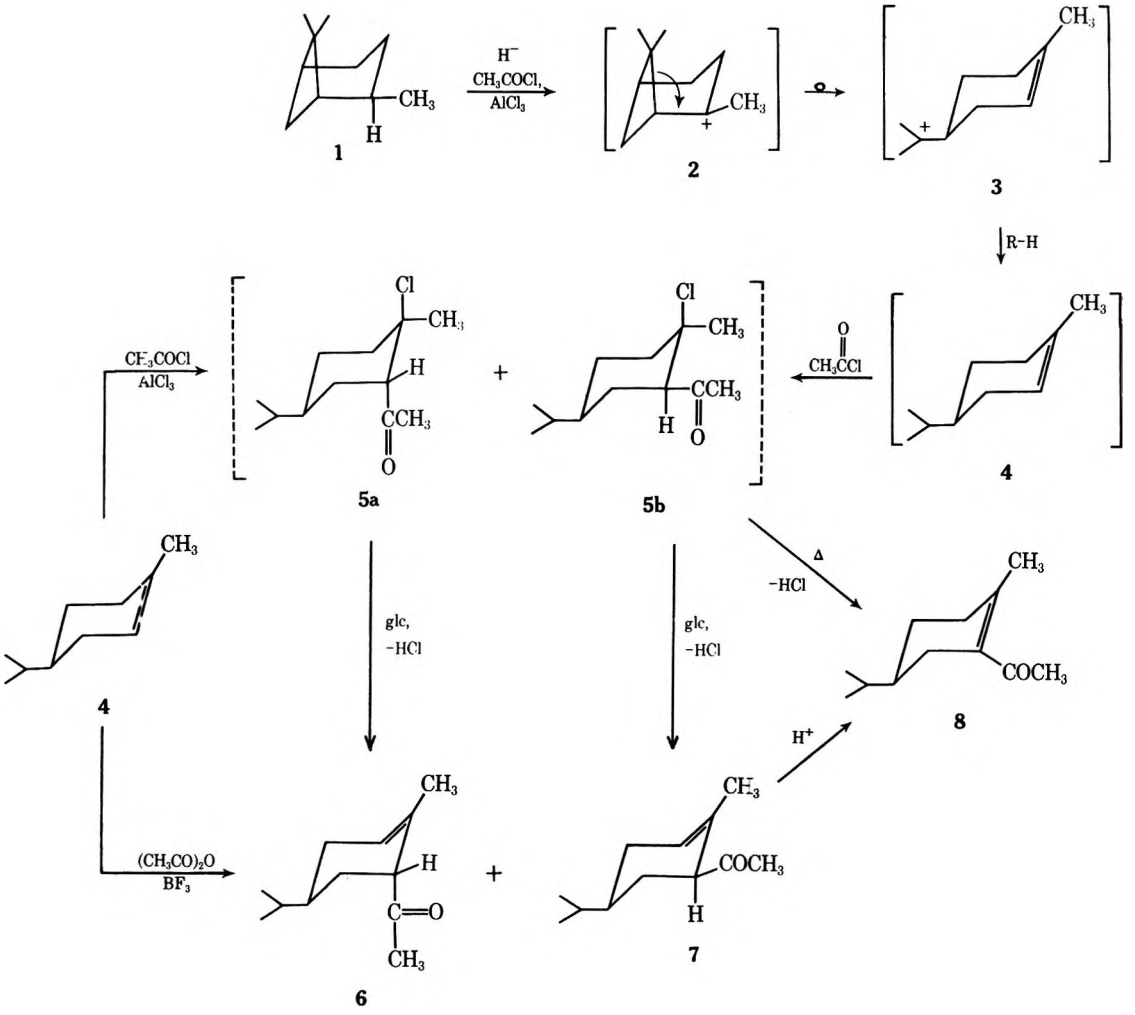
(9) G. A. Olah, ed., "Friedel-Crafts and Related Reactions," Vol. I, Interscience, New York, N. Y., 1964, p 135; Vol. III, pp 1069–1077.

(10) I. Tabushi, K. Fujita, and R. Oda, *Tetrahedron Lett.*, 4247 (1968); 5455 (1968).

(11) G. Baddeley, B. G. Heaton, and J. W. Rasburn, *J. Chem. Soc.*, 4713 (1960).

(12) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1959, p 116.

SCHEME I

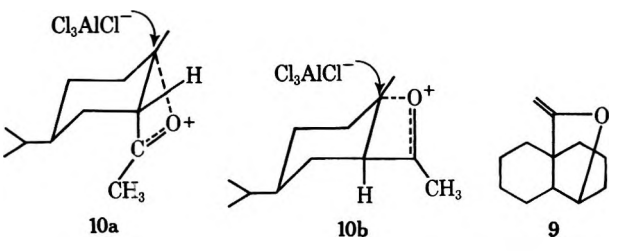


group is quasiequatorial plus an α,β-unsaturated ketone **8**. The structures of the β,γ-unsaturated ketones were based on the observation that the proton α to the carbonyl in isomer **6** gave an nmr signal which was only half as broad as the corresponding proton of isomer **7** indicating that the former was quasiequatorial and the latter quasiaxial.[13]

Recent evidence on the ir spectra of 4-alkyl-1-methylcyclohexyl chlorides[14] indicates that those compounds in which the chlorine is axial have carbon–chlorine stretching bands at 560 ± 20 cm^{-1} and those in which the chlorine is equatorial have bands at 650 ± 20 cm^{-1}. The presence of a strong band at 540 cm^{-1} (and no evidence of any in the 650-cm^{-1} region) for both **5a** and **5b** clearly suggest that the chlorine is axial in both isomers as indicated in Scheme I. It is not surprising, therefore, that the higher boiling fractions decompose more rapidly since they are enriched in **5b** which can decompose to **8** *via* a trans diaxial elimination.

Scheme I suggests a mechanism to explain the products formed. The acetyl chloride–aluminum chloride complex can abstract a hydride ion from *cis*-pinane to produce a carbonium ion **2** which can rearrange and abstract a hydride ion to form 1-*p*-menthene (**4**). The source of the hydride ion could be **1** or some other hydrocarbon species in the medium.[9] An alternative mechanism involving α-pinene, formed by the loss of a proton from **2**, is not likely since α-pinene produced only residue under these reaction conditions while **4** produced the β-chloro ketones **5a** and **5b**.

That only axial chloro compounds were detected can be rationalized from either kinetic or thermodynamic considerations. A four-membered transition state such as **10a** can be considered in which the oxygen sta-



bilizes the carbonium ion and requires that the chlorine attack from the least hindered side leading to **5a**. Such a four-centered transition state was first proposed by Cope.[15] More recently they have been considered by

(13) (a) F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967). (b) A possible anomaly appears in that the equatorial methine proton of **6** (τ 6.94) appears at higher, not lower, field than the axial proton of **7** (τ 6.82). This reversal could be due to the shielding effects of the carbonyl in much the same manner as occurs in cyclohexanone. See K. M. Wellman and F. G. Bordwell, *Tetrahedron Lett.*, 1073 (1963).

(14) C. Altona, H. J. Hageman, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **87**, 353 (1968); C. Altona, *Tetrahedron Lett.*, 2325 (1968).

(15) A. C. Cope, T. A. Liss, and D. S. Smith, *J. Amer. Chem. Soc.*, **79**, 240 (1957).

TABLE I

Fraction	Bp, °C	Wt, g	$n^{20}D$	Analysis by glc[a] % 6	% 7	% 8
1	40–80	63.0	1.4572	0.0	0.0	0.0
2	92	25.0	1.4764	56.6	4.3	5.6
3	97	22.0	1.4775	68.9	7.4	5.9
4	97	27.5	1.4785	64.2	14.6	7.2
5	97	27.0	1.4792	53.2	14.5	18.8
6	107	20.0	1.4802	41.3	17.3	34.0
7	107	6.5	1.4802	38.5	21.3	32.9
8	107	3.5	1.4805	35.3	24.3	33.1
Residue		101.0				

[a] glc shows only decomposition products of **5**.

Experimental Section[18]

2-Acetyl-1-chloro-4-isopropyl-1-methylcyclohexane (5). A.—To a mixture of 200 g (1.5 mol) of $AlCl_3$ in 450 ml of ethylene dichloride was added 235 g (3.0 mol) of acetyl chloride while maintaining a temperature of 15°. After the dark brown solution was stirred for an additional 20 min, it was added over a 2-hr period to a solution of 276 g (2.0 mol) of pinane (90% cis) and 100 ml of ethylene dichloride at −5°. Stirring was continued for an additional 1 hr at −5° and then the reaction mixture was poured onto 2.5 l. of ice and water and the layers were allowed to separate. The aqueous layer was extracted with 200 ml of ethylene dichloride. The organic layers were combined and washed twice with 200-ml portions of HCl, twice with 200-ml portions of 10% NaOH, and then with water until neutral to litmus. The ethylene dichloride was removed at atmospheric pressure and the batch distilled under vacuum (1.0 mm) (see Table I).

By preparative glc, the major peaks were collected. The first sample contained a mixture of the first two major peaks (60.2% **6** and 37.1% **7**) and the second was primarily the third major peak (98.9% **8**). The structures were identified by comparison of the nmr and ir with authentic samples prepared by an independent syntheses described later. Spectral data are included in Table II.

B.—According to the procedure described above (A), a solution composed of 133.5 g (1 mol) of $AlCl_3$, 300 ml of ethylene dichloride, and 80 g (1.02 mol) of acetyl chloride was added to a solution of 150 g (1.1 mol) of 1-*p*-menthene in 75 ml of ethylene dichloride. The product was distilled under vacuum (4.0 mm) (Table III).

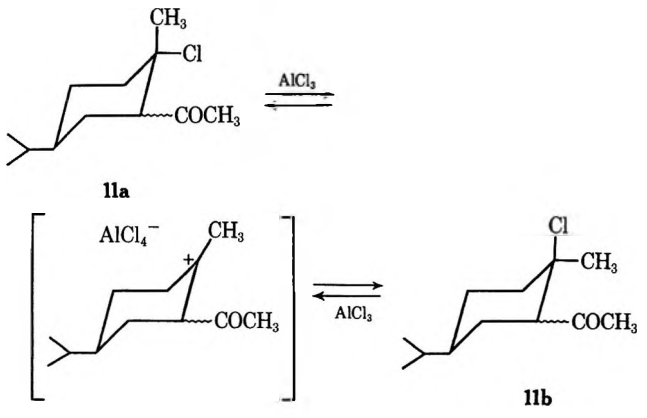
TABLE II

SPECTRAL DATA

Compd	Ir, cm^{-1} >=O	Ir, cm^{-1} C—Cl	Nmr, τ —C(COCH₃)—H	—C(=O)CCH₃	—C(CH₃)—Cl	=CH(CH₃)	=CH—	—C(CH₃)₂
6	1710		6.94	7.81		8.34	4.33	9.12
7	1710		6.82	7.88		8.40	4.33	9.10
8	1685			7.77		8.13		9.08
5a	1715	540	6.83	7.82	8.35			9.22
5b	1715	540	7.30	7.77	8.35			9.26

others[9,16] as the initially formed species to explain acylation results which led to the vinyl ether **9** from cis decalin and to a mixture of β-, γ-, and δ-chlorocyclohexyl methyl ketones from cyclohexene. The formation of **5b** could result either from epimerization of **5a** or from **10b**.

However, since both **5a** and **5b** are tertiary chlorides, it is not unreasonable that a process involving epimerization *via* chloride exchange could conceivably occur under the reaction conditions as illustrated below.



If all other factors are considered negligible, the compound having an axial chlorine (**11b**) is favored by about 1.4 kcal/mol over the epimer (**11a**).[17] Such an energy difference between isomers would require that a true equilibrium would be composed of about 93% **12b**. Hence, the observed result could be rationalized on both kinetic and thermodynamic considerations.

TABLE III

Fraction	Bp, °C	Wt, g	$n^{20}D$	Analysis by glc % 6	% 7	% 8
1	63–93	21.0	1.4640	Mostly lights		
2	100	4.7	1.4732			
3	105	8.7	1.4755	66.9	15.9	6.5
4	105	4.8	1.4762	74.7	13.5	5.3
5	110	5.1	1.4765	63.0	20.8	7.1
6	112	16.5	1.4782	50.3	32.8	9.4
				(39.2)[a]	(35.6)	(19.6)
7	112	15.0	1.4792	36.6	39.8	18.2
				(29.0)	(35.7)	(31.3)
8	112	4.8	1.4805	30.5	32.4	32.6
				(28.0)	(26.9)	(41.4)
9	112	5.1	1.4848	Some heavies		
Residue		76.0				

[a] Figures in parentheses are those which represent the glc analysis after samples stood for 5 days.

(16) M. S. Ahmad, G. Baddeley, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc., London*, 395 (1959).

(17) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 103.

(18) The spinning-band distillation was done on an NFA-100 Nester-Faust auto annular Teflon spinning-band column. All glc analyses were obtained from an F & M Model 720 using a 4-ft column of 0.25-in. diameter packed with 25% SE 30 on Gas-Chrom P. Infrared spectra were obtained neat on a Perkin-Elmer Model 457 grating infrared spectrometer utilizing KBr demountable cells, and nmr spectra were obtained from a Varian Associates A-60A spectrometer utilizing TMS as internal standard.

C.—Samples of crude **5** showed large increases in the amount of **8** (by glc and nmr analysis) when subjected to the following conditions: (1) refluxed for 3 hr in 20% NaOH; (2) heated to 150° for 5 hr; and (3) a solution of **5** in ethylene dichloride is stirred overnight at room temperature in the presence of stannic chloride.

The products from procedures A and B gave similar ir and nmr spectra as described in the text. The presence of some **8** in the higher boiling fractions could be determined by the presence of an ir band at 1685 cm^{-1} and a peak in the nmr at τ 8.13 (see Table II).

6-Acetyl-4-isopropyl-1-methylcyclohexene (6 and 7).—1-*p*-Menthene (100 g, 0.72 mol) was added to a mixture of 98 g (0.96 mol) of acetic anhydride and 8.0 ml of $BF_3 \cdot O(C_2H_5)_2$ over a 40-min period at 36°. After an additional stirring period of 2 hr, 150 ml of H_2O was added and the mixture stirred for 2 hr. The layers were separated, washed with 10% NaOH, and then made neutral to litmus with water. Distillation yielded a main fraction, 25.2 g (19% theory), bp 95–96° (7 mm), which was composed of 5.1% hydrocarbons, 52.0% **6**, 32.7% **7**, and 10.2% **8**. These glc retention times were identical (peak enhancement) with those produced in the glc of **5**. Spinning band distillation of the above yielded purified samples of **6** (98.5% by glc) and **7** (95.2% by glc).

Registry No.—**1**, 6876-13-7; **5a**, 30338-42-2; **5b**, 30338-43-3; **6**, 30338-44-4; **7**, 30338-45-5; **8**, 30338-46-6.

Acknowledgment.—We are indebted to Professors J. A. Marshall and W. G. Dauben for valuable discussions, Mr. P. Porcaro for spectroscopic determinations, and Dr. H. U. Daeniker for his support and encouragement during this project.

A Synthesis of *N*-Methyl-1,9-ethenophenothiazine, a Bridged *syn*-Metacyclophane[1,2]

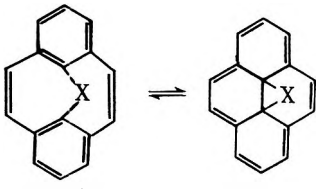
V. BOEKELHEIDE* AND RICHARD A. HOLLINS[3]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received February 1, 1971

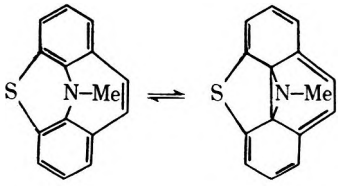
A synthesis of *N*-methyl-1,9-ethenophenothiazine (**5**) is described. Analogously to the two other known examples of bridged *syn*-metacyclophanes, **5** undergoes thermal extrusion of the methylamino bridge to give **19**.

As part of our studies of 15,16-dihydropyrene derivatives,[4] we have been concerned with the synthesis of such derivatives in which the internal substituents at the 15 and 16 positions are oriented cis to each other.[5] In particular we have studied those examples where a bridging heteroatom, as part of a three-membered ring, constitutes the cis substituents.[6,7] In the approach employed, the synthesis of the bridged *syn*-[2.2]metacyclophane-1,9-dienes (**1** and **2**) was first accomplished and then their possible valence tautomerization to the corresponding pyrene *cis*-15,16-epoxide (**3**) and pyrene *cis*-15,16-imine (**4**) was studied.



1, X = O
2, X = N,R
3, X = O
4, X = N,R

Although substitution of a sulfur atom for a carbon–carbon double bond is well known in aromatic heterocyclic systems, examination of molecular models suggested that the substitution of a sulfur atom for a carbon–carbon double bond in **1** or **2** would lead to a very marked increase in ring strain. We undertook the synthesis of the sulfur analog **5**, therefore, both to see whether it could exist and, if so, what effect the additional ring strain might have on the equilibrium between the valence tautomers **5** and **6**.[8]



5 **6**

The synthesis of **5** was modeled after that employed for the synthesis of 8,16-imino[2.2]metacyclophane-1,9-diene.[7] Treatment of phenothiazine (**7**) with oxalyl chloride and aluminum chloride, following the Stollé isatin procedure,[9] gave **8** in 75% yield. Hydrolysis of **8** with aqueous base followed by addition of hydrogen peroxide gave the corresponding acid **9**, which was converted by reaction with diazomethane to the methyl ester **10** for isolation and purification. The overall yield for these three steps was 65%.

When **10** was subjected to the Stollé isatin synthesis followed by a repetition of the above sequence, the diester **12** was readily formed. The nmr spectrum of **12** exhibited three types of aromatic protons: a pair of doublets at τ 2.33 (J = 7.5, J = 2 Hz), a pair of doublets at τ 3.03 (J = 7.5, J = 2 Hz), and a triplet at τ 3.29 (J = 7.5, J = 7.5 Hz), each of equivalent integrated area, as would be expected for **12**.

Treatment of **12** with sodium hydride followed by an excess of methyl iodide gave the *N*-methyl derivative **13** in 95% yield. Lithium aluminum hydride reduction of **13** led to the corresponding diol **14** in 96% yield. This, on reaction with phosphorus tribromide in ben-

(1) We thank the National Science Foundation for their support of this work.

(2) This is paper XXVIII in our series on Aromatic Molecules Bearing Substituents within the Cavity of the π-Electron Cloud. For the preceding communication, see V. Boekelheide and J. Lawson, *Chem. Commun.*, 1558 (1970).

(3) NDEA Fellow, 1967–1970.

(4) For a review, see V. Boekelheide, *Proc. Welch Foundation*, **12**, 83 (1968).

(5) R. H. Mitchell and V. Boekelheide, *Chem. Commun.*, 1555 (1970).

(6) B. A. Hess, Jr., A. S. Bailey, B. Bartusek, and V. Boekelheide, *J. Amer. Chem. Soc.*, **91**, 1665 (1969).

(7) B. A. Hess, Jr., and V. Boekelheide, *ibid.*, **91**, 1672 (1969).

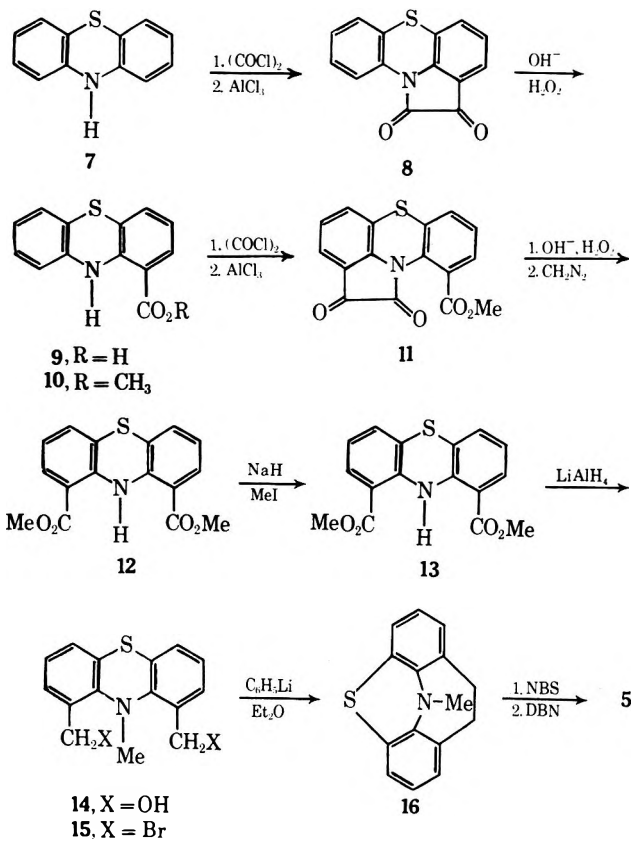
(8) Because of the importance of physiologically active phenothiazine derivatives, it was also of interest in this regard to prepare a phenothiazine derivative having a rigid, butterfly geometry.

(9) R. Stollé, *Ber.*, **46**, 3915 (1913).

zene, was converted in quantitative yield to the dibromide **15**. It is of interest that the steric crowding of the *N*-methyl group is sufficiently large to prevent free rotation about the carbon–carbon bonds at the 1 and 9 positions. Thus, the methylene protons of the hydroxymethyl groups in **14** appear in its nmr spectrum as an AB quartet rather than a singlet. Similarly, the methylene protons of the bromomethyl groups in **15** appear as an AB quartet.

When a solution of the dibromide **15** in ether was treated with phenyllithium, a Wurtz cyclization occurred to give the bridged *syn*-metacyclophane **16** in 16% yield. The spectral properties of **16** are in good accord with its assigned structure. To effect dehydrogenation of the ethano bridge, **16** was treated with *N*-bromosuccinimide (NBS) and the resulting bromo derivative was heated with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN). This gave the desired *N*-methyl-1,9-ethenophenothiazine (**5**) as a pale yellow oil in 35% yield. The reactions leading to the synthesis of **5** are summarized in Scheme I.

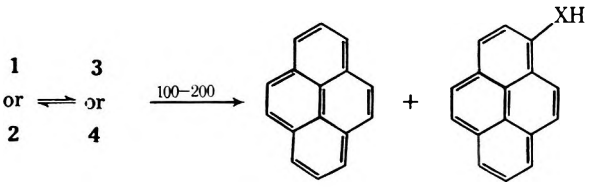
SCHEME I



7 8 9, R = H 10, R = CH_3 11 12 13 14, X = OH 15, X = Br 16

The properties of the final product were clearly in accord with structure **5** and not that of its valence tautomer **6**. Thus, its longest wavelength absorption in the ultraviolet was a broad band centered around 350 nm and there was no absorption in the visible region analogous to that of the dihydropyrenes.[4] Similarly, its nmr spectrum showed the signal for the aromatic protons in the usual region, with the vinyl protons as a singlet at τ 3.28 and the NCH_3 protons as a singlet at τ 6.98. These properties are in accord with structure **5** and indicate that valence tautomerization to **6** is not occurring to any significant degree at room temperature. In this respect the behavior of *N*-methyl-1,9-ethenophenothiazine is quite analogous to that of 8,16-oxido[2.2]metacyclophane-1,9-diene (**1**)[6] and 8,16-imino[2.2]metacyclophane-1,9-diene (**2**).[7]

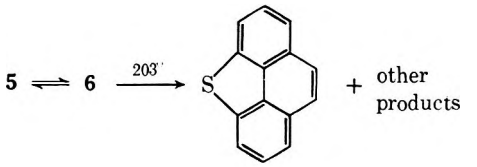
Both **1** and **2** underwent thermal rearrangements which were most readily explained by postulating isomerization to the corresponding valence tautomers **3** and **4** followed by either expulsion of the heteroatom to give pyrene (**17**) or migration of the heteroatom to the periphery as in **18**. It was of interest to see whether



17 18

5 would exhibit a similar rearrangement or expulsion of the bridging nitrogen atom.

The first evidence was derived from the mass spectrum of **5**. In addition to the expected molecular ion at *m/e* 237, there was a signal of major intensity at *m/e* 208, corresponding to loss of NCH_3. When **5** was heated at 203° in benzene, analysis by thin layer chromatography showed five products were formed with the major one being phenanthro[4,5-*bcd*]thiophene (**19**).[10] A plausible interpretation for the formation of **19** at elevated temperatures would be valence tautomerization of **5** to **6** followed by expulsion of the bridging NCH_3 group. Whether any of the other products formed in this thermal reaction correspond to the various structures possible for migration of the NCH_3 group was not determined due both to lack of material and lack of authentic samples for comparison.



19

Despite the additional ring strain which must be present in **5**, as indicated from molecular models, the formation of **5** and its thermal behavior are quite analogous to the corresponding metacyclophane derivative **2**.

Experimental Section[11]

1,10-Oxalylphenothiazine (8).—To a boiling solution of 30 ml of oxalyl chloride in 200 ml of benzene under a nitrogen atmosphere there was added dropwise over a period of 45 min a solution of 44.0 g of phenothiazine in 600 ml of benzene. The resulting solution was boiled under reflux an additional 4.5 hr and then concentrated under reduced pressure. The remaining pale green solid was taken up in 500 ml of carbon disulfide and added dropwise with stirring over a 2-hr period to a boiling slurry of

(10) We thank Professor Klemm for his kindness in providing us with a sample of phenanthro[4,5-*bcd*]thiophene (**19**) for comparison. For the preparation of **19**, see L. H. Klemm, D. R. McCoy, and D. R. Olson, *J. Heterocycl. Chem.*, **7**, 1347 (1970).

(11) Microanalyses were performed by Micro-Tech Laboratories and A. Bernhardt Microanalytical Laboratories. Spectral measurements were made with a Cary Model 15, a Beckman IR-5A, a Varian A-60, and a CEC-110-21B. We thank the National Science Foundation for funds used toward the purchase of the Varian A-60 and the CEC-110-21B mass spectrometer.

50 g of aluminum chloride in 300 ml of carbon disulfide. When addition was complete, the reaction mixture was boiled under reflux an additional 16 hr. After the mixture had cooled to room temperature, the carbon disulfide was removed by decantation. To the remaining solid residue cooled in an ice bath there was added slowly 200 ml of concentrated hydrochloric acid followed by 200 ml of water. The resulting mixture was extracted repeatedly with chloroform (6 l., total). The combined chloroform extracts were washed with water, dried, and concentrated to give 56 g of a black solid. This was recrystallized from a benzene–methanol mixture to give 42 g (75%) of black crystals, mp 200–203°. A small sample was chromatographed over silica gel using a 1:1 benzene–hexane solution for elution to give black crystals: mp 203.0–203.5°; uv max (95% ethanol) 246 nm (ϵ 40,700) and 302 (6490); ir ($CHCl_3$) 1740 and 1725 cm^{-1} (C=O); nmr ($CDCl_3$) τ 1.28–1.47 (m, 1, Ar H), 2.54–3.12 (m, 6, Ar H).

Anal. Calcd for $C_{14}H_7NO_2S$: C, 66.39; H, 2.79; N, 5.53; S, 12.66. Found: C, 66.12; H, 2.83; N, 5.92; S, 12.71.

1-Carbomethoxyphenothiazine (10).—To a solution of 44.0 g of sodium hydroxide in 8 l. of water there was added with stirring 42.0 g of **8**. Solution was complete in about 1 hr. There was then added over a period of 20 min with stirring a solution of 40 ml of 30% hydrogen peroxide in 500 ml of water. The resulting solution was stirred at room temperature for 1 hr before acidification with concentrated hydrochloric acid. The yellow solid, which precipitated, was collected by filtration, dried, and redissolved in 10 l. of ether. To this was added dropwise with stirring an ethereal solution of diazomethane until there was no longer evidence of reaction. Concentration of the ethereal solution gave a yellow oil which was chromatographed over silica gel using a 1:1 benzene–hexane mixture as solvent. Elution of the main yellow band gave 37.0 g (65%) of yellow crystals: mp 114.0–114.5°; uv (95% ethanol) 241 nm (ϵ 21,900), 257 (22,100), 261 (22,300), and 320 (3540); ir ($CHCl_3$) 3330 (NH) and 1670 cm^{-1} (C=O); nmr ($CDCl_3$) τ −0.13 (s, 1, NH), 2.41 (q, 2, J = 8.0, J' = 1.8 Hz, Ar H), 2.90–3.52 (m, 6, Ar H), and 6.15 (s, 3, OCH_3).

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.41; H, 4.30; N, 5.43; S, 12.48.

1-Carbomethoxy-9,10-oxalylphenothiazine (11).—To a boiling solution of 10 ml of oxalyl chloride in 10 ml of benzene there was added dropwise a solution of 3.2 g of **10** in 50 ml of benzene and the resulting mixture was boiled under reflux overnight. After concentration the residual green solid was taken up in 50 ml of carbon disulfide and added dropwise over a period of 1 hr with stirring to a slurry of 4.0 g of aluminum chloride in 20 ml of carbon disulfide. The mixture was boiled under reflux with stirring for an additional 1 hr before removal of the carbon disulfide by decantation. The residual solid was cooled in an ice bath and decomposed by addition of 10 ml of concentrated hydrochloric acid with stirring followed by 20 ml of water. The mixture was extracted repeatedly with chloroform (600-ml total). After it had been dried over magnesium sulfate, the chloroform extract was concentrated to give a black solid. This was taken up in benzene and chromatographed over silica gel to give 0.8 g of recovered **10** plus 1.1 g (39%, based on unrecovered **10**) of black crystals. A sample of these was recrystallized from a benzene–methanol mixture giving very dark red crystals: mp 236–238°; uv (95% ethanol) 222 nm (ϵ 25,900), 253 (24,000), and 327 (3740); ir ($CHCl_3$) 1730 and 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_9NO_4S$: C, 61.74; H, 2.91; N, 4.50; S, 10.31. Found: C, 61.72; H, 3.00; N, 4.36; S, 10.21.

1,9-Dicarbomethoxyphenothiazine (12).—To a solution of 15 g of sodium hydroxide in 300 ml of water there was added 7.8 g of **11** with stirring. As soon as solution was complete, the mixture was diluted by addition of 200 ml of water and a solution of 8 ml of 30% hydrogen peroxide in 30 ml of water was added with stirring. When the mixture had been stirred for 15 min, it was acidified with concentrated hydrochloric acid and the yellow precipitate was collected by filtration. The carefully dried yellow solid was taken up in 200 ml of ether and an ethereal solution of diazomethane was added with stirring until no further reaction ensued. After concentration, the residual solid was taken up in benzene and chromatographed over silica gel to give 4.4 g (56%) of yellow crystals, mp 133–135°. A sample recrystallized from ether gave yellow plates: mp 134.5–135.5°; uv (95% ethanol) 225 nm (ϵ 24,800), 244 (19,500), 262 (17,300), and 390 (7250); ir ($CHCl_3$) 3260 cm^{-1} (NH) and 1710 (C=O); nmr ($CDCl_3$) τ −0.79 (s, 1, NH), 2.33 (q, 2, J = 7.5, J = 2.0 Hz, Ar H), 3.03 (q, 2, J = 7.5, J = 2.0 Hz, Ar H), 3.29 (t, 2, J = 7.5, J = 7.5 Hz, Ar H), and 6.04 (s, 6, OCH_3).

Anal. Calcd for $C_{16}H_{13}NO_4S$: C, 60.95; H, 4.16; N, 4.44; S, 10.15. Found: C, 61.07; H, 4.38; N, 4.44; S, 10.00.

***N*-Methyl-1,9-dicarbomethoxyphenothiazine (13).**—To a solution of 8.0 g of **12** in 300 ml of dry dioxane there was added 9 g of sodium hydride (59% dispersion in oil) and 70 ml of methyl iodide. The resulting mixture was boiled under reflux for 8 hr before destroying the excess sodium hydride by addition of methanol. Then, water was added and the mixture was extracted with ether. The combined ether extracts were washed with water, dried, and concentrated. The residual yellow solid was recrystallized from an ether–hexane mixture to give 8.0 g (95%) of pale yellow crystals: mp 104–105°; uv (95% ethanol) 223 nm (ϵ 20,900), 259 (17,100), and 338 (3280); ir ($CHCl_3$) 1725 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.58 (q, 2, J = 7, J = 2 Hz, Ar H), 2.78 (q, 2, J = 7, J = 2 Hz, Ar H), 3.03 (t, 2, J = 7, J = 7 Hz, Ar H), 6.03 (s, 6, OCH_3), and 6.75 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 62.00; H, 4.59; N, 4.25; S, 9.72. Found: C, 61.89; H, 4.59; N, 4.24; S, 9.93.

***N*-Methyl-1,9-bis(hydroxymethyl)phenothiazine (14).**—A solution of 6.1 g of **13** in 350 ml of ether was added dropwise with stirring over a period of 20 min to a boiling slurry of 4.5 g of lithium aluminum hydride in 450 ml of ether. After the mixture had boiled under reflux an additional 1 hr, it was cooled to 0° and 10 ml of a saturated aqueous sodium sulfate solution was added with stirring. The ether solution was decanted from the precipitated crystalline solid and the precipitate was washed twice with ether by decantation. Then the combined ether extracts were dried and concentrated yielding 5.2 g of a white solid. This, on recrystallization from an ether–hexane mixture gave 4.8 g (96%) of white needles: mp 118.0–119.5°; uv (95% ethanol) 245 nm (ϵ 16,500) and 283 (3300, sh); ir ($CHCl_3$) 3390 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.72–3.18 (m, 6, Ar H), 5.38 (q, 4, CH_2OH), 5.77 (s, 2, OH), and 7.08 (s, 3, NCH_3).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.93; H, 5.53; N, 5.13; S, 11.73. Found: C, 65.86; H, 5.63; N, 4.92; S, 11.68.

***N*-Methyl-1,9-bis(bromomethyl)phenothiazine (15).**—A solution of 4.7 g of **14** and 8 ml of phosphorus tribromide in 250 ml of benzene was boiled under reflux for 1 hr. After the solution had been cooled to 0°, 100 ml of ice water was added, the benzene layer was separated, and the aqueous layer was extracted with benzene. The combined benzene extracts were washed with water and then concentrated to give 6.9 g (100%) of a yellow solid. This was satisfactory for use in the next step without further purification. However, a sample was recrystallized from an ether–hexane mixture to give white crystals: mp 125.0–125.5°; nmr ($CDCl_3$) τ 2.52–3.05 (m, 6, Ar H), 5.15 (q, 4, CH_2Br), and 6.83 (s, 3, NCH_3).

Anal. Calcd for $C_{15}H_{13}Br_2NS$: C, 45.09; H, 3.31; N, 3.60; Br, 39.96; S, 8.04. Found: C, 45.27; H, 3.28; N, 3.51; Br, 40.06; S, 8.13.

***N*-Methyl-1,9-ethanophenothiazine (16).**—To a boiling solution of 5.5 ml of a 2.11 *N* solution of phenyllithium in benzene in 800 ml of ether was added dropwise with stirring a solution of 1.45 g of **15** in 80 ml of ether. The mixture was boiled under reflux an additional 1 hr and cooled, and water was added. Separation of the ether layer followed by concentration gave a tan solid. This was chromatographed over silica gel using hexane for elution to give 130 mg (16%) of white crystals. These, on recrystallization from methanol, gave white needles: mp 164–165°; uv (95% ethanol) 216 nm (ϵ 18,900), 234 (20,700), 267 (5720, sh), and 308 (3140); nmr ($CDCl_3$) τ 2.58–3.55 (m, 6, Ar H), 6.82 (q, 4), and 7.02 (s, 3, NCH_3); mass spectrum (70 eV) m/e 239.077 (mol wt calculated for $C_{15}H_{13}NS$, 239.077).

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.30; H, 5.48; N, 5.85; S, 13.37. Found: C, 75.15; H, 5.33; N, 5.96; S, 13.42.

***N*-Methyl-1,9-ethenophenothiazine (5).**—A mixture of 100 mg of **16**, 75 mg of *N*-bromosuccinimide, and a small amount of azobisisobutyronitrile in 30 ml of carbon tetrachloride was boiled under reflux for 1.5 hr. After the solution had cooled, it was filtered to remove the solids present and the filtrate was concentrated. The residual solid from the filtrate was taken up in 125 ml of benzene, 125 mg of 1,5-diazabicyclo[4.3.0]non-5-ene was added, and the mixture was boiled under reflux for 30 min. After the solution had cooled, it was washed with water and concentrated. The residual yellow oil was chromatographed over silica gel using a 1:9 benzene–hexane mixture as solvent. Elution of the main band gave 35 mg of a pale yellow oil: uv (cyclohexane) 248, 272.5, 284, 297, 309, 334, 342, and 362 nm

(because of the instability of 5 toward handling in the pure state, quantitative extinction coefficients were not obtained); nmr ($CDCl_3$) τ 1.95–3.50 (m, 6, Ar H), 3.28 (s, 2, CH=CH), and 6.98 (s, 3, NCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 237 (100) and 208 (26).

Anal. Calcd for $C_{15}H_{11}NS$: mol wt, 237.061. Found: (high-resolution mass spectrum), 237.061.

Thermal Decomposition of 5.—A solution of 8 mg of 5 in 0.5 ml of benzene was placed in a thick-walled tube, degassed, sealed, and heated in an oil bath maintained at 203 ± 0.5° for 20 hr. After the tube had been cooled, it was opened and the solution was concentrated. Analysis of the residue by tlc over silica gel using benzene for elution showed five components. The major component, also the one of highest R_f value (0.8), had a characteristic bright blue fluorescence. This was separated and rerun in a tlc comparison with an authentic sample of 19. Both showed the same blue fluorescence and both were identical in their tlc behavior.

Registry No.—**5**, 29939-42-2; **8**, 29939-43-3; **10**, 4063-33-6; **11**, 29939-45-5; **12**, 29939-46-6; **13**, 29939-47-7; **14**, 30115-51-6; **15**, 29939-48-8; **16**, 29939-49-9.

Intramolecular Nitrone–Olefin Cycloadditions. The Stereochemistry of Hexahydro-2,1-benzisoxazoline Formation[1]

Norman A. LeBel* and Eugene G. Banucci

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

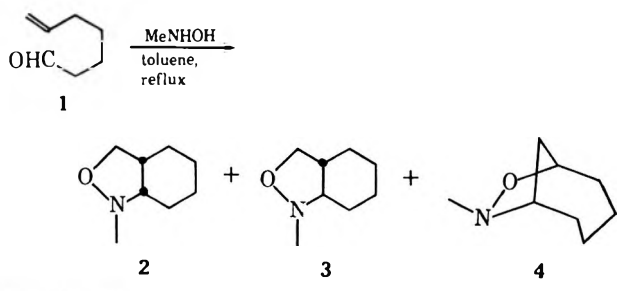
Received February 4, 1971

The stereochemistry of the intramolecular, 1,3-dipolar cycloaddition of several methyl-substituted *N*-methyl-*C*-6-heptenylnitrones was studied. The major product isoxazolidines were confirmed to have the 7-aza-8-oxabicyclo[4.3.0]nonane (3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline, hydrindan) skeleton. The stereochemistry at the ring fusion was assigned primarily on the basis of nmr spectral evidence. It was found that cyclization of the nitrones at 76° gave primarily the trans-fused isomers in all cases, and the ratio between cis and trans isomers was influenced mainly by substitution in the five-membered isoxazolidine ring. Interconversion of the isoxazolidines in the temperature range 180–300° occurred by retro-1,3-dipolar cycloaddition. At these temperatures the thermodynamically more stable cis-fused isomers predominated. These results correlate well with what is known concerning the relative stabilities of *cis*- and *trans*-hydrindan. The retro-1,3-dipolar cycloaddition of bicyclic isoxazolidines promises to be a valuable method for relative stability studies of fused heterobicyclo[*n*.3.0] derivatives.

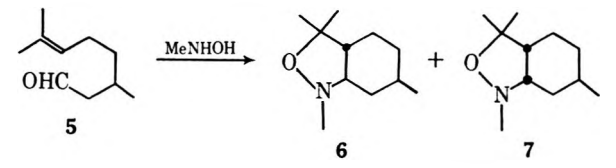
Part A

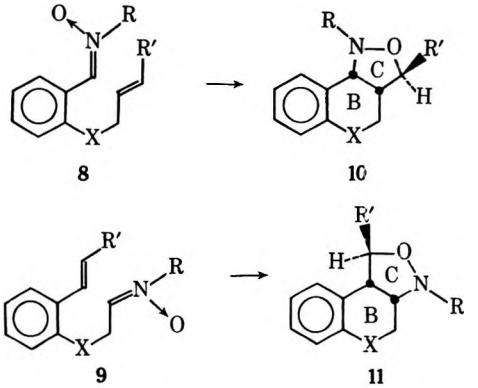
In the intramolecular 1,3-cycloaddition of *N*-alkyl-*C*-5-hexenyl- and -6-heptenylnitrones to give fused bicyclic isoxazolidine products, cis–trans isomerism at the ring juncture is a source of configurational ambiguity. For every case of product formation involved with the creation of a 2-aza-3-oxabicyclo[3.3.0]octane skeleton (*N*-alkyl-*C*-5-hexenylnitrones) a cis fusion was noted. Ring closure to give the more highly strained trans isomer would require a transition state of prohibitive energy.[2] However, with the homologous series mixtures of isomers having the azaoxabicyclo[4.3.0]nonane (5-aza-6-oxahydrindanyl, 3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline) ring system were obtained,[2a] and the relative amounts of the isomers were shown to be temperature dependent in at least one case.[2b]

For example, the unsubstituted compound **1** led to a 3:1:1 mixture of cis (**2**), trans (**3**), and bridged bicyclic isomers **4**, respectively.[2a] On the other hand,



condensation of (+)-citronellal (**5**) with *N*-methylhydroxylamine gave isomer ratios for **6**:**7** ranging from 97:3 at 25° to 87:13 at 138°.[2] In this case, predominant formation of the trans isomer is found. Very recently, a series of papers has revealed the intramolecular cyclizations of nitrones of the types **8** and **9**.[3] The products, tetrahydrobenzopyrano[4,3-*c*]isoxazoles (**10**, X = O), the analogous quinoline analogs (**10**, X = NH), and the tetrahydrobenzopyrano[3,4-*c*]isoxazoles (**11**, X = O), were found in almost every case to contain a cis juncture between the B and C rings. In only





(1) We gratefully acknowlege the National Science Foundation for support under Grant No. GP14114.

(2) (a) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, **86**, 3759 (1964); (b) M. E. Post, unpublished data.

(3) (a) W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1117, 4313 (1970); (b) W. Oppolzer and H. P. Weber, *ibid.*, 1121 (1970).

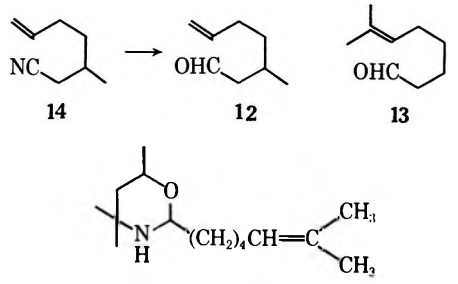
one example was a trans B/C ring fusion noted, and the product ratio was 51:17, cis to trans, respectively.[3a]

Any attempt at rationalization of these divergent data must take into account that nitrone–olefin cycloadditions are reversible.[4-6] We have shown previously that isoxazolidines **6** and **7** are configurationally stable at all temperatures used in their preparation (<200°) but that they are in equilibrium with a third isomer at higher temperatures. However, it was emphasized that the two isomers produced in the *nonstereoselective* cyclization of an analog of **8** (*vide supra*) were not interconverted at 110°.[3a] There remains, of course, the possibility that equilibrium had already been attained in this last example.

In this manuscript we summarize data which amplify and explain the stereochemical observations encountered in the formation of 6,5-fused heterocycles by way of this intramolecular cyclization reaction.

Results

Two additional olefinic aldehydes (**12** and **13**) intermediate in substitution between the two extremes **1** and **5**, were selected, and an analysis of the stereochemistry of the products from intramolecular 1,3 cycloaddition of the nitrones was conducted. The synthesis of 3-methyl-6-heptenal (**12**) was straightforward,



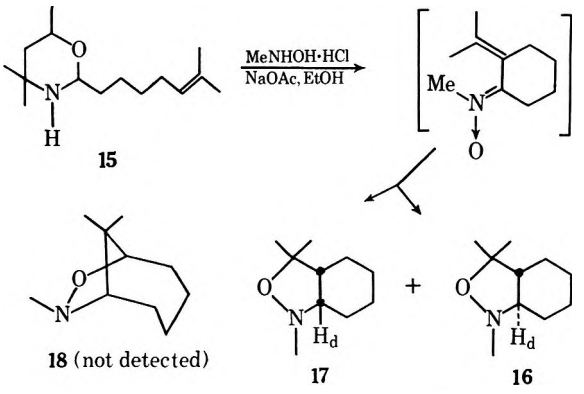
14 12 13

15

because the commercially available allylacetone could be easily homologated by way of the alcohol and then the bromide or tosylate to 5-cyano-1-hexene. Alcoholysis of this nitrile gave an ester which was reduced with lithium aluminum hydride to 2-methyl-5-hexen-1-ol. The *p*-toluenesulfonate of this alcohol was subjected to displacement with cyanide to obtain nitrile **14**. Reduction of 1-cyano-2-methyl-5-hexene (**14**) with diisobutylaluminum hydride (DIBAH) gave the desired aldehyde **12** (68% yield) which was characterized as the 2,4-dinitrophenylhydrazone.

Initial attempts to synthesize adequate quantities of 7-methyl-6-octenal (**13**) by a similar sequence proved unrewarding. The difficulty was encountered in the last step involving reduction of 7-cyano-2-methyl-2-heptene[7] with DIBAH which led to large amounts of tar. The Meyers' synthesis of aldehydes[8] seemed to offer a satisfactory alternative approach, and to this end quantities of the tetrahydro-1,3-oxazine (**15**) were prepared by borohydride reduction of the dihydrooxazine obtained by alkylation of the lithio salt of 2,4,-4,6-tetramethyl-4,5-dihydro-1,3-oxazine[8] with 6-bromo-2-methyl-2-hexene. However, acid-catalyzed hydrolysis of **15** resulted in the production of substantial amounts of nonvolatile residues, again attesting to the sensitivity of the olefinic aldehyde **13**. An obvious consideration was the possibility that the aldehydes from cleavage of tetrahydro-1,3-oxazines such as **15** could be trapped as nitrones if the reaction was carried out in the presence of N-substituted hydroxylamines. This hope was realized in the isolation of the known *N*-methyl-*C*-phenylnitrone from reaction between 4,4,6-trimethyl-2-phenyltetrahydro-1,3-oxazine and *N*-methylhydroxylamine hydrochloride in 95% ethanol containing some sodium acetate. Moreover, when the same reaction was carried out with 2-(5-hexen-1-yl)-4,4,6-trimethyltetrahydro-1,3-oxazine, the nitrone of 6-heptenal (**1**) was not isolated; rather, intramolecular 1,3-dipolar cycloaddition occurred *in situ;* and the isomeric isoxazolidines **2**, **3**, and **4** were obtained. Extension of this technique to other tetrahydrooxazines having olefinic C-2 substituents should greatly extend the scope of the intramolecular nitrone–olefin reaction.

Reaction of **15** with *N*-methylhydroxylamine under the same conditions gave a 23% yield of isoxazolidines **16** and **17** in the ratio 85:15, respectively. The two isomeric tetrahydrobenzisoxazolines **16** and **17** could be



15

18 (not detected) 17 16

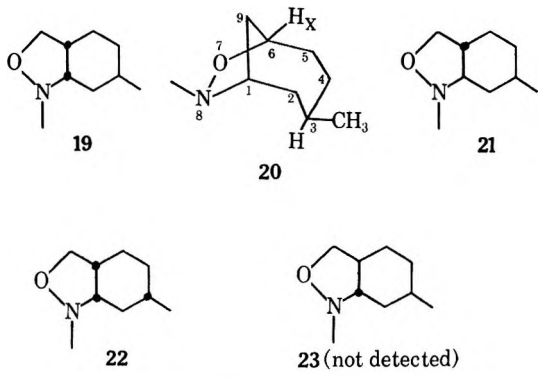
separated by elution chromatography. The major isomer **16** was collected and shown to be homogeneous by vpc and tlc. Reaction of the slightly impure **17** with methyl iodide in ether selectively removed all traces of the trans compound **16**, giving the homogeneous cis isomer **17**. Elemental analysis and spectral evidence showed that the two components were saturated isoxazolidines. As with the case of 6-heptenal (which leads to **2**, **3**, and **4**, *vide supra*), three isoxazolidines are theoretically possible: **16**, **17**, and the bridged bicyclic isomer **18** resulting from orientation in the opposite direction. Both of the isoxazolidines **16** and **17** were confirmed to have the fused (hexahydro-2,1-benzisoxazoline) skeleton rather than the alternative bridged bicyclic structure **18** because of the absence in their nmr spectra of proton absorption at lower field than δ 3.30. It was expected that the bridgehead hydrogen atom of **18** (α to oxygen, *i.e.*, at C-6) would result in absorption in the region around δ 4.5 (*cf.* **4**, δ 4.3[2a]).

The stereochemistry of the fused products **16** and **17** was deduced from the close nmr spectral similarities to those isoxazolidines resulting from condensation of (+)-citronellal and *N*-methylhydroxylamine. The de-

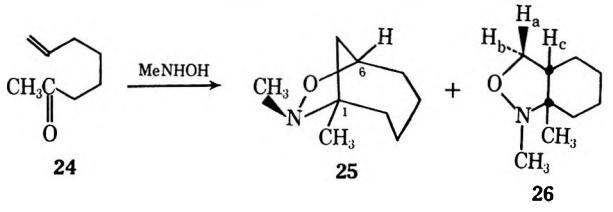
(4) G. Delpierre and H. Lamchen, *J. Chem. Soc.*, 4693 (1963).
(5) N. A. LeBel and T. A. Lajiness, *Tetrahedron Lett.*, 2173 (1966).
(6) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, **101**, 2548, 2559, 2568 (1968).
(7) Prepared by sequential homologation from 5-bromo-2-methyl-2-pentene, or by Beckmann fragmentation of 2,2-dimethylcycloheptanone oxime: R. T. Conley and B. E. Novak, *J. Org. Chem.*, **27**, 3196 (1962).
(8) A. I. Meyers, A. Nabeya, H. W. Adikes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969).

tails of the structural analysis are given in Part B, p 2445.

The condensation between 3-methyl-6-heptenal (12) and *N*-methylhydroxylamine afforded four isoxazolidines in the ratio 19.4:5.0:60.1:15.5 when the reaction was carried out in refluxing toluene (110°). The distribution in refluxing ethanol (76°) was 14.3:3.5:74.0:8.2. The products were separated by elution chromatography and were characterized as **19**, **20**, **21**, and **22**, respectively. Vpc indicated that the separated products (in order of elution) were homogeneous (except for **20**, which was about 89% pure), and elemental analysis combined with spectral evidence showed them to be saturated isoxazolidines. Six bicyclic isoxazolidines are theoretically possible. Four of these, represented by **19**, **21**, **22**, and **23**, have fused rings. Two, represented by the two possible isomers at C-3 of **20**, would have bridged structures. Structural assignments to all of these isomers were made on the basis of nmr comparisons with analogs of known stereochemistry and also by comparisons of the order of elution from alumina. The specifics are given in Part B.



Cyclization of the keto nitrone derived from 7-octen-2-one (**24**)[2a] was reexamined. A product was obtained which seemed homogeneous by vpc and tlc, but whose nmr indicated the presence to two isomeric isoxazolidines in the ratio 63:38. Over a limited temperature range (76–116°) this kinetic ratio does not seem to be temperature dependent. Assignment of structure to the minor isomer **25** was made possible by the presence of a distinctive doublet centered at δ 4.6 indicative of a single hydrogen on a bridgehead carbon next to oxygen (O–C-6–H). The nmr spectrum of the major component **26** shows a quartet for H_a but a triplet for H_b, which with higher resolution can also be shown to be a quartet. The rationale for the assignment is similar to that used for assigning the structure of isomer **22**, which is conformationally identical with that of **26**. The kinetic product ratios at 76° are summarized in Table I.



Thermal Isomerizations.—Most of the pure bicyclic isoxazolidines were pyrolyzed either neat or as 33% (w/w) solutions in tridecane or hexadecane at temperatures ranging from 180 to 235°. Mixtures of isomers were recovered and the relative compositions were determined by vpc analysis. These isomerizations can be attributed to retro-1,3-dipolar cycloadditions,[5] and approximate equilibrium values are summarized in Table II.

Table I
Kinetic Product Distributions for the Intramolecular Cycloadditions of *N*-Methyl-*C*-6-heptenylnitrones at 76°

Carbonyl compd	Ratio, trans:cis
5	93 (6):7 (7)
13	85 (16):15 (17)
12	76 (21):24 (19 + 22)
1	66 (3):34 (2)
24	0:100 (26 only)

Table II
Approximate Equilibrium Product Distributions of Bicyclic Isoxazolidines

Starting isoxazolidine	Temp, °C	Ratio (% compd) trans:cis:bridged
3	200	0 (3):100 (2 only):0
6 or 7	300	50 (6):50 (34% 7, 16% 30):0
16	300	30 (16):70 (17):0
21, 19, or 22	235	0 (21):92 (62% 19, 30% 22):8 (20)
26 + 25	285	0:100 (26 only):0

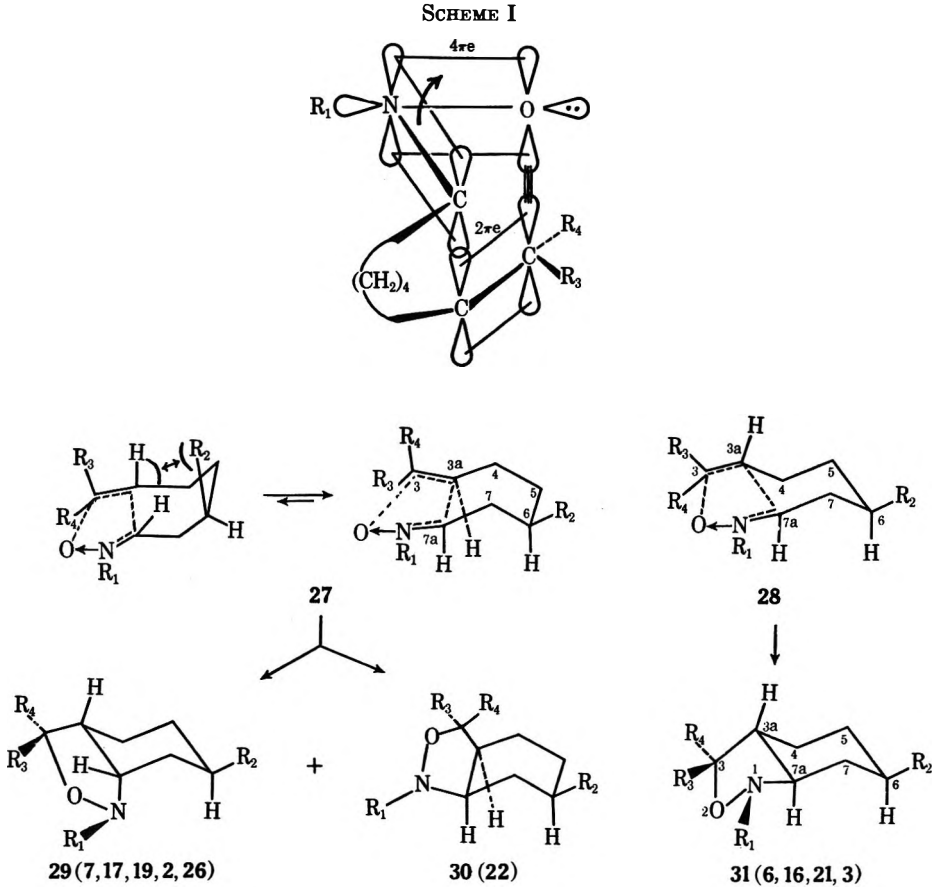
Discussion

The steric course of the intramolecular reaction to form the bicyclo[4.3.0]nonane system may now be considered. In the cyclization itself, two transition states, **27** leading to a cis ring fusion and **28** leading to the trans isomer, appear to have the most favorable conformations. Two different possibilities for orbital overlap leading to cis-fused products **29** and **30** are represented. Both of these require the incipient six-membered carbocyclic ring to adopt a twist conformation. On the other hand, **28** assumes a slightly deformed chair arrangement for this portion of the molecule in order to lead to trans-fused product **31**. In this analysis, we assume that syn $\rightleftarrows$ anti interconversions of the intermediate nitrones are rapid under the reaction conditions[9] and that the product ratios are dependent only upon the respective transition state energies (however, the rationale would not be significantly different if this were not the case). Apparently in the unsubstituted case (1 → **3** + **2**), the transition states are nearly equivalent in energy, since kinetic ring closure leads to only a slight favoring for trans (**3**) over cis (**2**) product. Introduction of a methyl substituent (R_2) in the methylene chain imparts a slight additional favoring of "trans" transition state **28** (relative to **27**) [**12** → **21** (major) + **19** + **22**], probably because of the increased eclipsed interaction in **27** that would result when R_2 is methyl as opposed to hydrogen. This same effect can be seen in comparing **13** (R_2 = H) → **16** + **17** and **5** (R_2 = CH_3) → **6** + **7** (Scheme I).

A different effect is observable upon the introduction of the *gem*-dimethyl (3,3-dimethyl) grouping in the potential five-membered ring. In terms of steric bulk, the group extending from C-3a in transition states **27** and

(9) For a review of such isomerizations, see M. Lamchen in "Mechanisms of Molecular Migrations," Vol. I, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1968, pp 54–58.

SCHEME I



28 ($R_1 = R_3 = R_4 = CH_3$; $R_2 = H$) should approximate a *tert*-butyl group. An equatorial position is therefore demanded by this grouping, eliminating any transition state conformation with axial orientation of this group and restricting considerably the flexibility of both cis products and cis transition states. In addition, the twist arrangement of the tetramethylene side chain will be associated with a C-4 methylene, C-3 methyl group ($R_4 = CH_3$) interaction. Transition state 28, however, accommodates a more favorable equatorial position for the *gem*-dimethyl grouping and minimizes serious eclipsing interactions. Experimentally, the trans:cis (16:17) distribution of 85:15 is not unexpected. Finally, in the cyclization of the nitrone derived from citronellal (5) both effects reinforce each other accounting for the overwhelming formation of the trans,trans product 6.

With the nitrone from ketone 24, a transition state similar to 28 would require the C-7a methyl group to be axial, a situation that is sufficiently unfavorable to cause transition state 27 leading to cis product 26 to become dominant (note also the high proportion of bridged bicyclic compound 25 formed).

The temperature effect, which results in increased proportion of the cis isomers in these examples, is readily understandable in terms of a higher entropy for the "cis" transition state(s) 27.

The conditions of the thermal isomerizations, involving for the most part high temperatures, sealed tubes, and vapor as well as condensed phases, mitigated against determination of accurate thermodynamic quantities. Nevertheless, it is quite apparent that the relative stabilities of the various isoxazolidine isomers at lower temperatures correspond fairly closely to the situation with hydrindan itself. Furthermore, the effect of substitution on these equilibria parallels the kinetic trends: *gem*-dimethyl in the five-membered heterocyclic ring and/or methyl substitution (not at the ring fusion) in the six-membered carbocyclic ring favor the trans isomers.

The data available for hydrindan indicate an enthalpy difference of only 1.07 ± 0.09[10a] or 0.58 ± 0.05 kcal/mol[10b] between *cis*- and *trans*-hydrindan, with the cis isomer having the higher enthalpy.[10] On the other hand, $-\Delta H^0$ (cis ⇄ trans) amounts to 2.7 kcal/mol for the decalins.[11] The difference in the two systems has been ascribed to the fact that in *cis*-hydrindan an axial and an equatorial bond of the adjacent ring-juncture atoms in the six-membered ring must be twisted toward one another to accommodate the more nearly planar five-membered ring. With *trans*-hydrindan, the corresponding twist involves two equatorial bonds, a distinctly higher energy process.[10a,12]

The relative stabilities of the hydrindans is highly dependent upon the relative entropies of the isomers. Below 466°K, *trans*-hydrindan predominates; however, above this temperature *cis*-hydrindan becomes more favorable.[10a] The entropy of the cis isomer is higher than that of the trans by 1.0[10b]–2.3 eu.[10a] Apparently with *trans*-hydrindan, the five-membered ring is more rigid than the same ring in *cis*-hydrindan; thus the five-membered ring is more capable of pseudorotation in the latter isomer leading to a higher entropy.

(10) (a) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **82**, 2553 (1960); (b) K. R. Blanchard and P. v. R. Schleyer, *J. Org. Chem.*, **28**, 247 (1963).

(11) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959).

(12) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 37.

It is probable that the vicinal substitution of small heteroatoms (*e.g.*, oxygen, nitrogen) in the five-membered ring of the hydrindanyl system has no large quantitative effect on the relative stabilities of the cis and trans ring junctures.[13] On this basis, the higher stability of **2** (cis) over **3** at temperatures above 100° (373°K) is reasonable. The same logic holds well for the methyl-substituted isoxazolidines **19**, **21**, and **22**. Here again, the cis-fused ring juncture is favored in pyrolysis to the virtual exclusion of the trans isomer. In the case of the *gem*-dimethyl compounds, **6** and **7** from **5** and **16** and **17** from **13**, the substitution of two methyl groups on the five-membered ring should lower substantially the entropy difference between the cis and trans isomers, since the large steric bulk of this grouping should inhibit pseudorotation in the cis compound. Stereomodels confirm this logic since the *gem*-dimethyl grouping must maintain an equatorial position. As entropy effects diminish, the slight enthalpy difference favoring the trans isomer appreciates. Therefore, in the citronellal system, the additional methyl group in the carbocyclic ring only slightly increases the free energy of the cis isomers, but this appears to be sufficient to allow this to be the one case where the trans isomer is the most thermodynamically stable up to 300°.

The 8-methylhydrindan system may be approached in the same way as were the previous cases. It is clear from equilibration studies that the cis isomer has the more negative free energy in this system.[14] Substitution of the 8-methyl group into *trans*-hydrindan would be expected to increase its heat content more than would the same substitution in the cis system, because only in the latter can the methyl group be put into a favorable equatorial position[15] (*i.e.*, there are more gauche butane interactions in the trans). Thus, in this work we find that *cis*-1,7a-dimethylhexahydrobenzisoxazoline (**26**) is the kinetically and thermodynamically favored isoxazolidine from 7-octen-2-one (**24**).

As for the cyclizations of compounds **8** and **9**,[3] it seems reasonable to expect that the observed cis isomers are favored both kinetically and thermodynamically, probably because of the two sp^2 hybridized carbon atoms associated with the fused benzene ring and also because of the additional heteroatom. In our own work, this effect has been noted in that *cis*-1,3,-3,6-tetramethyl-3a,4,5,7a-tetrahydro-2,1-benzisoxazoline (analogous to **7** but with a Δ^6 double bond) was the major kinetic product from the intramolecular cycloaddition of the nitrone from citral, and this cis-fused compound was the only isomer found after thermal isomerization.[5]

Experimental Section[16]

N-**Methylhydroxylamine**.—The zinc dust–ammonium chloride procedure of Beckmann[17] for the reduction of nitro compounds to hydroxylamines was employed. Alternatively, commercial grade *N*-methylhydroxylamine hydrochloride (Aldrich Chemical Co.) was used without further purification.

3-Methyl-6-heptenal (**12**).—Into a three-necked, round-bottomed flask equipped with an addition funnel, low temperature thermometer, stirrer, and a Friedrich's condenser with a nitrogen outlet was placed a solution of 24.0 g (0.195 mol) of 1-cyano-2-methyl-5-hexene (**14**) in 250 ml of ether. The system was flushed with nitrogen, and a solution of 33.5 g (0.234 mol) of diisobutylaluminum hydride (DIBAH) (Texas Alkyls, Inc.) in 50 g of hexane was added dropwise at 0°. After the addition was completed, the ice bath was removed and the mixture was stirred for 0.5 hr at room temperature. The mixture was then recooled and 10% sulfuric acid was added slowly until the mixture became acidic. After stirring for 0.5 hr at 25°, the organic layer was separated and the aqueous solution was extracted twice with ether. The extract was washed with saturated sodium bicarbonate solution followed by brine, dried (Na_2SO_4), concentrated, and distilled to give 18.0 g (65%) of aldehyde **12**: bp 35–36° (6 mm); ir 2720, 1725, 1625, 985, and 900 cm^{-1}.

Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.19; H, 11.14.

Treatment of the aldehyde, with ethanolic 2,4-dinitrophenylhydrazine produced the 2,4-dinitrophenylhydrazone, which melted at 64.5–66.0° after recrystallization from ethanol.

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.90; H, 5.87; N, 18.30. Found: C, 54.84; H, 5.92; N, 18.06.

1,6-Dimethylhexahydro-2,1-benzisoxazoline (**19–22**). **Method A**.—To a 500-ml flask, equipped with a stirrer, Dean-Stark water separator, Friedrich's condenser, and addition funnel, was added 220 ml of dry toluene. The toluene was heated to reflux and 12.6 g (0.10 mol) of 3-methyl-6-heptenal (**12**) was added all at once followed immediately by the dropwise addition of a solution of *N*-methylhydroxylamine, prepared in the following manner.

To a cold solution of 10.0 g (0.12 mol) of *N*-methylhydroxylamine HCl in 15 ml of dry, reagent grade methanol was added rapidly 9.84 g (0.18 mol) of dry sodium methoxide with vigorous stirring. The cooling bath was removed, and the mixture was stirred at room temperature for 0.5 hr and filtered, and the filter cake was washed with 4 ml of methanol. The combined filtrate and wash were refiltered and mixed with 65 ml of toluene. The resultant two-phase system was then added to the aldehyde in refluxing toluene over a 3-hr period. Two 25-ml portions of azeotrope were removed during the addition, combined, and recycled. Following the recycle, an additional 40 ml of distillate was removed.

The mixture was stirred at reflux overnight and was then cooled to room temperature (total reaction time, 19 hr). The solution was extracted with four 40-ml portions of 10% HCl. The acid extract was back-washed with 60 ml of pentane, 60 ml of ether, and again with 60 ml of pentane. The aqueous acidic solution was basified with 30% KOH and was extracted with six 70-ml portions of pentane. The pentane extract was washed twice with 100 ml of water and dried ($MgSO_4$). The extract was concentrated and the residue was distilled at 72–74° (5 mm) to give 12.41 g (80.5%) of distillate. Examination of the distillate by vpc (column C) at 110° showed the four products **19**, **20**, **21**, and **22** in the ratio 19.4:5.0:60.1:15.5, respectively. The isomers were separated by elution chromatography using Merck alumina (acid washed) and were shown to be homogeneous by vpc.

cis,trans-**1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**19**): bp 72.0° (5.0 mm); $n^{25}D$ 1.4682; mass spectrum *m/e* (rel intensity) 155 (98, M^+), 154 (45), 140 (10), 98 (100), 84 (35), 73 (35), 70 (55), 67 (25), 60 (15), 57 (20), 55 (30), 42 (45), 41 (30); nmr δ 0.94 (d, 3, J = 6 Hz, C-6 CH_3), 2.77 (dd, 1, J = 7.5, 2.5 Hz, H_b), 4.20 (dd, 1, J = 7.5, 6 Hz, H_a).

3,8-Dimethyl-7-oxa-8-azabicyclo[4.2.1]nonane (**20**): bp 72.5° (5.0 mm); $n^{25}D$ 1.4711; mass spectrum *m/e* (rel intensity) 155 (70), 154 (11), 140 (11), 109 (27), 100 (18), 98 (30), 84 (100),

(13) For recent comments, see (a) C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. IV, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1969, Chapter 2; (b) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).

(14) W. E. Backmann and A. S. Dreiding, *J. Amer. Chem. Soc.*, **72**, 1323 (1950).

(15) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

(16) Melting points and boiling points are uncorrected. The ir spectra were determined with a PE Model 237-B Infracord recording spectrophotometer, using sodium chloride plates for the liquid films and 0.1-mm matched cells for CCl_4 or $CHCl_3$ solutions. The analyses were by Midwest Microlabs, Indianapolis, Ind. Nmr determinations were carried out on Varian Models A-60A or T-60 instruments. Approximately 30% (w/v) solutions in CCl_4 or $CHCl_3$ were employed with TMS as the internal standard. Mass spectra were determined with a AEI Model MS-902 double focusing spectrometer at 70-eV ionization potential and 100-μA emission. Vpc analyses were carried out on ar. HP Model 5750 dual flame ionization unit with a 6 ft × 1/8 in. aluminum column containing 8% (w/w) Dow Polyglycol E-20M on Chromosorb W (column A) and an 8 ft × 1/8 in. aluminum column containing 20% (w/w) E-20M on Chromosorb W (column B). Additional vpc analyses were performed on a PE Model F-11 flame ionization unit with a 50 ft × 0.020 in. stainless steel column containing XE-60 liquid phase (column C). Nitrogen was the carrier gas at 4 psig.

(17) E. Beckmann, *Justus Liebigs Ann. Chem.*, **365**, 204 (1909).

81 (16), 73 (50), 70 (16), 67 (27), 57 (30), 55 (26); nmr δ 1.0 (d, 3, $J \leq 2$ Hz, C-3 CH_3), 2.67 (s, 3, NCH_3), 4.70 (d br, 1, $J \sim 7$ Hz, O–C-6–H).

trans,trans-**1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**21**): bp 73.5° (5.0 mm); $n^{25}D$ 1.4681; mass spectrum *m/e* (rel intensity) 155 (96), 154 (67), 140 (9), 112 (16), 109 (34), 98 (88), 95 (18), 86 (56), 84 (100), 81 (30), 73 (53), 70 (30), 68 (26), 67 (42), 57 (98), 56 (87); nmr δ 1.03 (d, 3, J = 6 Hz, C-6 CH_3), 2.73 (s, 3, NCH_3), 3.62 (m, 1, H_b), 4.08 (m, 1, H_a).

cis,cis-**1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**22**): bp 73.0° (5.0 mm); $n^{25}D$ 1.4705; mass spectrum *m/e* (rel intenstiy) 155 (89), 154 (56), 99 (23), 98 (100), 85 (23), 84 (39), 81 (27), 73 (32), 70 (23), 68 (24), 67 (30), 57 (24), 55 (41), 42 (64), 41 (56); nmr δ 0.97 (d, 3, C-6 CH_3), 2.70 (s, 3, NCH_3), 3.63 (dd, 1, J = 7.3, 8 Hz, H_b), 4.20 (dd, 1, J = 7.3, 9 Hz, H_a).

Isoxazolidine **21** on treatment with methyl iodide in ether gave a methiodide, which on recrystallization from ethanol showed mp 135.5–136.5°.

Anal. Calcd for $C_{10}H_{20}NOI$: C, 40.40; H, 6.73; N, 4.71. Found: C, 40.64; H, 6.70; N, 4.70.

Method B.—A mixture of 9.8 g (0.12 mol) of anhydrous sodium acetate and 200 ml of absolute ethanol was brought to reflux, and 12.6 g (0.10 mol) of 3-methyl-6-heptenal (**12**) was added all at once, followed immediately by the dropwise addition of 10.0 g (0.12 mol) of *N*-methylhydroxylamine HCl in 65 ml of absolute ethanol over a period of 1 hr. After 75% of the *N*-methylhydroxylamine solution had been added, 42.6 g (0.30 mol) of anhydrous sodium sulfate was added, and the addition was completed. The mixture was stirred at reflux for 40 hr, cooled to 50°, and filtered. The filtrate was concentrated at atomospheric pressure to 30 ml and poured into 200 ml of pentane. The solution was then extracted with five 20-ml portions of 10% HCl and the extracts were combined and back-washed with ether. The aqueous acidic layer was basified with 40% KOH and extracted with pentane. The combined extract was washed with brine, dried, concentrated, and distilled at 72–74° (5 mm) to give 10.7 g (69.2%) of product. Examination of the distillate by vpc (column C, 110°) showed the four isomers **19**, **20**, **21**, and **22** in the ratio 14.3:3.5:74.0:8.2.

2-(6-Methyl-5-hepten-1-yl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine.—A 500-ml, three-necked flask equipped with a magnetic stirring bar, an addition funnel topped with a rubber septum, and a nitrogen-inlet tube was successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14.1 g (0.10 mol) of 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine[18] was added from a syringe. The stirred solution was cooled to −78° and 47 ml (0.11 mol, 2.35 *M*) of *n*-butyllithium in hexane (Lithium Corp.) was injected into the funnel. The *n*-butyllithium solution was added dropwise over 1 hr. Upon complete formation of the anion, 19.5 g (0.11 mol) of 6-bromo-2-methyl-2-hexene in 25 ml of anhydrous THF was injected into the funnel and was slowly added over 0.5 hr. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then poured into 100 ml of ice water and acidified with 9 *N* HCl. The acidic solution was extracted with pentane and then made basic by the slow addition of 40% NaOH. The resulting oil was extracted with ether and the extract was dried (K_2CO_3). The solution was concentrated to give the crude dihydro-1,3-oxazine in 89% yield (21.0 g), ir 1660 cm^{-1} (C=N). The product was used without further purification.

2-(6-Methyl-5-hepten-1-yl)-4,4,6-trimethyltetrahydrooxazine (**15**).[18]—In a 600-ml beaker were placed 100 ml of THF, 100 ml of 95% ethanol, and the crude dihydrooxazine (21 g) obtained in the preceding experiment. The mixture was cooled to between −35 and −40°, and HCl (9 *N*) was added to the stirred solution until an approximate pH of 7 was obtained. Sodium borohydride solution was prepared by dissolving 3.78 g (0.10 mol) in a minimum amount of water to which 1 drop of 40% NaOH was added. The sodium borohydride solution and the 9 *N* HCl were added alternately to the stirred mixture so that pH 6–8 was maintained. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of the borohydride was completed, the solution was stirred with cooling for an additional hr (a pH 7 was maintained by the occasional addition of HCl). The contents were then poured into 100 ml of water, made basic, and extracted with ether. The organic extract was washed with brine, dried, and concentrated to give 20.8 g of crude tetrahydrooxazine **15** which was used without further purification.

cis- **and** *trans*-**1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**16 and 17**). *In Situ* **Formation and Cyclization of Nitrones Derived from Substituted Tetrahydrooxazines.**—In a three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser, and an addition funnel were placed 23.9 g (0.1 mol) of crude tetrahydrooxazine **15**, 3.28 g (0.04 mol) of anhydrous sodium acetate, and 200 ml of 95% ethanol. *N*-Methylhydroxylamine HCl (8.35 g, 0.1 mol) in 100 ml of ethanol was added dropwise over 1 hr. The solution was brought to reflux and stirred for 24 hr. The mixture was allowed to cool and was poured into 200 ml of water. After acidification to pH 2 with 10% HCl, the mixture was extracted with ether and basified with 20% NaOH. The basic solution was then extracted with ether, and the extract was washed with brine, dried, and concentrated. Distillation at 72–78° (15 mm) afforded 7.8 g of basic materials, determined to be three components by vpc on column C (110°). Further purification by elution chromatography using Merck alumina (acid washed) and pentane as eluent gave 3.8 g [22.5% overall yield, 58.5% based on the amount of aldehyde **13** (DNP, mp 90–91°) produced in separate experiments] of material showing no hydroxyl absorbance in the ir. Only two components were seen on vpc, **16** and **17**, in the ratio 85.0:15.0, respectively. The isomers were separated by chromatography and were shown to be homogeneous by vpc and tlc on silica gel using a chloroform–hexane solvent system.

cis-**1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**17**): bp 76.0° (5 mm); $n^{25}D$ 1.4633; mass spectrum *m/e* (rel intensity) 169 (76), 168 (14), 155 (27), 154 (100), 152 (17), 140.5 (m*), 123 (94), 112 (28), 98 (46), 95 (42), 86 (89), 81 (62), 73 (49), 70 (62), 68 (49), 67 (65), 60 (42), 58 (68), 43 (99); nmr δ 1.23 (s, 3, CH_{3b}), 1.32 (s, 3, CH_{3a}), 2.78 (s, 3, NCH_3), 3.05 (m, 1, H_d).

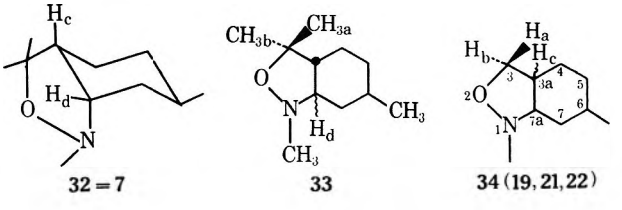
trans-**1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**16**): bp 76.0° (5 mm); $n^{25}D$ 1.4621; mass spectrum *m/e* (rel intensity) 169 (14), 156 (10), 155 (81), 154 (60), 123 (54), 109 (19), 99 (20), 98 (100), 95 (26), 86 (33), 84 (39), 82 (24), 81 (41), 67 (47), 55 (69), 43 (70), 42 (91), 41 (69); nmr δ 1.00 (s, 3, CH_{3b}), 1.23 (s, 3, CH_{3a}), 2.57 (s, 3, NCH_3).

The latter compound, when stirred in ether with methyl iodide, formed a methiodide. After recrystallization from ethanol it showed mp 188.5–189.5°.

Anal. Calcd for $C_{11}H_{22}NOI$: C, 42.44; H, 7.07; N, 4.50. Found: C, 42.60; N, 6.89; N, 4.34.

Part B

Structural Assignments of Bicyclic Isoxazolidines.—Condensation of citronellal and *N*-methylhydroxylamine followed by *in situ* cyclization in ethanol provided a 93:7 ratio of trans,trans (**6**) and cis,trans (**7**) isomers, respectively. This first study established the absolute configuration of the major isomer **6** by degradation to (−)-*N*,*N*-dimethylmenthylamine,[2a] and the cis,trans structure for **7** was confirmed later, primarily (but not exclusively) on the basis of the unique low field resonance (δ 2.78) for the equatorial hydrogen α to nitrogen (see H_d in conformational structure **32**).[5]



32 = 7 **33** **34 (19, 21, 22)**

By analogy, therefore, assignment of cis stereochemistry to isoxazolidine **17** is readily made by its distinctive H_d resonance at δ 2.95. No absorbance below δ 2.50 is found in the spectrum of **16**. Additional evidence is found in the relative chemical shifts of the geminal methyl substituents. In a series of eight, pre-

(18) Procedures for the preparation, alkylation, and reduction of dihydro-1,3-oxazines were kindly supplied by Professor A. I. Meyers; see also ref 8.

viously synthesized,[2,5] fused bicyclic isoxazolidines with this grouping (structure **33**) $\Delta\nu_{trans}$ (CH_{3a}, CH_{3b}) = 10–14 Hz, whereas $\Delta\nu_{cis}$ (CH_{3a}, CH_{3b}) = 4–6 Hz. For isoxazolidine **16**, $\Delta\nu$ (CH_{3a}, CH_{3b}) = 12 Hz supporting the trans ring fusion assignment. Isoxazolidine **17** shows this value as 4 Hz, confirming cis stereochemistry. The stereochemical assignments are further supported by the observation of a greater thermodynamic stability at temperatures above 200° (*vide infra*) for **17** relative to **16**, and the fact that **17** (axial R_3N:) is eluted from alumina before **16** (equatorial R_3N:).

Examination of **20** by nmr showed a distinctive doublet at δ 4.65, characteristic of a single bridgehead hydrogen (H_x) adjacent to oxygen. The area around δ 3.1 also showed an isolated multiplet, undoubtedly due to the bridgehead hydrogen adjacent to nitrogen (C-1 H). Further evidence providing a distinction between isomers at C-3 was not available; however, the exo stereochemistry for the C-3 methyl group of **20** is most reasonable.

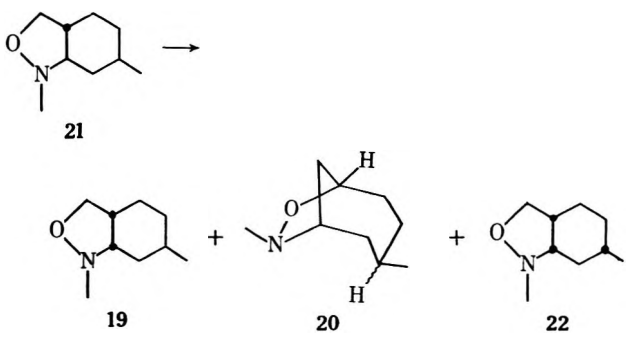
Assignment of structure to the remaining fused, bicyclic isomers was made possible through examination of the nmr spectra between δ 3.3 and 4.3. In this region, resonance characteristic of the methylene protons of the $NOCH_2$ moiety absorb. The multiplets for each of these hydrogens (H_a and H_b in structure **34**) are well separated, and from earlier work[5] we assign the lower field resonance to the exo C-3 proton H_a. For both the compounds **19** and **22** (general structure **34**), two well-spaced multiplets are seen. The absorbances for these protons in **34** can be treated as the AM portion of a AMX spectrum. Examination of stereomodels of the two cis diastereomers **19** and **22** indicates that H_c is in a bisecting conformation relative to H_a and H_b for isomer **19**. This is not the case for **22**, since the methylene group in question is now axially oriented as opposed to the equatorial position it occupies in **19**. Utilizing the Karplus equations, a predicted pattern may be derived for each compound. These predicted spectral patterns are very closely approximated by the experimental spectra; the multiplet for H_b of **19** appears as a pair of doublets, whereas the pattern for H_b of **22** resembles a triplet. This latter occurs since the coupling constant for J_{H_c,H_b} ($\phi \sim 150°$) is nearly equal to J_{H_a,H_b}; the two center lines overlap resulting in the observation of a near 1:2:1 triplet. The H_a resonance of **22** shows as a doublet of doublets rather than a triplet because J_{H_a,H_c} ($\phi \sim 30°$) is smaller than J_{H_a,H_b}.

Assignment of stereochemistry to the final isomer **21** was more difficult because of the poorer resolution of the H_a and H_b multiplets. However, further examination of stereomodels indicated that the other possibility, isomer **23**, would be forced to adopt a twist conformation in order to maintain the methyl group of the cyclohexane ring in an equatorial position. Thus, **23** would be a higher energy stereoisomer, and the transition state leading to it would be of higher energy than that leading to **21** (to the extent that the transition states resemble the respective products). Newman projections of the predicted most stable conformations of **21** and the alternative **23** suggest substantial differences in the comparative dihedral angles between H_a and H_c and H_b and H_c. An analysis similar to that used above would suggest that the H_a,H_b pattern for **21** should very much resemble that of **22**, except that H_a (the lower field multiplet) would now appear as a near triplet, and H_b would show the four-line pattern. The experimental spectrum of the only isolated trans isomer is not inconsistent with this prediction.

An isomer having the same relative stereochemistry as **23** is a possible product from the intramolecular cycloaddition of (+)-citronellal-*N*-methylnitrone; however *this compound was not produced* in the ring closure reaction. This compound was obtained by an alternative route;[5] however, it was not present to any extent in the interconversion studies of **6** and **7**, and it was very readily hydrogenolyzed. Thus the cis,trans stereochemistry present in structures like **33** and **34** represents an unstable isomer, and the trans-fused compound isolated in this work must be **21** rather than **23**.

The order of elution of the isomers from acid-washed alumina also supports the stereochemical assignments; **19** (cis fusion, axial R_3N–equatorial CH_2O) is eluted before **22** (cis fusion, equatorial R_3N–axial CH_2O) which is eluted before **21** (trans fusion, equatorial R_3N–equatorial CH_2O). Finally, the trans,trans isomer **21** reacts rapidly with methyl iodide to give the quaternary salt in the presence of **19** and **22**, which undergo only slow conversion.

Equilibration Studies.—Pyrolysis of pure **21**, either neat or as a 33% (w/w) solution in tridecane resulted in the formation of **19**, **20**, and **22**. After the complete

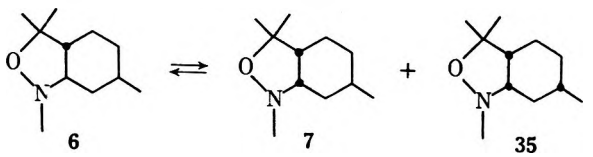


disappearance of isomer **21** (219 hr at 180°, 12 hr at 200°, 0.75 hr at 235°), a distribution consisting of compounds **19**, **20**, and **22** in the approximate ratio 39:10:51, respectively, was obtained. Further pyrolysis of this mixture led to a 62:8:30 mixture of the respective isomers. Interconversion at 235° of each of the pure isomers **19**, **20**, and **22** also led to this final approximate ratio.

Pyrolysis of pure **16** (trans, 3,3-dimethyl) in hexadecane resulted in a thermal isomerization of the isoxazolidine to an equilibrium concentration of isomers **16** and **17** (cis). At 300° the isomer ratio was found to be approximately 30:70 trans (**16**):cis (**17**) isomers, respectively. This equilibrium could also be attained at lower temperatures (235°, 270°) by longer reaction times. However, at temperatures above 300° rapid decomposition of material occurs. At reaction temperatures less than 235°, the rate of isomerization was found to be extremely slow.

The isomerization of isoxazolidine **3** (trans, unsubstituted), on the other hand, was extremely rapid even at temperatures around 200°. The thermal equilibrations resulted only in the recovery of **2**, showing that the cis isomer **2** is the more thermodynamically stable species at these temperatures.

Previous studies with isoxazolidine **6** (trans,trans) indicated that the thermal isomerizations can be attributed to retro-1,3-dipolar additions which regenerate the unsaturated nitrones from the isoxazolidines.[5] In this series, pyrolysis of **6** resulted in the formation of two additional isomers, **7** (cis,trans) and **35** (cis,cis).



6 **7** **35**

The equilibrium concentration of isomers **6**, **7**, and **35** at 300° was found to be approximately 50:34:16, respectively, representing a trans:cis-fused ratio of about 50:50.

Finally, when the 62:38 mixture of **26** (cis, 7a-methyl) and **25**, respectively, the products of the keto nitrone cyclization, was pyrolyzed at 285° for 0.5 hr, the only detectable product was the cis-fused isomer **26**.

Experimental Supplement[16]

5-Cyano-1-hexene.—Allylacetone was reduced with sodium borohydride in 89% yield to give 5-hexen-2-ol, bp 138–139° (atmospheric pressure) (lit.[19] bp 138°). Reaction of this alcohol with phosphorus tribromide and pyridine in ether gave 5-bromo-1-hexene (58%), bp 131–134° (lit.[19] bp 142°). Conversion of 30.74 g (0.188 mol) of the bromide to the nitrile was carried out by heating at 80° with a solution of 10.2 g (0.21 mol) of sodium cyanide in 80 ml of dry DMSO for 0.5 hr. After work-up, distillation afforded 18.1 g (83%) of 5-cyano-1-hexene: bp 55–56° (6 mm); ir 3060, 2240, and 1650 cm^{-1}. This compound was also made by reaction of the *p*-toluenesulfonate of 5-hexen-2-ol with sodium cyanide in DMSO at 90°.

1-Cyano-2-methyl-5-hexene (14).—Alcoholysis of 5-cyano-1-hexene with refluxing anhydrous ethanol saturated with hydrogen chloride to which slightly more than 1 equiv of water was slowly added gave, after work-up, ethyl 2-methyl-5-hexenoate: bp 74–75° (6 mm); ir 3060, 1725, 1640, 990, and 910 cm^{-1}. Reduction with lithium aluminum hydride in ether afforded an 89% yield of 2-methyl-5-hexen-1-ol: bp 84–85° (8 mm); ir 3350, 3060, and 1645 cm^{-1}. The *p*-toluenesulfonate was prepared (89%, crude oil). Displacement of 86.0 g of the tosylate with sodium cyanide in DMSO at 90° gave 36.5 g (89%) of nitrile **14**: bp 65–66° (7 mm); ir 3075, 2240, 1630, 995, and 910 cm^{-1}.

Anal. Calcd for $C_8H_{13}N$: C, 78.04; H, 10.56; N, 11.36. Found: C, 78.00; H, 10.66, N, 11.24.

Vpc analysis on column B at 130° showed one peak. The identical compound was also prepared by pyrolysis at 550° of 1-cyano-1-carboethoxy-2-methyl-5-hexene, which in turn was obtained by alkylation of ethyl sodiocyanoacetate with 5-bromo-1-hexene.

5-Methyl-4-hexen-1-ol.—2-Methyl-3-carboxy-5,6-dihydropyran (mp 115°)[20] was decarboxylated by distillation at 150° and a 60% yield of 2-methyl-5,6-dihydropyran was obtained: ir 1670 cm^{-1} (sharp fingerprint region). Bromination of 98 g (1.0 mol) of this compound in 250 ml of ether at −55° gave a suspension of the dibromide which was added slowly to a stirred solution of 1.0 mol of methylmagnesium bromide. After 90-min additional stirring, the mixture was poured onto crushed ice and ammonium chloride. Separation of layers and work-up gave 165 g (86%) of crude 2,2-dimethyl-3-bromotetrahydropyran, which was used without further purification. To a stirred solution of 50 g (2.2 g-atoms) of finely divided sodium in ether was added dropwise 193 g (1.00 mol) of 2,2-dimethyl-3-bromotetrahydropyran in 500 ml of ether.[21] After completion of the addition water was added until two clear phases were obtained. The mixture was extracted with ether and the extract was dried, concentrated, and distilled at 62–63° (13 mm), yielding 98 g (86%) of 5-methyl-4-hexen-1-ol: ir 3350 (broad), 1385, and 1375 cm^{-1}.

(19) H. B. Wood and E. C. Horning, *J. Amer. Chem. Soc.*, **75**, 5511 (1953).

(20) J. Perkin, *J. Chem. Soc.*, **51**, 702 (1887).

(21) R. P. Linstead and E. N. Rydon, *ibid.*, 1995 (1934).

Alternatively, this compound could be prepared as follows. Reaction of methylmagnesium bromide with methylcyclopropyl ketone (Aldrich Chemical Co.) gave dimethylcyclopropyl carbinol. The alcohol was then rearranged to 5-bromo-2-methyl-2-pentene with 48% HBr in 80% yield.[22] The bromide was subsequently homologated by the regular route of cyanide displacement, hydrolysis, and reduction to give 5-methyl-4-hexen-1-ol in 23% overall yield.

6-Bromo-2-methyl-2-hexene.—A solution of 41.4 g (0.152 mol) of phosphorus tribromide in 100 ml of dry ether was slowly treated with 7.25 g (0.091 mol) of pyridine. The reaction mixture was cooled to −20° by means of a carbon tetrachloride–Dry Ice bath. 5-Methyl-4-hexen-1-ol (42.4 g, 0.372 mol), containing 2.5 g of pyridine, was added, and the mixture was stirred for 24 hr at room temperature. The mixture was transferred to a 500-ml side-necked flask, the ether was distilled, and the residue was pyrolyzed at 150° (50 mm). The pyrolysate was collected in a Dry Ice trap and diluted with an equal amount of water. The organic layer was separated and was washed with 10% HCl, followed by brine. The extract was dried, concentrated, and distilled to give 61.0 g (93%) of bromide: bp 67–68° (20 mm); ir 1665, 1385, and 1375 cm^{-1}.

1-Methyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (2, 3).—Reaction of tetrahydrofurfuryl chloride with sodium metal in ether produced 4-penten-1-ol, which was converted to 1-bromo-4-pentene by the phosphorus tribromide–pyridine procedure. The bromide was used to alkylate 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine in the manner previously described for the production of **15**. The crude dihydrooxazine was subsequently reduced to the tetrahydrooxazine, which was used without further purification.

A method similar to that described for the production of **16** and **17** was employed to convert the crude tetrahydrooxazine to a mixture of isomeric isoxazolidines. Reaction of 4.18 g (0.050 mol) of *N*-methylhydroxylamine HCl, 3.28 g (0.04 mol) of sodium acetate, and 23.9 g (0.11 mol) of tetrahydrooxazine in 200 ml of 95% ethanol gave 5.0 g (38.5%) of a 30:57:13 ratio of isomers **2**:**3**:**4**, respectively. The compounds were identified by admixture on vpc and spectral comparisons with a mixture of isomers prepared by the condensation of 6-heptenal and *N*-methylhydroxylamine.[2a] The latter cyclization, conducted in refluxing toluene for 4 hr, gave an isomer ratio of 42.4:42.3:15.3 for **2**:**3**:**4**, respectively. Continued refluxing in toluene for 15 hr converted this ratio to approximately 50:40:10. Pyrolysis of this mixture at 250° for 15 min gave only the cis isomer **2**.

Separation of Isomers. A. Elution Chromatography.—Generally, it was found that Merck acid-washed alumina provided the best separation for the isoxazolidines prepared in this study. A column was constructed of 1095 g of alumina. Purified pentane was the solvent and 35.0 g of the mixture of isomers **19**–**22** was placed on the column. Fractions of 1 l. were collected (see Table III). Rechromatography of fractions 8 and 9–11 afforded pure samples of isomers **20** and **22**, respectively.

TABLE III

Fraction	Eluent (%)	Wt, g	% composition by vpc			
			19	**20**	**21**	**22**
1	Pentane					
2–4	Ether (1)	0.5	Only			
5	Ether (1)	0.8	95	5		
6	Ether (1)	1.3	93	5		2
7	Ether (2)	1.7	81	15		4
8	Ether (2)	0.7	5	85		10
9	Ether (2)	1.2		15		85
10	Ether (5)	3.9		10		90
11	Ether (5)	3.6		5		95
12–15	Ether (5)	6.2			60	40
16	Ether (10)	4.6			95	5
17–23	Ether (50)	6.7			Only	
		32.2 = 89.5%				

In similar fashion, a mixture of **16** and **17** could be separated. The column contained 425 g of alumina, with pentane as the solvent, and an 8.5-g quantity of the isomer mixture **16** and **17**

(22) A. M. Moreno and G. I. Fernandez, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **16**, 59 (1964); *Chem. Abstr.*, **63**, 4333*f* (1965).

Table IV
Equilibration of 17 in Hexadecane

Time, hr	Temp, °C	% 16	% 17	% dec
3	235	4	96	5
25		37	63	25
48		44	56	33
60		60	40	38
74		67	33	45
91		70	30	62
1.2	270	25	75	11
2.5		65	35	36
6.5		69	31	64
8.5		71	29	84
2.7	300	69	31	62
3.7		70	30	81
6.5		70	30	95

Table V
Thermal Isomerizations of 21 in Tridecane

Time, hr	Temp, °C	% 19	% 20	% 21	% 22	% dec
31	180	3.4	0.5	91.6	4.5	3
43.5		6.0	0.4	86.9	6.7	6
48		6.6	2.1	84.5	6.8	10
52		10.2	3.2	74.3	12.3	10
65		10.7	3.3	73.1	12.9	12
78.5		13.2	4.1	66.5	16.2	15
103		17.5	5.6	52.0	24.8	17
130		24.0	8.3	38.8	28.9	19
175.5		34.0	9.7	9.4	46.9	20
219		38.0	11.0		51.0	25
219		37.8	11.5		50.6	25
2	200	5.5	1.6	85.2	7.7	10
4.5		18.1	5.1	51.1	25.7	20
7		18.9	7.7	42.8	30.6	25
12		39.0	10.6		50.4	34
24		39.6	12.4		48.0	48
0.25	235	3.5		96.5		12
0.50		27.0	5.3	40.6	27.0	40
0.75		36.1	11.3	2.0	50.6	49
1.00		48.0	10.5		41.5	69
1.50		56.7	9.6		33.7	76
2.00		59.7	8.6		31.7	80

in the ratio 85.0:15.0 was separated. Fractions of 350 ml were collected, and a 90.5% recovery was realized.

B. Preferential Methiodide Formation.—To a solution of 0.37 g (0.0022 mol) of an isomer mixture containing **16** and **17** in the ratio 20:80, respectively, in 10 ml of ether, was added 0.38 g (0.0027 mol) of methyl iodide. The mixture was stirred at room temperature overnight and then filtered, and the filter cake was washed with ether. The combined filtrate and wash was concentrated and the residue was distilled at 76° (5 mm) to give 0.28 g (94.5%) of pure **17**.

***cis*-1,7a-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (26) and 1,8-Dimethyl-7-oxa-8-azabicyclo[4.2.1]nonane (25).**—From 8.3 g (0.066 mol) of 7-octen-2-one and an excess of *N*-methylhydroxylamine according to method A, there was obtained 7.0 g (68%) of basic material, bp 71° (4.5 mm), n^{25}D 1.4767. Vpc analysis on a variety of columns and tlc suggested that the material was homogeneous. However, the nmr spectrum indicated two isomers present in the ratio 62 (**26**):38 (**25**): nmr (100 MHz) δ 2.58 (s, **26** NCH_3), 2.63 (s, **25** NCH_3), $\Delta\nu$ = 6 Hz.

Anal. Calcd for $C_9H_{17}NO$ (a 38:62 mixture of isomers): C, 69.63; H, 11.04; N, 9.02. Found: C, 69.64; H, 11.16; N, 8.89.

Interconversions of Bicyclic Isoxazolidines at Various Temperatures.—The thermal rearrangements were conducted in a Wood's metal bath. Samples were placed in 8 × 10 × 200 mm Pyrex No. 8640 combustion tubes and purged with argon, and the tubes were sealed. The samples were generally prepared as 33% by weight solutions in hexadecane or tridecane, although limited samples of the minor isomers necessitated 10% by weight solutions. The solvent also functioned as an internal standard on vpc. In all cases runs in triplicate were performed, and periodic checks of the spectral properties of the components confirmed the vpc analyses. The results are given in Tables IV–VI.

Thermal Interconversions of 19, 20, and 22 at 235°.—Solutions of pure **19**, **20**, and **22** (10% by weight) in tridecane were employed and the results are tabulated in Table VII. No **21** was detected in any of the equilibrations.

Table VI
Thermal Isomerizations of 6 in Tridecane

Time, hr	Temp, °C	% 7 + 35	% 6	% dec
3	235	3	97	5
25		39	61	16
60		43	59	19
91		45	55	25
1.2	270	21	79	12
2.5		37	63	12
6.5		46	54	13
8.5		47	53	17
2.7	300	47	53	24
3.7		50	50	33
6.5		49	51	55

Table VII
Equilibration of 19, 20, and 22

Time, hr	% 19	% 20	% 22	% dec
	Equilibration of 19			
2.5	95.1	1.5	4.4	3
5.0	90.5	2.5	7.0	10
7.5	79.3	3.6	17.1	15
12.5	70.3	4.2	25.4	20
25.0	65.3	4.8	29.9	28
	Equilibration of 20			
2.5	31.9	22.4	45.7	11
5.0	50.4	16.4	33.2	29
7.5	62.8	6.2	31.0	38
	Equilibration of 22			
1.0	5.4	1.4	93.2	2
2.5	12.8	2.0	85.2	5
5.0	30.0	3.8	66.2	12
7.5	36.8	4.7	58.5	20
10.0	45.0	5.3	49.7	24
15.0	53.7	6.3	40.0	29
25.0	58.3	8.5	33.2	43

Thermal Equilibration of 16.—Pyrolysis of **16** in hexadecane at 300° for 2 hr gave a 70.5:29.5 ratio of **16** to **17**, respectively.

Thermal Interconversion of Isoxazolidines 26 and 25.—Pyrolysis of a 62:38 mixture of *cis*-isoxazolidine **26** and bicyclic isoxazolidine **25**, respectively, in a sealed tube at 280° gave only the cis isomer **26** after 2 hr: nmr δ 1.12 (s, 3, C-7a CH_3), 2.57 (s, 3, NCH_2), 3.69 (t, 1, J = 7.5 Hz, H_b), 4.10 (dd, 1, J = 7.5, ~ 10 Hz, H_a).

Registry No.—**6**, 6501-80-0; **12**, 30315-97-0; **12** 2,4-DNP, 30315-98-1; **14**, 30315-99-2; **16**, 30318-71-9; **16** methiodide, 30318-72-0; **17**, 30318-73-1; **19**, 30318-74-2; **20**, 30318-75-3; **21**, 30318-76-4; **21** methiodide, 30318-77-5; **22**, 30318-78-6; **25**, 30477-03-3; **26**, 30318-79-7; 5-cyano-1-hexene, 30316-00-8; 2-methyl-5-hexen-1-ol, 30315-99-2; 6-bromo-2-methyl-2-hexene, 30316-02-0.

1,4-Benzoxazines. Conversion to a Benzoxazole and an Indolo[3,2-*b*][1,4]benzoxazine[1]

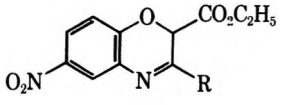
RAYMOND W. HENDESS

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

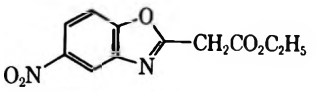
Received January 12, 1971

Reaction of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) with phenylhydrazine in dimethylformamide led to 2-carbethoxymethyl-5-nitrobenzoxazole (**2**) by reductive ring contraction. Also isolated was 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (**1c**). When phenylhydrazine *hydrochloride* in benzene–dimethylformamide was used, the expected 2-carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (**1b**) was obtained. The latter compound underwent cleavage and cyclization to 11a-carbethoxy-5,11a-dihydro-8-nitroindolo[3,2-*b*][1,4]benzoxazine (**3**) on brief heating with sulfuric acid in acetic acid.

The ring contraction of 3-hydroxy-4-methyl-1,4-benzoxazine to a mixture of dihydroxyindoles[2] and of a 1,4-benzthiazine to a benzthiazole[3] have been reported. Recently, during the treatment of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) with phenylhydrazine in dimethylformamide, I observed a ring contraction of **1a** to a benzoxazole. Th emajor product was identified as 2-carbethoxymethyl-5-nitrobenzoxazole (**2**) by the identity of the infrared and nuclear magnetic resonance (nmr) spectra with those of a sample prepared by an unambiguous route.[4] The expected 3-phenylhydrazino compound **1b** was not obtained.



1a, R = SCH_3
b, R = $NHNHC_6H_5$
c, R = $N{=}NC_6H_5$
d, R = OH
e, R = SH

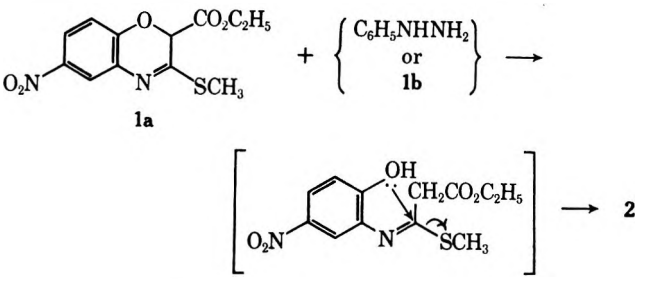


2

A yellow solid, isolated in low yield, has been assigned the phenylazo structure **1c**. This assignment is based on a peak at *m/e* 354 in the mass spectrum of the compound, assigned to the parent molecular ion; the phenylhydrazine **1b** (*vide infra*) exhibited a parent molecular ion at *m/e* 356. Both **1b** and **1c** gave fragment peaks corresponding to the loss of the nitro and carbethoxy groups. Significantly, however, **1c** gave a fragment peak at *m/e* 277, which has been attributed to the loss of the phenyl group. This fragmentation establishes that a monosubstituted benzene ring is present and is consistent with the presence of a phenylazo group. No corresponding peak was found in the spectrum of the phenylhydrazine **1b**.

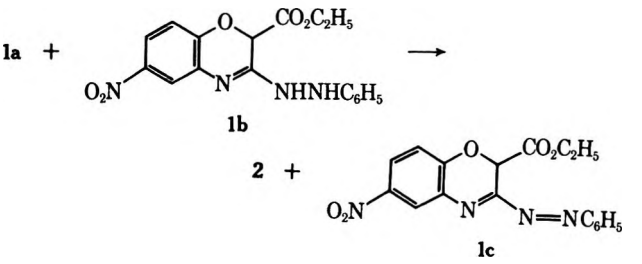
The formation of the benzoxazole **2** from the benzoxazine **1a** requires reductive cleavage of the 1,2 bond of **1a**. Although the exact route of the conversion cannot be specified, it appears that phenylhydrazine and/or the hydrazine **1b** may be involved as reductants.

Reduction of ether linkages[5] and nitro groups[6] by phenylhydrazine has been reported. The probable by-



1a

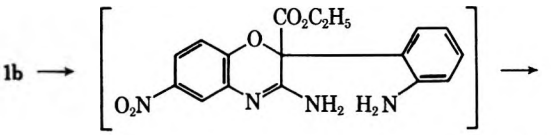
products are nitrogen and benzene.[6] Nmr and gas chromatographic examination of the first cut from a distillation of the reaction mixture indicated the presence of more benzene than could be obtained from a control of phenylhydrazine and dimethylformamide. This suggests that phenylhydrazine is the reductant. On the other hand, the phenylazo compound **1c** and the benzoxazole **2** could arise from reduction of the ether linkage by the hydrazine **1b**.

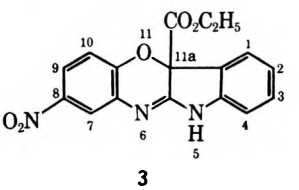


1b

1c

By using phenylhydrazine *hydrochloride* in benzene–dimethylformamide, the formation of the benzoxazole **2** is avoided and the hydrazine **1b** is obtained. Heating this compound with sulfuric acid in acetic acid resulted in rapid conversion of **1b** to **3**, an example of the previously unknown indolo[3,2-*b*][1,4]benzoxazine ring system. The reaction may be considered to be an example of the *o*-benzidine rearrangement with subse-





3

(1) R. W. Hendess, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Paper No. 78.

(2) (a) J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 739 (1955); (b) E. Kretz, J. M. Muller, and E. Schlittler, *Helv. Chim. Acta*, **38**, 520 (1952).

(3) M. A. T. Rogers and W. A. Sexton, *J. Chem. Soc.*, 1619 (1947).

(4) This compound was prepared by Dr. D. E. Machiele of the Kodak Research Laboratories.

(5) K. J. Clark, *J. Chem. Soc.*, 1511 (1956).

(6) H. Bredereck and H. v. Sehuh, *Chem. Ber.*, **81**, 215 (1948).

quent cyclization or an example of a Fischer indole synthesis from a hydrazidine.

The structure of compound **3** was determined by high-resolution mass spectrometry.[7] The spectrum exhibited a parent molecular ion, determined to be of mass 339.0842 by peak matching. This corresponds to a calculated value of 339.0855 for the empirical formula of $C_{17}H_{13}N_3O_5$. This same formula was arrived at by elemental analysis. As expected for cyclic compounds, the spectrum was relatively uncomplicated, showing fragment ions at *m/e* 266 ($M - CO_2C_2H_5$) and *m/e* 220 [$(M - CO_2C_2H_5) - NO_2$]. Infrared analysis confirmed the presence of the ester function (1750 cm^{-1}). The presence of intense absorption of 745 cm^{-1}, not observed in the spectrum of **1b**, is evidence for the new ortho-substituted benzene ring. The nmr spectrum exhibited only seven aromatic protons, in agreement with this structure.

Experimental Section

2-(α-Carbethoxyacetamido)-4-nitrophenol.—A suspension of 154 g (1.0 mol) of 2-amino-4-nitrophenol in 3 l. of *p*-xylene containing 320 g (2.0 mol) of diethyl malonate was refluxed for 4 hr with a condenser through which steam was being passed. The solution was cooled, and 215 g (80%) of the product was collected, washed with benzene, and dried. Recrystallization from ethyl acetate removed a small amount of insoluble diamide. The compound was used without further purification to prepare compound **1d**.

2-Carbethoxy-3-hydroxy-6-nitro-2*H*-1,4-benzoxazine (1d).—A suspension of 110 g (0.41 mol) of 2-(α-carbethoxyacetamido)-4-nitrophenol in 4 l. of ethyl acetate was heated to reflux to effect solution and then cooled to room temperature. To the resulting solution was added a solution of 33.2 ml (55.4 g, 0.41 mol) of sulfuryl chloride in 800 ml of ethyl acetate. The addition took 2 hr. The solution was stirred an additional 2 hr, filtered, and concentrated to 2.5 l. *in vacuo*. Triethylamine (113 ml, 83 g, 0.82 mol) was added and the solution was refluxed 0.5 hr and then cooled. The precipitated triethylamine hydrochloride was removed, the dark brown filtrate evaporated to dryness, and the residue triturated with methanol to give 40 g (37%) of a light tan solid. Recrystallization from methanol gave an analytical sample, mp 199–200°.

Anal. Calcd for $C_{11}H_{10}N_2O_6$ (266.21): C, 49.6; H, 3.8; N, 10.5. Found: C, 49.6; H, 3.6; N, 10.7.

2-Carbethoxy-3-mercapto-6-nitro-2*H*-1,4-benzoxazine (1e).—A solution of 20 g (0.075 mol) of 2-carbethoxy-3-hydroxy-6-nitro-2*H*-1,4-benzoxazine (**1d**) and 15 g (0.068 mol) of phosphorus pentasulfide in 700 ml of pyridine (dried over sodium hydroxide) was refluxed for 6 hr. The dark brown solution was cooled to 15°, and 3 l. of water was added to precipitate the product which was collected, washed with water, and dried (20 g, 94%). Recrystallization from methanol with charcoal gave yellow needles, mp 169–171°. Further recrystallization gave an analytical sample, mp 172–173°.

Anal. Calcd for $C_{11}H_{10}N_2O_5S$ (282.28): C, 46.8; H, 3.5; N, 9.9; S, 11.4. Found: C, 46.7; H, 3.5; N, 10.0; S, 11.4.

2-Carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (1a).—To a suspension of 54.4 g (0.20 mol) of 2-carbethoxy-3-mercapto-6-nitro-2*H*-1,4-benzoxazine (**1e**) in 1 l. of ethanol was added 11.2 g of 85% potassium hydroxide dissolved in 200 ml of ethanol. (This is 0.17 mol based on 85% KOH present; use of 0.20 mol of KOH inhibits crystallization of the product.) After complete solution was obtained, 200 ml of methyl iodide was added and the resulting solution was stirred for 0.5 hr. Concentration to 800 ml *in vacuo*, followed by addition of 1 l. of water, gave 51.8 g of the product as a tan solid. Recrystallization from 1 l. of methanol gave 30 g (51%) of pale yellow crystals, mp 105–107°.

Anal. Calcd for $C_{12}H_{12}N_2O_5S$ (296.31): C, 48.6; H, 4.1; N, 9.4; S, 10.8. Found: C, 48.2; H, 4.0; N, 9.7; S, 11.0.

2-Carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (1c).—A solution of 12 g (0.04 mol) of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) and 4.0 ml (0.041 mol) of phenylhydrazine in 100 ml of dimethylformamide was heated on a steam bath for 3.5 hr and then cooled. Dilution with 100 ml of water gave a yellow solid which was collected, washed with water, dried, and recrystallized from 800 ml of ethanol. The solid (6.0 g) was dissolved in hot acetonitrile; addition of water to the cloud point gave 0.3 g of 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine after cooling. Recrystallization from 15 ml of benzene with charcoal gave bright yellow needles: mp 212–215°; nmr ($CDCl_3$) τ 8.53 (t, *J* = 7 Hz, 3 H) and 5.51 (q, *J* = 7 Hz, 2 H) due to the ethyl group, 2.60 (m, 5 H) phenyl group, 2.23 (d, *J* = 9 Hz, 1 H), 1.60 (m, 1 H), and 1.30 (d, *J* = 2 Hz, 1 H) the remaining aromatic protons.

Anal. Calcd for $C_{17}H_{14}N_4O_5$ (354.31): C, 57.6; H, 4.0. Found: C, 57.3; H, 3.6.

2-Carbethoxymethyl-5-nitrobenzoxazole (2). A.—The acetonitrile–water filtrate from the isolation of 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (**1c**) was diluted further with water to give 5.7 g (57%) of 2-carbethoxymethyl-5-nitrobenzoxazole, which was recrystallized from 200 ml of methylcyclohexane with charcoal to give white needles: mp 101–102°; nmr ($CDCl_3$) τ 8.75 (t, *J* = 7 Hz, 3 H) and 5.77 (q, *J* = 7 Hz, 2 H) due to the ethyl group, 5.95 (s, 2 H) due to the methylene, and 2.39 (d, *J* = 9 Hz, 1 H), 1.71 (m, 1 H), and 1.45 (d, *J* = 2 Hz, 1 H) due to the aromatic protons.

Anal. Calcd for $C_{11}H_{10}N_2O_5$ (250.21): C, 52.8; H, 4.0. Found: C, 52.8; H, 4.0.

B.—A mixture of 16 g (0.10 mol) of 2-amino-4-nitrophenol and 20 g (0.12 mol) of ethyl β,β-dimethoxyacrylate was heated at 70–80° for 1 hr under nitrogen. Upon cooling, the reaction mixture solidified. Recrystallization from methanol gave 19 g (76%) of product, mp 100–102°.

Anal. Found: C, 53.1; H, 4.3.[4]

2-Carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (1b).—A slurry of 10 g (0.034 mol) of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) and 5.0 g (0.035 mol) of phenylhydrazine hydrochloride (both dried *in vacuo* at 60° for 12 hr) in 1 l. of dry benzene was heated to boiling in an open three-neck flask. While boiling was maintained, 700 ml of dimethylformamide was slowly added. A condenser was placed on the flask and the orange solution was refluxed for 1.5 hr. The solution was cooled, the benzene removed *in vacuo*, and the red dimethylformamide solution poured into 1200 ml of ice and water. The brown solid (10.8 g, 88%) which separated was collected and recrystallized from 800 ml of ethanol. Recrystallization from ethanol gave orange crystals: mp 205–206°; nmr (DMSO-d_6) τ 8.82 (t, *J* = 7 Hz, 3 H) and 5.78 (q, *J* = 7 Hz, 2 H) due to the ethyl group, 6.67 (s, 1 H) broad NH, 4.58 (s, 1 H) 2-H, 2.95 (m) and 2.28 (m) 8 aromatic protons, and 1.59 (s, 1 H) a hydrogen-bonded NH.

Anal. Calcd for $C_{17}H_{16}N_4O_5$ (356.33): C, 57.3; H, 4.5; N, 15.7. Found: C, 57.3; H, 4.8; N, 16.2.

11a-Carbethoxy-5,11a-dihydro-8-nitroindolo[3,2-*b*][1,4]benzoxazine (3).—A suspension of 1.0 g (0.0028 mol) of 2-carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (**1b**) in 25 ml of acetic acid containing 0.40 ml of concentrated sulfuric acid was heated rapidly to boiling and then boiled for 5 min. The solution was cooled and diluted with 4 vol of water to give 0.8 g (84%) of a yellow solid. Recrystallization from acetonitrile with charcoal gave white crystals: mp 230–231°; nmr (DMSO-d_6) τ 0.5 (t, *J* = 7 Hz, 3 H) and 5.93 (q, *J* = 7 Hz, 2 H) due to the ethyl group, and a complex multiplet centered at τ 2.26 of the 7 aromatic protons.

Anal. Calcd for $C_{17}H_{13}N_3O_5$ (339.30): C, 60.2; H, 3.9; N, 12.4. Found: C, 60.2; H, 4.1; N, 12.2.

Registry No.—**1a**, 30135-28-5; **1b**, 30135-29-6; **1c**, 30275-68-4; **1d**, 30135-30-9; **1e**, 30135-31-0; **2**, 30135-32-1; **3**, 30135-33-2.

(7) This structure was first suggested by Mr. D. P. Maier of the Kodak Research Laboratories.

Formation of 1,3-Oxazine and 2-Pyrone Derivatives from the Reaction of Pyridinium Ylides with Diphenylcyclopropenone[1]

Tadashi Sasaki,* Ken Kanematsu, and Akikazu Kakehi

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Received December 21, 1970

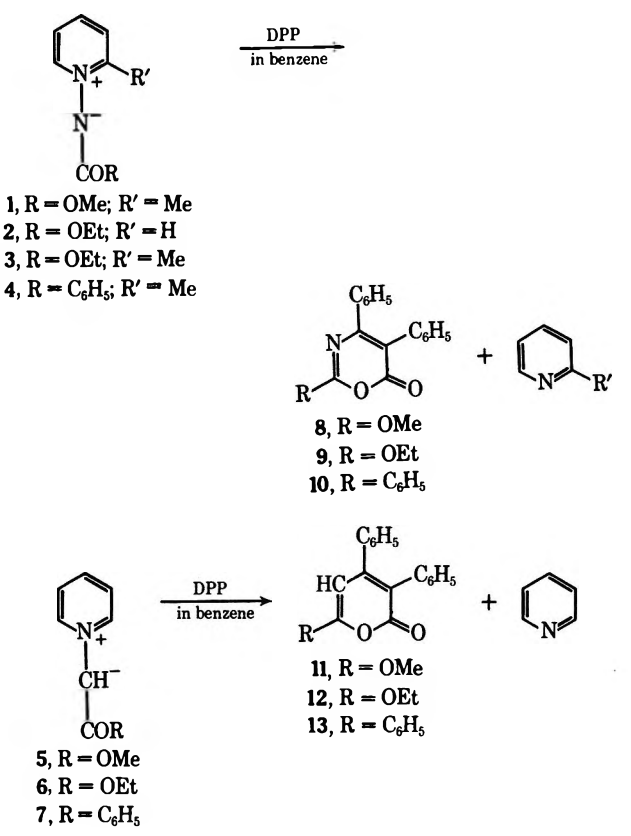
Reactions of iminopyridinium *N*-ylides (1–4) and pyridinium *N*-methylides (5 and 6) with diphenylcyclopropenone (DPP) gave 1,3-oxazine and 2-pyrone derivatives, respectively. Structural elucidation of the products was accomplished by spectral means. Some mechanisms for the formation of the products are discussed.

The utility of the 1,3-dipolar cycloaddition reaction of heteroaromatic nitrogen ylides with acetylenic dipolarophiles for the synthesis of bicyclic heterocyles is well documented.[2–4] As a continuation of work in this area, this paper deals with the reactions of *N*-iminopyridinium ylides with diphenylcyclopropenone (DPP). In addition, the reactions of *N*-alkoxycarbonylpyridinium methylides with DPP have been examined, since the related reactions of pyridinium phenacylide with DPP and methylenecyclopropene have been reported by Eicher and Hansen.[5] A variety of 2 + 3 cycloadditions of DPP to the azomethine ylides have been described. The reactions of DPP with 3-aroylaziridines to form 4-aroyl-4-oxazolines are plausibly interpreted to proceed by initial 2 + 3 cycloaddition of an azomethine ylide to the carbonyl bond of DPP, followed by rearrangement.[6] Another 2 + 3 cycloaddition to DPP is reported in which diazomethane adds to the carbon–carbon double bond.[7]

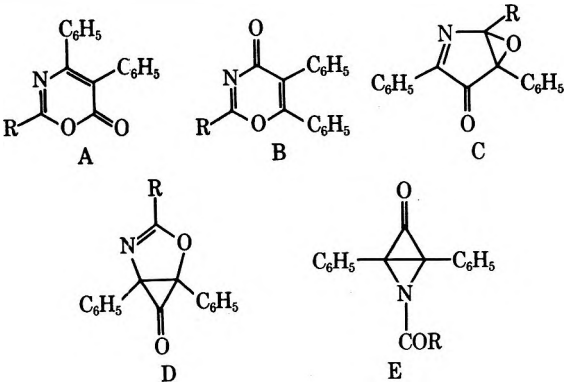
Results and Discussion

Reactions of the Pyridinium Ylides with DPP.— The reactions of the *N*-alkoxycarbonyliminopyridinium ylides (1 and 2) and *N*-benzoyliminopyridinium ylide (4) with DPP in benzene proceeded at room temperature or under reflux to give the corresponding stable compounds 8–10 in good yields together with the corresponding pyridine bases (by glpc inspection) as shown in Scheme I. When pyridinium *N*-ylide (2) was employed, the reaction solution became dark even at room temperature and gave the product 9 together with considerable amounts of tar. However, when there is a 2-methyl substituent (3) on the pyridine ring, the product 9 was obtained in 80% yield. Similar reactions of *N*-alkoxycarbonylpyridinium methylides (5 and 6), prepared *in situ* from alkyl bromoacetate adducts of pyridine and triethylamine, with DPP in benzene resulted in the formation of the adducts together with pyridine (by glpc inspection). The reaction mixture was then separated by column chromatography, but in each case a minor product could not be purified.

Scheme I



Structural Elucidation of the Products (8–12).— Several 1,3-dipolar cycloaddition reactions of the pyridinium ylides and DPP could be expected, since the carbonyl groups in both compounds are highly polarizable. On the basis of the reported chemistry of DPP[5–7] a variety of possible structures A–E for



the adducts 8 and 9 could be postulated. The structural elucidation was based on spectral properties. The ir and uv data as well as the nmr spectral evidences indicated the absence of the pyridine moiety in these

(1) Studies of Heteroaromaticity. LIII. For part LII of this series, see T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jap.*, **44**, 803 (1971).

(2) For leading references, see (a) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, Chapter 11, p 739; (b) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).

(3) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C*, 481 (1970).

(4) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.*, **36**, 813 (1971).

(5) T. Eicher and A. Hansen, *Tetrahedron Lett.*, 1169 (1967).

(6) J. W. Lown, T. W. Maloney, and G. Dallas, *Can. J. Chem.*, **48**, 584 (1970).

(7) P. T. Izzo and A. S. Kende, *Chem. Ind. (London)* 839 (1964).

TABLE I

IR, UV, AND NMR SPECTRA OF 1,3-OXAZINE AND 2-PYRONE DERIVATIVES

Compd no.	Ir, cm^{-1} $\nu_{C=O}^{KBr}$	Ir, cm^{-1} $\nu_{C=N}^{KBr}$	Uv, λ_{max}^{MeOH}, nm (ϵ)	Nmr,[a] τ (CDCl₃)
8	1735	1626	319 (8.82×10^3)	2.84 (10 H, s, 2 C_6H_5)
			231 (1.66×10^4)	5.95 (3 H, s, OCH_3)
9	1732	1616	320 (8.38×10^3)	2.85 (10 H, s, 2 C_6H_5)
			231 (1.90×10^4)	5.53 (2 H, q, J = 7.0 Hz, OCH_2)
				8.54 (3 H, t, J = 7.0 Hz, OCH_2CH_3)
10	1727	1610	341 (1.19×10^4)	1.68 (2 H, m, ortho and ortho′ protons of C_6H_5)
			265 (2.17×10^4)	2.60 (3 H, m, meta, meta′, and para protons of C_6H_5)
				2.80 (10 H, s, 2 C_6H_5)
11	1710	1623	345 (8.27×10^3)	2.99 (10 H, s, 2 C_6H_5)
			238 (1.45×10^3)	4.68 (1 H, s, ring proton)
				6.13 (3 H, s, OMe)
12	1697	1623	348 (1.00×10^4)	2.98 (10 H, s, 2 C_6H_5)
			237 (1.72×10^4)	4.67 (1 H, s, ring proton)
				5.70 (2 H, q, J = 7.0 Hz, OCH_2)
				8.55 (3 H, t, J = 7.0 Hz, OCH_2CH_3)
13	1695	1623	358 (1.53×10^4)	2.20 (2 H, m, ortho and ortho′ protons of C_6H_5)
			254 (1.88×10^4)	2.65 (3 H, m, meta, meta′, and para protons of C_6H_5)
			240 (shoulder)	2.95 (10 H, s, 2 C_6H_5 2)
				3.32 (1 H, s, ring proton)

[a] s = singlet, t = triplet, q = quartet, m = multiplet.

adducts. In the ir, they showed absorptions at 1727–1735 cm^{-1} due to six-membered carbonyl bands rather than to those of carboxamide bands,[8,9] in comparison with a known structure of **10**, which has been prepared by the reaction of 2,3,5-triphenylpyrrole and hydrogen peroxide in acetic acid.[10] Furthermore, these compounds also gave a negative reaction with sodium thiosulfate reagent (oxiran ring test). Thus, the structures B–E could be ruled out from the possibilities for compounds **8** and **9**. On the other hand, compounds **11** and **12** showed absorptions at 1710 and 1697 cm^{-1}, respectively, attributable to carbonyl bands of the α-pyrone moiety, in comparison with a known structure of **13**, which has been prepared by the similar reaction of pyridinium *N*-phenacylide and DPP.[5] The nmr spectra of **8**, **9**, **11**, and **12** contained peaks at τ 2.80–2.99 (almost singlets) due to two phenyl protons. The uv absorption spectra showed two maxima at 231–265 and 319–358 nm.[11] Their ir, uv, and nmr spectra are summarized in Table I. The mass spectra of the oxazines and pyrones were characterized by fragment ion peaks (M − CO).[12]

On the basis of the above, spectral evidence, structures **8**, **9**, **11**, and **12** were assigned as 2-methoxy- and 2-ethoxy-4,5-diphenyl-1,3-oxazin-6-one and 6-methoxy- and 6-ethoxy-3,4-diphenyl-2-pyrone, respectively. Considering these results, the reactions seem to proceed *via* the cycloaddition reactions of DPP and acylnitrenes and acylcarbenes, generated from the corresponding pyridinium *N*-ylides. However, DPP proved to be inert to the reaction with ethyl azidoformate even under more drastic conditions.

(8) *Cf.* $\nu_{C=O}$ 1730–1760 cm^{-1} in 1,3-oxazin-6-one; see H. B. Kogan, *Bull. Soc. Chim. Fr.*, 1819 (1966).

(9) *Cf.* $\nu_{C=O}$ 1750–1780 cm^{-1} in 1,3-oxazin-4-ones; see T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **15**, 1334 (1967).

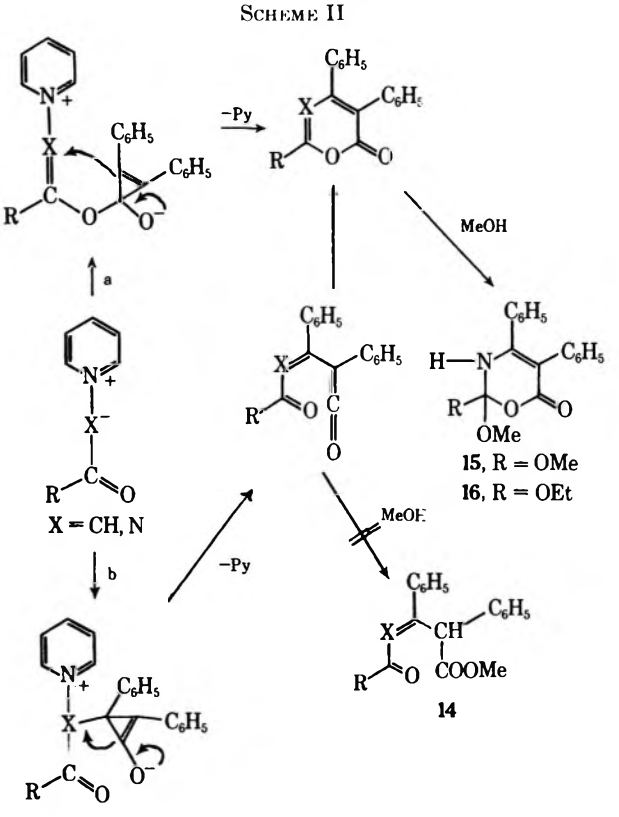
(10) I. V. Sprio, *Gazz. Chim. Ital.*, **85**, 569 (1955).

(11) $\lambda_{max}^{dioxane}$ 340 nm in 2,5-diphenyl-1,3-oxazin-6-one; see F. Eiden and B. S. Nagar, *Naturwissenschaften*, **50**, 403 (1963).

(12) Mass spectral data for compounds **8**–**13**, **15**, and **16**, with a suggested fragmentation scheme, will appear immediately following this article in the microfilm edition of the journal. Single copies may be obtained from the Reprint Department, ACS Publication, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

Mechansitic speculation leads to consideration of paths a and b, with initial nucleophilic attack of the *N*-ylides to the carbonyl bond of DPP or to the carbon–carbon double bond, respectively, followed by rearrangement to give 1,3-oxazine and/or 2-pyrone derivatives (Scheme II), as suggested by Eicher and Hansen.[5] However, an attempt to quench the ketene intermediate (*via* path b) by methanol in the reaction of **2** and DPP gave compound **9** accompanied by a small amount of **16** instead of the expected compound **14**, as revealed by thin layer chromatography and nmr analyses. Upon treating **8** and **9** with refluxing methanol, compounds **15** and **16** were obtained in

SCHEME II



quantitative yields, respectively. The nmr spectra indicate the two methoxyl groups as singlets at τ 6.36 and 6.44 and NH proton at τ −1.08 (broad singlet) in **15** and the ethoxyl protons at τ 5.91 (2 H, q, J = 7.0 Hz) and 8.82 (3 H, t, J = 7.0 Hz), the methoxyl protons at τ 6.46 (3H, s), and NH proton at τ −1.06 (broad singlet) in **16**. Thus compounds **15** and **16** were assigned as 2,2-dimethoxy- and 2-ethoxy-2-methoxy-4,5-diphenyl-2,3-dihydro-1,3-oxazin-6-one, respectively.

Attempts to effect the reactions of troponoids with *N*-alkoxycarbonyliminopyridinium ylides were unsuccessful even under more drastic conditions, although the similar reactions of troponoids with pyridinium phenacylide and sulfonium ylides have been reported to lead to a convenient one-step syntheses of azaazulene and 2,3-homotropone derivatives.[13]

Experimental Section[14]

2-Methoxy-4,5-diphenyl-1,3-oxazin-6-one (**8**).—To a solution of **1** (150 mg, 1 mmol) in benzene (30 ml), DPP (100 mg, 0.5 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel) using chloroform as eluent to give colorless crystals of **8** (110 mg, 79%, mp 111–112°) as the first fraction, which was recrystallized from carbon tetrachloride–*n*-hexane.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.08; H, 4.81; N, 4.92.

2-Ethoxy-4,5-diphenyl-1,3-oxazin-6-one (**9**).—(a) From **2** (500 mg, 1.5 mmol) and DPP (210 mg, 1 mmol) there was obtained colorless crystals **9** (180 mg, 61%, mp 94–95°). (b) From **3** (180 mg, 1 mmol) and DPP (100 mg, 0.5 mmol) there was obtained colorless crystals of **9** (120 mg, 82%, mp 94–95°).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 73.70; H, 5.15; N, 4.98. Found: C, 73.92; H, 5.24; N, 4.74.

2,4,5-Triphenyl-1,3-oxazin-6-one (**10**).—To a solution of **4** (210 mg, 1 mmol) in benzene (20 ml), DPP (100 mg, 0.5 mmol) was added, and then the mixture was refluxed for 4 days. The mixture was concentrated *in vacuo* and the residue was worked up as described above. Pale yellow crystals were obtained as the first fraction, which was recrystallized from carbon tetrachloride–*n*-hexane to give **10** (130 mg, 80%, mp 207–208°). Compound **10** was also identified by the comparison of a mixture melting point with the melting point of an authentic sample.[10]

6-Methoxy-3,4-diphenyl-2-pyrone (**11**).—To a solution of pyridine–methyl bromoacetate adduct (300 mg) in benzene (30 ml) in the presence of triethylamine (0.5 ml), DPP (100 mg, 0.5 mmol) was added and stirred overnight at room temperature. The reaction solution was removed *in vacuo*, and the residue was separated by column chromatography using benzene as eluent; the product was recrystallized from benzene to give colorless crystals of **11** (90 mg, 67%, mp 134–135°).

Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.75; H, 5.10.

6-Ethoxy-3,4-diphenyl-2-pyrone (**12**).—From pyridine–ethyl bromoacetate adduct (300 mg), triethylamine (0.3 ml), and DPP (100 mg, 0.5 mmol) there was obtained **12** (60 mg, 41%) as colorless crystals, mp 104–106°.

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.10; H, 5.50.

2,2-Dimethoxy-4,5-diphenyl-2,3-dihydro-1,3-oxazin-6-one (**15**).—A solution of **8** (50 mg) and methanol (30 ml) was refluxed for about 2 days and the solvent was removed *in vacuo*. The residue was recrystallized from ether–*n*-hexane to give colorless crystals, mp 166–169°, in quantitative yield; $\nu_{C=O}^{KBr}$ 1750 cm^{-1}; λ_{max}^{MeOH} 290 nm (ϵ 1.34 × 10^4); nmr τ (CCl_4) 6.44 (s, 3), 6.36 (s, 3), 3.03 (m, 10), −1.08 (NH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.89; N, 4.31. Found: C, 69.50; H, 5.59; N, 4.58.

2-Ethoxy-2-methoxy-4,5-diphenyl-2,3-dihydro-1,3-oxazin-6-one (**16**).—(1) A solution of **9** (50 mg) and methanol (20 ml) was refluxed for about 2 days and the solvent was removed *in vacuo*. The residue was recrystallized from ether–*n*-hexane to give colorless crystals, mp 136–139°, in quantitative yield: $\nu_{C=O}^{KBr}$ 1756 cm^{-1}; λ_{max}^{MeCH} 289 (ϵ 1.16 × 10^{-4}); nmr τ (CCl_4) 8.84 (t, 3), 6.46 (s, 3), 5.91 (q, 2), 3.10 (m, 10), −1.06 (NH). (2) A solution of **2** (50 mg), DPP (30 mg), and methanol (30 ml) was stirred for 2 days at room temperature. The solvent was concentrated *in vacuo* and the residue was confirmed to be a mixture of **9** (as a major product) and **16** (minor) by tlc and nmr inspections. However, the reaction mixture was difficult to separate by means of column chromatography. Further treatment of the mixture with methanol under the refluxing condition afforded **16** in quantitative yield.

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.25; H, 5.89; N, 4.20.

Registry No.—**8**, 30237-76-4; **9**, 30237-77-5; **10**, 30237-78-6; **11**, 30237-79-7; **12**, 30237-80-0; **13**, 14961-31-0; **15**, 30237-82-2; **16**, 30237-83-3; DPP, 886-38-4.

(13) Y. Sugimura, I. Kawamoto, K. Ihno, and N. Soma, Abstracts of Papers, "International Symposium of the Chemistry of Non-benzenoid Aromatic Compounds," Sendai, Japan, 1970, p 67.

(14) All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. The microanalyses were performed on a Perkin-Elmer 240 elemental analyzer, while the ir and uv spectra were obtained on JASCO Models IR-S and ORD/UV-5 spectrometers, respectively. The nmr spectra were recorded with a JEOL Model C-60-XL spectrometer with tetramethylsilane as an internal standard. The glpc was done isothermally with an Hitachi K-23 gas chromatograph on a 3-ft, 5 wt % SE 30 (Chromosorb GNAW) column (flame-ionization detector). The mass spectra were obtained on a Hitachi RMU-D double-focusing mass spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150°.

Synthesis of Adamantane Derivatives. XV.[1] No Ring-Fission Aptitude of the Homoadamantan-4-one System in the Schmidt and Beckmann Rearrangements

TADASHI SASAKI,* SHOJI EGUCHI, AND TAKESHI TORU

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

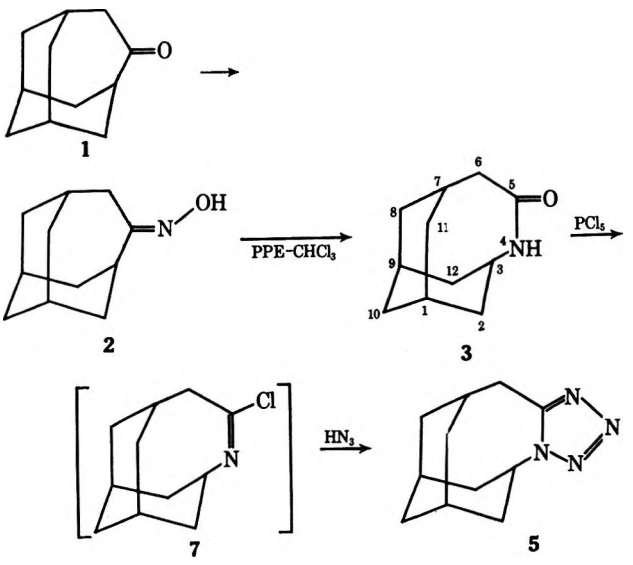
Received January 26, 1971

The stereospecific Beckmann rearrangement of *anti*-homoadamantan-4-one oxime (**2**) in PPE yielded 4-azabishomoadamantan-5-one (**3**) in 58% yield. **3** was converted to tetrazolo[4,5-*d*]-4-azabishomoadamantane (**5**) *via* an imino chloride intermediate (**7**). The same rearrangement of **2** in 85% H_2SO_4, however, afforded a 1:4 mixture of **3** and isomeric 5-azabishomoadamantan-4-one (**4**). The Schmidt reaction of homoadamantan-4-one (**1**) with equimolar sodium azide in CH_3SO_3H gave a 1:1 mixture of **3** and **4** (7%) and a 1:1 mixture of **5** and isomeric tetrazolo[4,5-*d*]-5-azabishomoadamantane (**6**) (48%), while that with 2.1 *M* sodium azide gave exclusively the tetrazole mixture (93.5%). The same reaction with equimolar sodium azide in CH_3SO_3H–AcOH (1:1 v/v) gave the lactam mixture (34%) and the tetrazole mixture (24%). These results differ from the adamantanone system and are rationalized by the postulation that the spatial arrangement of the participating bonds is one important factor for determining the Schmidt and Beckmann fission aptitude of these ring systems. A conformational problem of the 4-azabishomoadamantane skeleton is also discussed from nmr data.

Recently, we reported the formation of 4(e)-methylsulfonoxyadamantan-2-one in excellent yield from adamantanone and sodium azide in CH_3SO_3H;[2] this reaction has been demonstrated to proceed *via* a Schmidt fission and recombination path.[2b] A similar type of the reactions has also been reported for adamantanone oxime.[3] Furthermore, the principle of these reactions has been extended to a general preparation of 2-substituted and 2,4-disubstituted adamantane derivatives by the so-called π route.[4] However, the behavior of homoadamantan-4-one (**1**)[5] in the Schmidt reaction and of its oxime **2**[5c] in the Beckmann rearrangement have not been studied. This paper describes the results of these reactions under several conditions. No ring fission was observed, in sharp contrast to the facile fission in the adamantanone system.[2,3]

Schmidt Reaction of 1 and Beckmann Rearrangement of 2.—The oximation of **1** with hydroxylamine in 95% ethanol in the presence of excess potassium hydroxide afforded only anti oxime **2**.[6] Treatment of **2** with PEE (polyphosphate ester) in chloroform at 80° resulted in a stereospecific rearrangement to give 4-azatricyclo[5.3.1.1^{3,9}]dodecan-5-one (**3**) (4-azabishomoadamantan-5-one)[7] in 58% yield and 32% recovery of **2**. **3** had a molecular formula $C_{11}H_{17}NO$ on the basis of analysis and mass spectrum, and characteristic nmr signals at τ 6.48 (q, J = 7.5 Hz, on deuteration changed to t, C_3 methine) and 7.34 (d, J = 3.7 Hz, C_6 methylene) permitted the assignment of formula **3**. **3** was converted to the corresponding tetrazole derivative **5** (tetrazolo[4,5-*d*]-4-azabishomoadamantane)

SCHEME I



via an imino chloride intermediate **7** (Scheme I). The nmr spectrum of **5** had characteristic signals at τ 4.68 (t, C_3 methine) and 6.67 (d, C_6 methylene), supporting structure **5** (Figure 1).

The Beckmann rearrangement of **2** in 85% H_2SO_4 also yielded **3**, accompanied by a large amount of an isomeric lactam **4** (5-azabishomoadamantan-4-one) (1:4 ratio). Considering that sulfuric acid is prone to cause the syn–anti isomerization of oximes, and that PPE in nonpolar solvents is least prone to cause the isomerization,[8] these results can be explained by the isomerization of **2** prior to rearrangement. The fact that no Beckmann fission had occurred even in 85% H_2SO_4 is of much interest compared with the facile ring fission of adamantanone oxime under the similar conditions.[3a]

The absence of ring fission was observed also in the Schmidt reaction of **1**; treatment of **1** with equimolar sodium azide in CH_3SO_3H afforded a lactam mixture of **3** and **4** and a tetrazole mixture of **5** and **6** (Scheme II). The nmr spectrum of the lactam mixture exhibited characteristic signals at τ 6.48 (q), 6.64 (t, partly overlapped with the quartet), 6.92 (t), and 7.34 (d) in a 1:2:1:2 ratio. By nmr spectral comparison with **3**, this mixture was found to be a 1:1 mixture of **3**

(1) Part XIV of this series: T. Sasaki, S. Eguchi, and T. Toru, *Chem. Commun.*, 1239 (1970).

(2) (a) T. Sasaki, S. Eguchi, and T. Toru, *J. Amer. Chem. Soc.*, **91**, 3390 (1969). (b) *J. Org. Chem.*, **35**, 4109 (1970); (c) *Chem. Commun.*, 1285 (1969).

(3) (a) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969); (b) V. L. Narayanan and L. Setescak, *J. Med. Chem.*, **6**, 445 (1969).

(4) (a) D. J. Raber, G. J. Kane, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4117 (1970); (b) M. A. McKervey, D. Faulkner, and H. Hamill, *ibid.*, 1971 (1970); (c) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970).

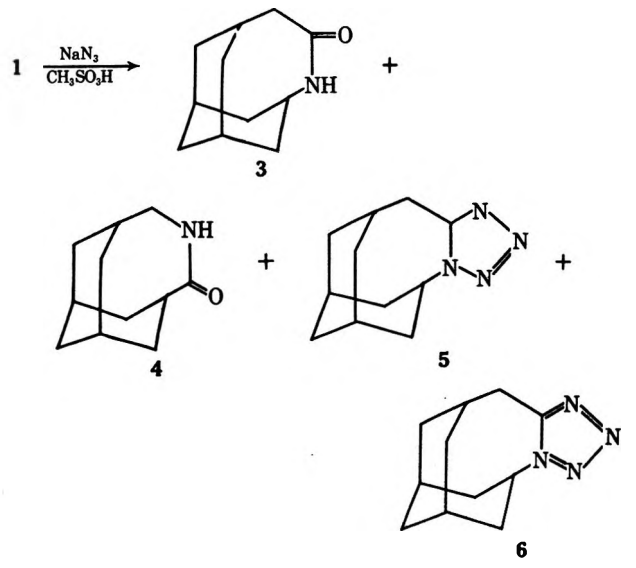
(5) (a) J. E. Nordlander, F. Y.-H. Wu, S. P. Jindal, and J. B. Hamilton, *J. Amer. Chem. Soc.*, **91**, 3962 (1969); (b) P. v. R. Schleyer, E. Funke, and S. H. Liggero, *ibid.*, **91**, 3965 (1969); (c) J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970); (d) I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **92**, 6670 (1970).

(6) The prefix "anti" refers to the direction of the oxime hydroxyl group with respect the methine group. The anti stereochemistry of **2** was based on nmr data. *Cf.* P. A. Smith, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 485, and also see ref 5c.

(7) This trivial name was used in this paper.

(8) See ref 6, pp 483–527.

SCHEME II



and **4**. The tetrazole mixture was similarly characterized as a 1:1 mixture of **5** and tetrazolo[4,5-*d*]-5-azabishomoadamantane (**6**) by its nmr signals at τ 4.68 (t), 5.45 (d), 6.00 (t), and 6.67 (d) in a 1:2:1:2 ratio. The reaction of **1** with 2.1 *M* sodium azide in CH_3SO_3H afforded exclusively the tetrazole mixture, while that with equimolar sodium azide in CH_3SO_3H–AcOH gave a somewhat higher yield of the lactam mixture than that of the tetrazole mixture (Table I).

TABLE I

PRODUCT DISTRIBUTION OF THE SCHMIDT REACTION OF HOMOADAMANTAN-4-ONE (**1**)

Catalyst–solvent	NaN_3 (molar ratio to **1**)	Products (yield, %) 3 + 4	5 + 6	Recovered **1**, %
CH_3SO_3H	2.1	0	93.5	0
CH_3SO_3H	1.0	7	48	29
CH_3SO_3H–AcOH (1:1 v/v)	1.0	34	24	17

Since tetrazole formation is indicative of the presence of an iminium cation,[9] the exclusive formation of **5** and **6** in the presence of excess hydrogen azide indicates that the Schmidt reaction of **1** proceeds *via* path B[10] and not *via* path A[11] (Scheme III) in contrast to the adamantanone system,[2b] where both reaction paths A and B are involved. Surprisingly, neither fission products nor their derivatives were found in the Schmidt reaction of **1** contrary to the reported facile ring fission of adamantanone *via* path B.[2b]

From these striking differences between **1** and adamantanone in the Schmidt and Beckmann rearrangements, it is concluded that the spatial arrangement of the participating bonds in these reactions is a prominent factor for determining the ring-fission aptitude. Although electronic factors such as the charge delocalization on the participating bonds, *e.g.*, a–e in **11** and **12**, are assumed to be more or less similar, the spatial arrangement of $H–C_\beta–C_\alpha–C{=}N{\sim}N_2^+$ is obviously different from **1** and adamantanone because

(9) For example, see P. A. S. Smith and W. L. Berzy, *J. Org. Chem.*, **26**, 27 (1961).

(10) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 320 (1948).

(11) M. S. Newman and H. Gildenhon, *ibid.*, **70**, 317 (1948).

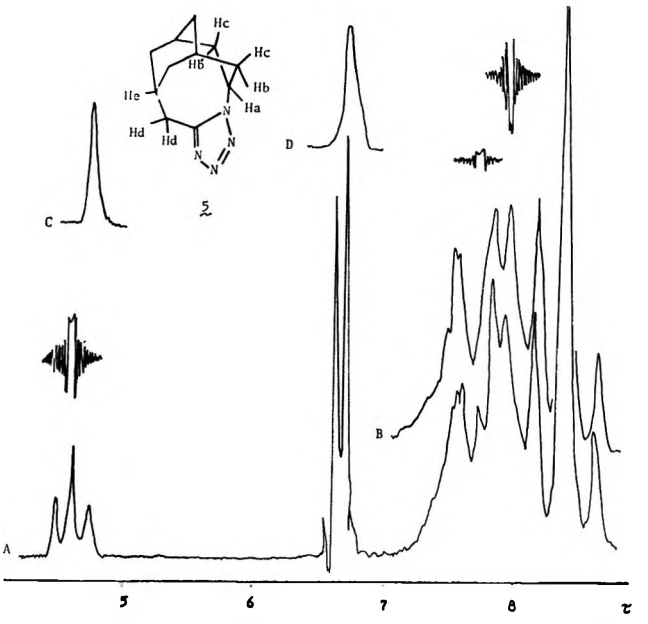


Figure 1.—Nmr spectrum of **5** ($CDCl_3$, 60 MHz): (A) standard spectrum; (B) spectrum decoupled from H_a; (C) H_a band decoupled from H_c; (D) H_d band decoupled from H_e.

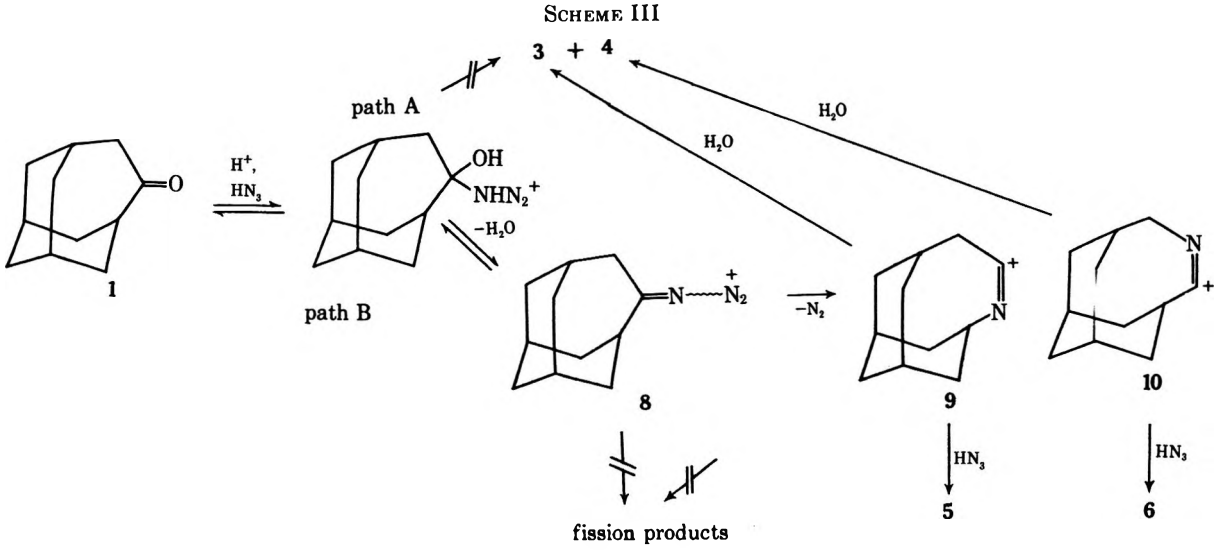
of the presence of seven-membered rings in **1**. An inspection on the Dreiding stereomodel suggested that the spatial arrangement of $H–C_4–C_3–C_2{=}N{\sim}N_2^+$ for adamantanone is almost ideally antiparallel for $C_2–C_3$ bond fission,[2b] but that of $H–C_2–C_3–C_4{=}NN{\sim}N_2^+$ and/or $H–C_6–C_5–C_4{=}N{\sim}N_2^+$ for **1** is deviated from the ideally antiparallel one for $C_3–C_4$ and/or $C_4–C_5$ bond fission assuming an untwisted conformation of **1**.[5,12] In addition, consideration of the energy balance due to the ring strain in the fission of the rearrangement (*i.e.*, the ring expansion) suggests that ring fission of **1** might be more favorable than rearrangement compared with adamantanone.[13]

Evidently, the Schmidt reaction of **1** proceeds *via* a different transition state from that of the Beckmann rearrangement of **2** with PPE, which seems to take place concertedly *via* **13** or **13′** from the observed stereospecificity. On the other hand, the nonstereospecific rearrangement of **1** in the Schmidt reaction could be explained reasonably by assuming the intervention of a highly energetic cationic species which is generated by the loss of nitrogen from **8**, and rearranges nonstereospecifically to **9** and **10** *via* **14a** and **14b**. The possibility that the relative population of isomeric diazonium cations **8a** and **8b** could determine the product ratio *via* their stereospecific rearrangement seems implausible because the Beckmann rearrangement of **2** under equilibrating conditions (85% H_2SO_4) affords the lactams in a different ratio from that in the Schmidt

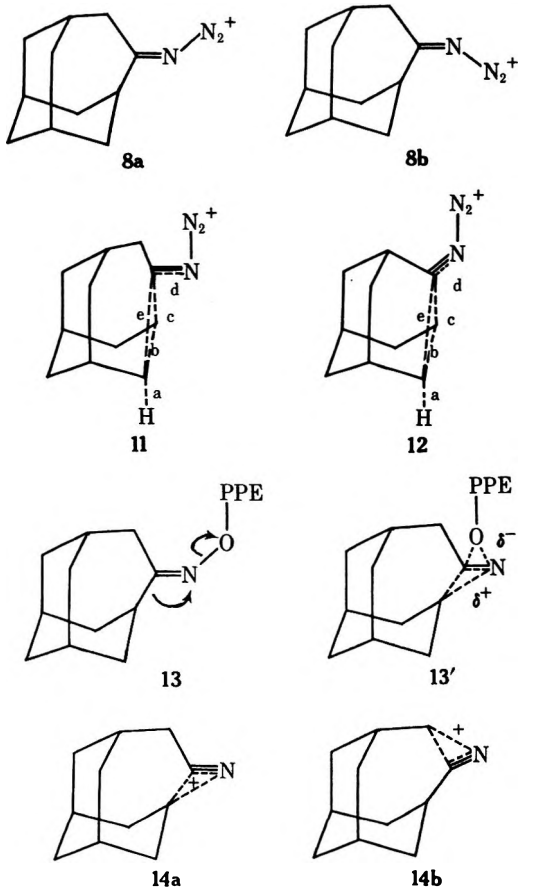
(12) The deviation of $H–C_6–C_5–C_4{=}N{\sim}N_2^+$ is less extent than that of $H–C_7–C_8–C_4{=}N{\sim}N_2^+$; however, the $C_4–C_5$ bond fission is disfavored by the fact that a primary carbonium ion adjacent to the carbonyl is possible; see ref 2b and references cited there.

(13) The calculated total strain energies for bicyclo[3.3.1]nonane, homoadamantane, and bishomoadamantane rings relative to adamantane ring are reported as *ca.* 12, 14, and 18–20 kcal/mol, respectively. Hence, a considerable strain increase could be expected for **1** → **9** + **10** conversion but no appreciable strain change for fission of **1**, while a large strain increase is accompanied for both rearrangement and fission of adamantanone. *Cf.* G. J. Gleicher and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967); P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *ibid.*, **92**, 2377 (1970); R. C. Fort, Jr., Ph.D. Thesis, Princeton University, Princeton, N. J., 1964.

SCHEME III



reaction, and also because of the possible steric preference of one isomer of **8** (*e.g.*, **8a**) to the other.



Conformational Study of the 4-Azabishomoadamantane Skeleton.—A conformational problem exists in the 4-azabishomoadamantane skeleton as in the homoadamantane ring.[5] Is the C_3–N_4–C_5–C_6–C_7 bond twisted or not?

The nmr spectrum of **5** is shown in Figure 1, in which the signals at τ 4.68, 7.75, 6.67, and 7.97 are assigned to H_a, H_c, H_d, and H_e, respectively, with the aid of spin-decoupling experiments. The appearance of C_6-methylene protons (H_d) in a doublet with J = 4.5 Hz indicates that the two protons are equivalent and that the dihedral angle for H_d and H_e is approximately 50° according to the Karplus relation. Similarly, a triplet with J = 6.4 Hz due to C_3-methine proton (H_a) indicates that $J_{a,c}$ = 6.4 and $J_{a,b}$ = 0 Hz, and hence the dihedral angle for H_a and H_e is *ca.* 30°, and that for H_a and H_b, is *ca.* 90°. These coupling patterns of H_a and H_d signals, therefore, suggest an untwisted bridged conformation of the eight-membered rings in **5**.[14] The preference of an untwisted conformation is also postulated in homoadamantane ring.[5]

The nmr spectrum of the lactam **3** had similar coupling patterns of C_3-methine and C_6-methylene protons as described above, suggesting also an untwisted conformation of **3**. A recent report[15] that 4,6-diazabishomoadamantan-5-one takes a partially flattened chair conformation of the two six-membered rings is compatible with the above conclusion for **3** and **5**.

Experimental Section[16]

Preparation of *anti*-Homoadamantan-4-one Oxime (2).—A mixture of homoadamantan-4-one (1) (1.0 g, 6.1 mmol), hydroxylamine hydrochloride (1.0 g, 14.4 mmol), and potassium hydroxide (4.0 g, 71.3 mmol) in 95% ethanol (20 ml) was refluxed overnight. The cooled mixture was evaporated under reduced pressure, diluted with water (30 ml), and extracted with ether (five 30-ml portions). The washed (water) and dried (Na_2SO_4) extract was evaporated to give a solid residue which was recrystallized from ethanol to afford anti oxime **2** (0.94 g, 76%) as colorless crystals: mp 158–159° (lit.[5c] 147–149°); ir (KBr) 3180, 3040, and 1635 cm^{-1}; nmr ($CDCl_3$) τ 1.35 (br s, 1, OH), 7.19 (m, 1, C_3 methine), 7.32 (d, 2, J = 3.5 Hz, C_5 methylene), and 7.60–8.85 (m, 13, other ring protons).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.77; H, 9.43; N, 7.71.

Beckmann Rearrangement of 2. A. With PPE.—A mixture of **2** (1.0 g, 5.6 mmol) and PPE (6.0 g) in chloroform (5 ml) was heated at 85° for 10 min. The mixture was diluted with water (100 ml), stirred for 1 day at room temperature, and then heated at 80° for 10 min. The cooled mixture was basified with 10% aqueous potassium hydroxide and extracted with chloroform (five 50-ml portions). The dried (Na_2SO_4) extract was evaporated to afford a brownish oil which was purified on a silica gel

(14) However, the possibility of a rapid equilibrium of more than two conformers on the nmr time scale could not be ruled out.

(15) V. G. Keizer, J. G. Korsloot, F. W. v. Deursen, and M. E. v. d. Heeden, *Tetrahedron Lett.*, 2059 (1970).

(16) All melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Nmr spectra were determined with a JEOL JNM-C-60HL spectrometer at 60 MHz and mass spectra with a JEOL JMS-01SG spectrometer at 70 eV. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer.

column eluting with chloroform to give recovered **2** (0.32 g, 32% recovery) and 4-azabishomoadamantan-5-one (**3**) (0.58 g, 58%) as colorless crystals from acetone: mp 184–185°; ir (KBr) 3440, 3240, 3140, 3000, and 1635 cm^{-1}; nmr ($CDCl_3$) τ 2.95 (br s, 1, NH), 3.52 (q, 1, J = 7.5 Hz, C_3 methine, t in $CDCl_3$–D_2O), 7.34 (d, 2, J = 3.7 Hz, C_6 methylene), and 7.48–8.85 (m, 13, other ring protons); mass spectrum m/e (rel intensity) 179 (M^+, 100), 164 (20) and 151 (50).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.36; H, 9.47; N, 7.89.

B. With Sulfuric Acid.—A solution of **2** (0.20 g, 1.3 mmol) in 85% (v/v) sulfuric acid (6.5 ml) was heated at 110° for 12 min. The cooled solution was poured onto ice–water (20 ml), neutralized with solid sodium bicarbonate, and extracted with chloroform (five 20-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford a 1:4 mixture of the lactams **3** and **4** (0.12 g, 60%).

Tetrazolo[4,5-*d*]-4-azabishomoadamantane (5).—To a solution of phosphorus pentachloride (0.20 g, 0.96 mmol) in chloroform (2 ml) was added a solution of **3** (0.20 g, 1.1 mmol) in chloroform (2 ml) with stirring at room temperature. After stirring was continued for 1 day, a mixture of sodium azide (0.20 g, 3.1 mmol) and sulfuric acid (0.1 ml) in benzene (10 ml) was added to the mixture. The resulting mixture was stirred for 10 hr at room temperature, basified with 10% aqueous potassium hydroxide, and extracted with chloroform (five 30-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford the tetrazole **5** as colorless crystals from acetone: mp 173–174°; ir (KBr) 1530 cm^{-1}; mass spectrum m/e (rel intensity) 204 (M^+, 20), 176 (15), 163 (30), and 149 (100).

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.49; H, 8.01; N, 27.14.

Schmidt Reaction of Homoadamantan-4-one (1). A. In CH_3SO_3H.—To an ice-cooled solution of **1** (0.50 g, 3.0 mmol) in CH_3SO_3H (5 ml) was added portionwise solid sodium azide (0.20 g, 3.1 mmol) during 4 hr with stirring. After stirring was continued for an additional 20 hr, the mixture was poured onto ice–water (30 ml), and the resulting mixture was neutralized with solid sodium bicarbonate and extracted with chloroform (five 30-ml portions). Work-up in the usual way afforded a solid product which was purified on a silica gel column, eluting with chloroform to give recovered **1** (0.145 g, 29% recovery), a 1:1 mixture of the tetrazoles **5** and **6** (0.30 g, 48%), mp 188–189°, and a 1:1 mixture of the lactams **3** and **4** (0.040 g, 7%), mp 153–160°.

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.44; H, 8.00; N, 27.04. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.40; H, 9.57; N, 7.83.

A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.41 g, 6.3 mmol) in CH_3SO_3H (8 ml) afforded a 1:1 mixture of the tetrazoles **5** and **6** (0.58 g, 93.5%).

B. In CH_3SO_3H–AcOH.—A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.20 g, 3.1 mmol) in CH_3SO_3H (2 ml)–AcOH (2 ml) and work-up as above afforded the tetrazole mixture (0.15 g, 24%), the lactam mixture (0.19 g, 34%), and recovered **1** (0.085 g, 17% recovery).

Registry No.—**2**, 26770-89-8; **3**, 29863-86-3; **4**, 29863-87-4; **5**, 29863-88-5; **6**, 29863-89-6.

Pyridazines. XXXVII. Pyrimido[1,2-*b*]pyridazines

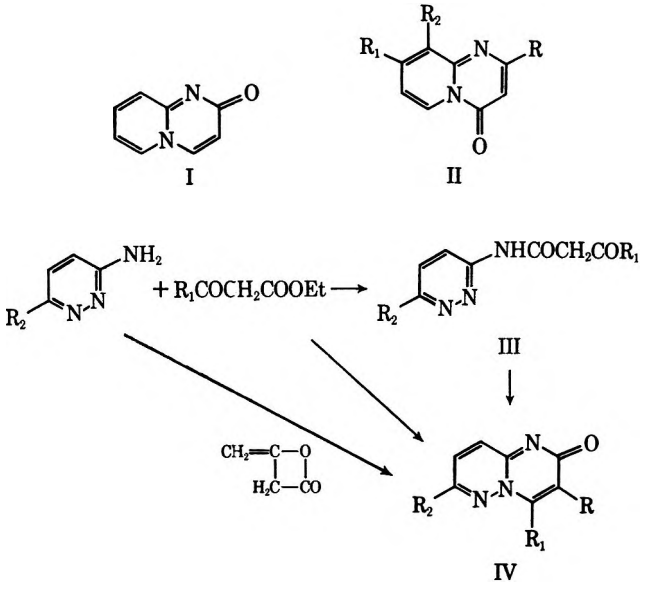
A. POLLAK, B. STANOVNIK, AND M. TIŠLER*

Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia

Received October 6, 1970

3-Aminopyridazines condense with 1,3-dicarbonyl compounds in polyphosphoric acid to give pyrimido[1,2-*b*]-pyridazines. With β-keto esters pyrimido[1,2-*b*]pyridazin-2-ones are formed, in contrast to 2-aminopyridines which give pyrido[1,2-*a*]pyrimidin-4-ones.

The intriguing structural problem concerning condensation products of amino heterocycles with β-keto esters and related compounds has recently received further interest. In the pyridine series, the controversy regarding the bicyclic products as pyrido[1,2-*a*]-pyrimidin-2-ones (I) or pyrido[1,2-*a*]pyrimidin-4-ones (II) has been solved in favor of the latter ones.[1] The 2-ones were prepared by cyclization of the addition products of the Michael type, formed from aminopyridines and acetylenic compounds.[2] Moreover, mechanism for the formation of 4-ones has been discussed[3] and the reaction was applied to 2-aminothiazoles.[4]



We have extended the reaction to 3-aminopyridazines and with several β-keto esters, derivatives of the recently described pyrimido[1,2-*b*]pyridazine system[5,6] were obtained. 3-Aminopyridazines do not condense with β-keto esters to acylamino derivatives III unless a base, such as triethylamine, is added. On the other hand, the formation of crotonates as intermediates is very unlikely. 3-Acetoacetylaminopyridazine, when heated in polyphosphoric acid (PPA), afforded 4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = Me) which can be obtained also from 3-aminopyridazine and diketene or in a straightforward

(1) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," part II, Interscience, New York, N. Y., 1961, p 1141.
(2) J. G. Wilson and W. Bottomley, *J. Heterocycl. Chem.*, **4**, 360 (1967).
(3) M. Shur and S. S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
(4) G. T. F. Galasko and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **22**, 121 (1969).
(5) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).
(6) S. Ostrovernšik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **41**, 135 (1969).

TABLE I

π BOND ORDERS FOR THE PYRIMIDINE PART

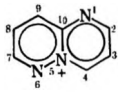
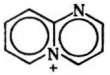
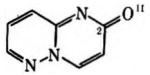
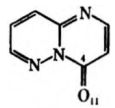
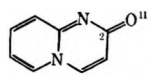
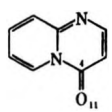
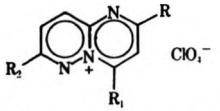
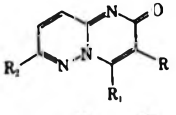
Bond						
1–2	0.683	0.703	0.499	0.651	0.505	0.639
2–3	0.612	0.583	0.485	0.661	0.489	0.663
3–4	0.715	0.761	0.806	0.492	0.814	0.542
4–5	0.497	0.409	0.416	0.371	0.386	0.321
2–11			0.630		0.618	
4–11				0.682		0.727

TABLE II

NMR DATA

	Registry no.	H_2	H_3	H_4	H_7	H_8	H_9	J_{23}	J_{34}	J_{24}	J_{78}	J_{89}	J_{79}	J_{49}	2Me	4Me	$J_{3,4Me}$
																	
R = R_1 = R_2 = H[a]	30247-51-9	0.21 (dd)	1.52 (dd)	0.0 (ddd)	0.34 (dd)	1.48 (dd)	0.97 (ddd)	4.5	6.7	1.8	4.5	9.4	1.8	0.9			
R = R_2 = H; R_1 = Me[a]	30247-52-0	0.45 (d)	1.54 (dd)		0.42 (dd)	1.66 (dd)	1.11 (dd)	4.2			4.3	9.0	1.8			6.96 (d)	0.8
R = R_1 = Me; R_2 = H[a]	30318-64-0		1.62 (q)		0.41 (dd)	1.52 (dd)	1.17 (dd)				4.5	9.2	1.8		7.08 (s)	6.95 (d)	0.9
R = Me; R_1 = Ph; R_2 = H[a]	30247-53-1		1.57 (s)		0.59 (dd)	1.60 (dd)	1.12 (dd)				4.2	9.0	1 8		7.03 (s)	2.30 (m, Ph)	
R = R_1 = Me; R_2 = Cl[a]	30247-54-2		1.70 (q)			1.48 (d)	1.18 (d)					9.0			7.13 (s)	7.07 (d)	0.4
																	
R = R_1 = R_2 = H[b]	30247-55-3		3.36 (d)	1.78 (d)	1.32 (dd)	2.48 (dd)	2.10 (dd)		6.3		4.9	8.9	2.1	0.1			
R = R_2 = H; R_1 = Me[b] (b)	30247-56-4		3.43 (q)		1.38 (dd)	2.46 (dd)	2.12 (dd)				3.9	9.0	2.0			7.51 (d)	0.8
R = H; R_1 = Me; R_2 = Cl[b]	30347-57-5		3.43 (q)			2.55 (d)	2.19 (d)					9.4				7.53 (d)	0.8
R = H; R_1 = Ph; R_2 = H[b]	30247-58-6		2.82 (s)		1.25 (dd)	2.42 (dd)	1.96 (dd)				3.8	8.8	1.8				
R = Br; R_1 = Me; R_2 = H[b]	30247-59-7				1.42 (dd)	2.60 (dd)	2.24 (dd)				3.9	9.7	1.8			7.38 (s)	

	Registry no.	H_2	H_3	H_4	H_6	H_7	H_8	H_9	J_{23}	J_{34}	J_{67}	J_{78}	J_{89}	J_{68}	J_{79}	J_{69}	Me groups
	30247-60-0		2.0 (q)		0.80 (dd)	1.95 (ddd)	1.55 (m)		0	0.8 (H_3Me_4)	6.7						7.20 (s) 7.03[b] (d)
	16075-67-5		3.42 (d)	1.70 (dd)	1.88 (dd)		2.80 (m)	2.22 (dd)		7.5	6.5	6.6	8.3	1.0	1.6	0.1	*c*
R = R_1 = R_2 = H	23443-10-9	1.74 (d)	3.60 (d)		0.93 (dd)	2.83 (ddd)	2.30 (m)		6.2		6.7	6.6	8.5	1.0	1.5		*b, d*
R = Me; R_1 = R_2 = H	1693-94-3		3.57 (s)		0.86 (dd)	2.75 (ddd)	2.25 (m)				6.7	6.6	8.5	1.0	2.0		7.43 (s) *b*
R = R_1 = Me; R_2 = H	30247-64-4		3.78 (s)		1.12 (d)	3.10 (dd)		2.69 (dq)			7.2				1.8		7.57 (s, 2Me) 7.52[b] (d)
R = R_2 = Me; R_1 = H	30247-65-5		3.65 (s)		1.08 (dd)	3.02 (t)[e]	2.41 (m)				6.6	6.6	0.8	0.9	1.2 (H_9 8Me)		7.54 (s, 2Me) 7.43[b] (s)

[a] In DMSO. [b] In $CDCl_3$. [c] In D_2O. [d] Prepared according to R. Adams and I. J. Pachter, *J. Amer. Chem Soc.*, **74**, 5491 (1952). [e] Degenerated quartet.

reaction with acetoacetic ester in the presence of PPA. The last-mentioned method proved to be the most convenient reaction for the synthesis of these and related bicyclic compounds V.

We have assigned to pyrimido[1,2-*b*]pyridazinones the structure of 2-ones rather than 4-ones on the basis of chemical evidence and of nmr spectroscopic correlations and π bond orders. The empirical relation between J_{ortho} and π bond order which was applied for a series of carbocyclic aromatic compounds[7] and recently redefined for six-membered carbocyclic aromatic molecules[8] was extended to several bicyclic heteroaromatic systems[9] and discussed in connection with the partial bond fixation. Table I presents the calculated values for p_{ij} for the pyrimidine part of the isomeric pyrimido-[1,2-*b*]pyridazin-2-ones and -4-ones as well as of pyrido[1,2-*a*]pyrimidin-2-ones and -4-ones.[10] There is an increase in bond order for $p_{3,4}$ of 2-ones as compared to $p_{2,3}$ of the isomeric 4-ones. As anticipated, this is reflected also in J_{ortho}. For an authentic pair of the isomeric pyrido[1,2-*a*]pyrimidin-2-one and -4-one, the observed $J_{3,4}$ and $J_{2,3}$, respectively, are in agreement with the aforementioned differences (Table II).

Similar regularities apply to pyrimido[1,2-*b*]pyridazinium perchlorate, prepared from 3-aminopyridazine and 1,1,3,3-tetraethoxypropane in the presence of PPA. The product (VI, R = R_1 = R_2 = H) is the first example of this fully aromatic bicyclic system and with other 1,3-dicarboxyl compounds related azinium perchlorates VI were synthesized.

As condensing agent PPA was found advantageous in the reaction between 3-aminopyridazines and ethoxymethylenemalonate to give the isomeric 4-ones (VIII). The previously reported[5] unsuccessful thermal cycliza-

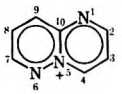
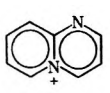
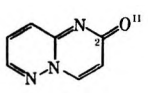
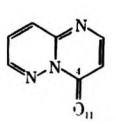
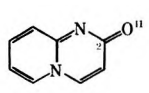
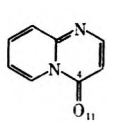
(7) N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, **36**, 2443 (1962).

(8) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

(9) A. J. Boulton, P. J. Halls, and A. R. Katritzky, *Org. Magn. Resonance*, **1**, 311 (1969).

(10) The authors are grateful to Professor Paudler, Ohio University, Athens, for a copy of the program according to which the reported values were calculated by Hückel method. The parameters used were in general those suggested by Streitwieser ("Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 135).

TABLE III
CALCULATED TOTAL π-ELECTRON DENSITIES

Position						
1	1.165	1.186	1.297	1.262	1.316	1.359
2	0.842	0.845	0.833	0.887	0.839	0.966
3	0.975	0.992	1.025	1.076	1.029	1.113
4	0.807	0.816	0.860	0.798	0.870	0.975
5	1.568	1.595	1.527	1.544	1.516	1.564
6	1.070	0.856	1.076	1.071	0.887	0.872
7	0.920	0.991	0.946	0.945	1.017	1.043
8	0.887	0.883	0.901	0.901	0.906	0.904
9	0.940	0.993	0.962	0.956	1.021	1.038
10	0.826	0.844	0.843	0.850	0.865	0.875
11			1.730	1.710	1.733	1.292

tion of VII (R = Cl) was now easily accomplished in PPA and VIII (R = Cl) was obtained.

It is noteworthy that compound VIII (R = H) underwent an acid-catalyzed addition of MeOH to the 4-carbonyl group and the formed adduct IX is upon heating reconverted to the starting 4-one. A nmr examination in $CDCl_3$ solution disclosed an equilibrium of about equal amounts of the 4-one VIII (R = H) and the adduct IX.

4-Methylpyrimido[1,2-*b*]pyridazin-2-one was brominated to form the 3-bromo derivative IV (R = Br; R_1 = Me; R_2 = H). The attack of the electrophile at position 3 is in agreement with the observed nmr data and was anticipated on hand of the calculated electron densities for this system (Table III).

In the pyrido[1,2-*a*]pyrimidone series nmr spectra permit distinction between the 2-one (I) and the 4-one (II, R = R_1 = R_2 = H), the $J_{3,4}$ being larger than $J_{2,3}$ of the 4-one. Moreover, a long-range coupling constant, $J_{4,9}$, was observed with the 2-ones of the pyrido[1,2-*a*]pyrimidine (I) or pyrimido[1,2-*b*]pyridazine (IV) series as well as with pyrimido[1,2-*b*]pyridazinium perchlorate (VI, R = R_1 = R_2 = H). Furthermore, only 4-methyl derivatives of all these systems display a small coupling constant between the 4-methyl group and H_3, whereas with 2-methyl derivatives such interactions with H_3 were not observed. According to previous[3] and these observations, pyrido[1,2-*a*]pyrimidones, obtained from 2-aminopyridines and acetoacetic ester, are in fact 4-ones and not 2-ones.[11]

The different reactivity of 3-aminopyridazines to give the bicyclic 2-ones as compared to 2-aminopyridines which gave the corresponding 4-ones may account for a lower basicity of 3-aminopyridazines. It is noteworthy that 5-nitro-2-aminopyridine failed to give a bicyclic product.[3]

Experimental Section

Melting points were taken on a Kofler melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord; ultraviolet spectra were recorded on a Beckman DU spectrophotometer and nmr spectra on a JEOL JNM-C-60HL spectrometer, using tetramethylsilane as internal standard.

3-Acetoacetylaminopyridazine (III, R = CH_3).—3-Aminopyridazine (1.9 g), acetoacetic ester (10 ml), and anhydrous Et_3N (1.0 ml) were heated under reflux for 2 hr at 135–140°. Upon standing overnight at room temperature diethyl ether (20 ml) was added, and the product was separated and washed with some ether (yield 2.0 g, 54%). For analysis a sample was recrystallized from methanol to give colorless needles: mp 179–180°; ir (KBr) 1721 and 1692 cm^{-1} (CO); nmr (CD_3SOCD_3) τ 1.80 (dd, H_4), 2.42 (dd, H_5), 1.12 (dd, H_6), 6.30 (s, CH_2), 7.78 (s, CH_3) ($J_{4,5}$ = 8.6, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.3).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.66; H, 4.95; N, 23.66.

In essentially the same manner the following compounds were prepared.

3-Benzoylacetylaminopyridazine (III, R_1 = C_6H_5) was prepared from ethyl benzoylacetate in 82% yield: mp 209–210° (from ethanol); nmr (CD_3SOCD_3) τ 1.69 (dd, H_4), 2.00 (dd, H_5), 1.03 (dd, H_6), 5.68 (s, CH_2), 2.40 (m, C_6H_5) ($J_{4,5}$ = 8.4, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.2).

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.98; H, 4.69; N, 17.35.

Cyclopentan-2-onecarboxylic acid 3-pyridazinylamide was obtained in 78% yield from ethyl cyclopentan-2-onecarboxylate: mp 186–187° (from methanol); nmr spectrum (CD_3SOCD_3) τ 1.75 (dd, H_4), 2.38 (dd, H_5), 1.10 (dd, H_6), 7.80 (m, cyclopentanonyl part) ($J_{4,5}$ = 8.6, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.2).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.65; H, 5.16; N, 20.57.

Pyrimido[1,2-*b*]pyridazin-5-ium Perchlorate (VI, R = R_1 = R_2 = H).—A solution of 3-aminopyridazine (2.85 g) in PPA[12] (50 g) was prepared at 110° and then cooled to 50°. Under stirring 1,1,3,3-tetraethoxypropane (6.6 g) was added and the mixture was left at this temperature for 3 hr. Upon 48 hr at room temperature the mixture was treated with crushed ice (50 g) and perchloric acid (5.0 g of 70%) was added. The product was crystallized from methanol and water (2:1) to give colorless crystals (3.4 g, 49%): mp 315–316°; uv (methanol) λ_{max} 240 and 296 nm (ε 6090 and 5850); ir (KBr) 1616 and 1517 cm^{-1} (C=C and C=N).

Anal. Calcd for $C_7H_6ClN_3O_4$: C, 36.33; H, 2.16; N, 18.21. Found: C, 36.60; H, 2.85; N, 18.37.

4-Methylpyrimido[1,2-*b*]pyridazin-5-ium Perchlorate (VI, R = R_2 = H; R_1 = CH_3).—3-Aminopyridazine (2.85 g) in PPA (40 g) at 75° was treated with 3-ketobutanal dimethyl acetal (4.0 g). The mixture was kept at 75° for 3 hr and then treated with ice (40 g) and perchloric acid (5.0 g, 70%). The product (5.2 g, 71%) was crystallized from 66% methanol: mp 278–279°; uv (methanol) λ_{max} 270 nm (ε 4950).

Anal. Calcd for $C_8H_8ClN_3O_4$: C, 39.12; H, 3.28; N, 17.11. Found: C, 39.44; H, 3.55; N, 17.07.

General Procedure for the Synthesis of Other Pyrimido[1,2-*b*]-pyridazin-5-ium Perchlorates (VI).—A 3-aminopyridazine (0.01–0.03 mol) and the 1,3-dicarbonyl compound (0.01–0.03 mol) were mixed with a sevenfold (by weight) quantity of PPA and the mixture was heated at 110–115°. After 1–1.5 hr when foaming has subsided, heating was discontinued and the clear reddish-

(11) G. Stöckelmann, H. Specker, and W. Riepe, *Chem. Ber.*, **102**, 455 (1969).

(12) Polyphosphoric acid (PPA) containing 83% P_2O_5 was used throughout this paper.

brown solution was cooled to room temperature and treated with ice (the same weight as PPA) and perchloric acid (0.012–0.035 mol, 70%). The precipitate was filtered off, washed with some water and methanol, and dried. In this manner the following compounds were synthesized.

2,4-Dimethylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R_2 = H; R_1 = CH_3) was obtained from acetylacetone in 74% yield: mp 227–228° (from 66% methanol); uv (methanol) λ_{max} and 260 nm (ϵ 32,250 and 5480).

Anal. Calcd for $C_9H_{11}ClN_2O_4$: C, 41.63; H, 3.88; N, 16.18. Found: C, 41.87; H, 4 04; N, 16.30.

2-Methyl-4-phenylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R = CH_3; R_1 = C_6H_5; R_2 = H) was prepared from benzoylacetone in 80% yield: mp 202–203° (from acetic acid); uv (methanol) λ_{max} 217 and 314 nm (ϵ 30,150 and 3870).

Anal. Calcd for $C_{14}H_{12}ClN_2O_4$: C, 52.27; H, 3.76; N, 12.92. Found: C, 52.51; H, 3.89; N, 13.02.

7-Chloro-2,4-dimethylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R = R_1 = CH_3; R_2 = Cl) was prepared from 3-amino-6-chloropyridazine and acetylacetone in 84% yield: mp 278–279° (from 66% methanol); uv (methanol) λ_{max} 232 nm (ϵ 43,500).

Anal. Calcd for $C_9H_9Cl_2N_3O_4$: C, 36.76; H, 3.08; N, 14.29. Found: C, 36.63; H, 3.26; N, 14.55.

7-Chloro-2,4-dimethylpyrido[3,2-*d*]pyrimido[1,2-*b*]pyridazin-5-ium perchlorate was obtained from 5-amino-8-chloropyrido-[2,3-*d*]pyridazine[13] and acetylacetone in 68% yield: mp 275–276° (from 50% methanol); uv (methanol) λ_{max} 241 nm (ϵ 45,500).

Anal. Calcd for $C_{12}H_{10}Cl_2N_4O_4$: C, 41.76; H, 3.50; N, 16.23. Found: C, 42.01; H, 3.29; N, 16.19.

Pyrido[1,2-*a*]pyrimidin-5-ium Perchlorate.—A solution of 2-aminopyridine (0.96 g) in methanol (10 ml), 1,1,3,3-tetraethoxypropane (2.2 g), and hydrobromic acid (2.0 g, 48%) was heated under reflux for 2 hr. The cooled mixture was treated with perchloric acid (2.5 g, 70%) and the obtained salt (1,3 g, 60%) was recrystallized from aqueous methanol to give colorless needles: mp 222–223°; uv (methanol) λ_{max} 226, 268, and 316 nm (ϵ 13,100, 4060, and 5150); ir (KBr) 1634 and 1504 cm^{-1} (C=C and C=N).

Anal. Calcd for $C_8H_7ClN_2O_4$: C, 41.67; H, 2.85; N, 12.15. Found: C, 41.69; H, 3.07; N, 12.19.

2,4-Dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate was obtained in the same manner in 78% yield: mp 229–230° (from 50% methanol); uv (methanol) λ_{max} 228, 274, and 312 nm (ϵ 35,000, 3050, and 5100).

Anal. Calcd for $C_{10}H_{11}ClN_2O_4$: C, 46.42; H, 4.28; N, 10.83. Found: C, 46.60; H, 4.25; N, 10.87.

General Procedure for the Synthesis of Pyrimido[1,2-*b*]pyridazin-2-ones (IV).—The corresponding 3-aminopyridazine (0.01–0.03 mol), an equivalent amount of a β-keto ester, and PPA (a sevenfold amount by weight) were heated under stirring at 110–120° for 1–2 hr until foaming subsided. The cooled mixture was diluted with water (double the weight of PPA) and solid sodium bicarbonate was added until pH 5–6. The mixture was repeatedly extracted with chloroform and from this solution the crude product was obtained after evaporation to dryness *in vacuo*. In this manner the following were prepared.

7-Chloro-4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = H; R_1 = CH_3; R_2 = Cl) in 72% yield from 3-amino-6-chloropyridazine and acetoacetic ester: mp 223–224° (from ethanol and ethyl acetate); uv (ethanol) λ_{max} 252 and 316 nm (ϵ 10,500 and 6000).

Anal. Calcd for $C_9H_7ClN_3O$: C, 49.12; H, 3.09; N, 21.48. Found: C, 49.29; H, 3.40; N, 21.37.

Cyclopenta-5,6-pyrimido[1,2-*b*]pyridazin-4-one (V) from ethyl cyclopenta-2-one carboxylate in 70% yield: mp 194–195° [sublimed at 160° (0.1 mm)]; uv (ethanol) λ_{max} 236 and 320 nm (ϵ 13,100 and 7200); nmr ($CDCl_3$) τ 2.15 (dd, H_6), 2.53 (dd, H_7), 1.24 (dd, H_8), 7.80 (m) and 6.95 [m, both for $(CH_2)_3$] ($J_{7,8}$ = 4.5, $J_{6,7}$ = 9.5, $J_{6,8}$ = 2.0).

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.20; H, 4.86; N, 22.06.

4-Phenylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = C_6H_5) was obtained from ethyl benzoylacetate in 78% yield: mp 204–205° (ethanol); uv (ethanol) λ_{max} 269 and 335 nm (ϵ 27,200 and 7100).

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.89; H, 4.11; N, 18.54.

4-Methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = CH_3). **A.**—According to the above method it was obtained in 83% yield from acetoacetic ester and sublimed at 160° (0.1 mm): mp 179–180°; uv (ethanol) λ_{max} 228 and 314 nm (ϵ 12,200 and 6800).

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.45; H, 4.65; N, 26.36.

B.—A solution of 3-aminopyridazine (1.9 g) in water (20 ml) was treated under vigorous stirring with diketene (2.0 g) dropwise during 30 min. Temperature was held at about 30° and after addition was complete, stirring was continued for 1 hr. The mixture was then extracted with chloroform and the crude product (1.1 g, 34%) crystallized from ethyl acetate, mp 179–180°. Ir and mixture melting point showed identity with the product obtained as described under A.

C.—Compound III (R = CH_3, 0.5 g) and PPA (5.0 g) were heated at 120° for 2 hr. Upon cooling water (20 ml) was added and the mixture neutralized with sodium bicarbonate to pH 6. Extraction with chloroform and evaporation of the solvent yielded a residue (0.2 g) which was sublimed at 140° (0.1 mm), mp 178–179°. Ir and mixture melting point showed identity with the specimen obtained under A.

4-Carbethoxypyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = $COOC_2H_5$).—A stirred mixture of 3-aminopyridazine (0.95 g), potassium salt of the enolic form of diethyl oxaloacetate (2.3 g), and PPA (20 g) was heated at 115° for 2 hr. The cooled mixture was treated with water (60 ml) and neutralized with sodium bicarbonate to pH 6. Extraction with chloroform (four times with 30 ml) gave upon evaporation the crude product (1.7 g, 78%). Upon sublimation at 160° (0.1 mm) the compound had mp 223–224°; uv (ethanol) λ_{max} 340 nm (ϵ 7300); ir (KBr) 1736 and 1695 cm^{-1} (CO); nmr ($CDCl_3$) τ 2.63 (s, H_3), 1.28 (dd, H_7), 2.46 (dd, H_8), 1.92 (dd, H_9), 5.52 (q, CH_2), 8.56 (t, CH_3) (J = 6.8, $J_{7,8}$ = 3.9, $J_{8,9}$ = 9.3, $J_{7,9}$ = 1.7).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 55.03; H, 4.31; N, 18.95.

Pyrimido[1,2-*b*]pyridazin-2-one-4-carboxylic Acid (IV, R = R_2 = H; R_1 = COOH).—The above ester (2.2 g) was left to stand at room temperature in aqueous KOH (15 ml, 10%) for 1 hr. Acidification with concentrated hydrochloric acid to pH 1 yielded colorless crystals (1.5 g, 79%): mp 280° dec (from water); uv (ethanol) λ_{max} 225 and 330 nm (ϵ 14,400 and 7200).

Anal. Calcd for $C_8H_5N_3O_3$: C, 50.27; H, 2.64; N, 21.98. Found: C, 50.03; H, 2.59; N, 21.93.

Pyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_1 = R_2 = H).—The above acid was thoroughly mixed with copper bronze (0.2 g). Portions of 100 mg of this mixture were sublimed at 270–275° (0.1 mm). The combined sublimates (210 mg) were resublimed and the pure compound (56%) had mp 169–170°; uv (ethanol) λ_{max} 228 and 318 nm (ϵ 12,250 and 7300); ir (KBr) 1709 cm^{-1} (CO).

Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.13; H, 3.13; N, 28.40.

3-Bromo-4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = Br; R_1 = CH_3; R_2 = H).—A stirred solution of IV (R = R_2 = H; R_1 = CH_3; 1.6 g) in glacial acetic acid (15 ml) was treated with bromine (1.6 g) and the mixture was heated for 5 min on a water bath. The separated product was washed with some acetic acid, suspended in a solution of sodium bicarbonate (25 ml, 10%). The remaining solid was filtered off, washed with water, and dried (1.7 g, 71%): mp (of colorless needles) 230–231° (ethanol); ir (KBr) 1701 cm^{-1} (CO).

Anal. Calcd for $C_8H_6BrN_3O$: C, 40.19; H, 2.59; N, 17.57. Found: C, 40.47; H, 2.55; N, 17.30.

3-Carbethoxypyrimido[1,2-*b*]pyridazin-4-one (VIII, R = H). **A.**—3-Aminopyridazine (1.9 g), diethyl ethoxymethylenemalonate (4.35 g), and PPA (40 g) were heated at 120° for 2 hr. Upon dilution with water (100 ml) and neutralization with sodium bicarbonate to pH 6, the product was filtered off, washed with some water, and dried *in vacuo* over KOH (3.7 g, 84%), mp 169–170° (ethanol).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 54.57; H, 3.91; N, 19.11.

B.—Compound VII (R = H) when heated in a sevenfold quantity of PPA at 120° for 2 hr afforded a product which was identical in all respects with the specimen under A (yield 80%).

3-Carbethoxy-7-chloropyrimido[1,2-*b*]pyridazin-4-one (VIII, R = Cl).—The compound was prepared according to the above

(13) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.*, **13**, 586 (1965).

procedure from 3-amino-6-chloropyridazine in 76% yield: mp 154–155° (ethanol); uv (ethanol) λ_{max} 254 and 340 nm (ϵ 11,000 and 8850); nmr ($CDCl_3$) τ 1.04 (s, H_2), 2.38 (d, H_8), 2.02 (d, H_9) ($J_{8,9}$ = 9.2), 5.56 (q, CH_2), 8.58 (t, CH_3) (J = 6.6).

Anal. Calcd for $C_{10}H_8ClN_3O_3$: C, 47.35; H, 3.17; N, 16.57. Found: C, 47.39; H, 3.09; H, 3.09; N, 16.80.

3-Carbethoxy-4-hydroxy-4-methoxypyrimido[1,2-*b*]pyridazine (IX).—Compound VIII (R = H; 0.5 g), methanol (10 ml), and few drops of concentrated hydrochloric acid were heated under reflux for 3 hr. Upon evaporation *in vacuo* to half of the original volume and after standing on ice overnight, the separated product (0.35 g) had mp 158–160° (at 150° on a preheated melting point apparatus); ir (Nujol) 2247 (hydrogen bonded OH) and 1754 cm^{-1} (CO). From the melt a new compound separated and had mp 168–170° (identical with the starting pyrimidopyridazinone): nmr of IX ($CDCl_3$) τ 0.95 (s, H_2), 6.00 (s, OCH_3), 1.14 (dd, H_7), 2.28 (dd, H_8), 1.95 (dd, H_9) ($J_{7,8}$ = 5.5, $J_{8,9}$ = 8.5, $J_{7,9}$ = 2.5), 5.55 (q, CH_2), 8.58 (t, CH_3).

From the nmr spectrum it is evident that the adduct is in equilibrium with the starting compound (ratio of about 1:1). When heated *in vacuo* the adduct is reconverted to the starting bicyclic compound.

2,9-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_1 = H; R = R_2 = CH_3).—The procedure for the synthesis of IV was followed, but using 2-amino-3-methylpyridine and acetoacetic ester (yield 71%), mp 131–132° (from *n*-hexane and ethyl acetate) (lit.[3] mp 131–132°).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.98; N, 16.08.

2,8-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_2 = H; R = R_1 = CH_3).—The compound was prepared as the above analog from 2-amino-4-methylpyridine in 74% yield, mp 136–137° (from *n*-hexane and ethyl acetate).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.64; H, 5.57; N, 16.20.

Registry No.—III (R_1 = CH_3), 30247-66-6; III (R_1 = C_6H_5), 30247-67-7; IV (R = R_2 = H; R_1 = $COOC_2H_5$), 30247-68-8; IV (R = R_2 = H; R_1 = COOH), 30247-69-9; V, 30247-70-2; VIII (R = H), 19111-57-2; VIII (R = Cl), 30247-72-4; IX, 30247-73-5; cyclopentan-2-onecarboxylic acid 3-pyridazinyl amide, 30318-65-1; 7-chloro-2,4-dimethylpyrido[3,2-*d*]-pyrimido[1,2-*b*]pyridazin-5-ium perchlorate, 30247-74-6; pyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-75-7; 2,4-dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-60-0.

Reaction of 4,6-Dimethoxy-5-nitropyrimidine with Methylhydrazine. Formation of 4-Hydrazino-6-hydroxypyrimidine

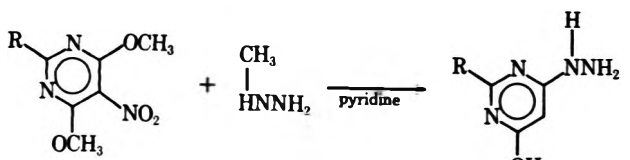
QUADE STAHL, FRANK LEHMKUHL, AND BERT E. CHRISTENSEN*

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

Received November 23, 1970

The reaction of 4,6-dimethoxy-5-nitropyrimidine (1) with methylhydrazine in refluxing pyridine or butanol is very complex involving the methylation of the solvent by 1 and the nucleophilic substitution and demethylation of the methylhydrazino substituent in the 5 position to yield 4-hydrazino-6-hydroxypyrimidine. The first step in this sequence of reactions involves the methylation of the solvent, followed by nucleophilic substitution of methylhydrazine in the 4 position, migration of its methyl substituent to form a carbon to oxygen bond with the adjacent nitro substituent, and eventual elimination of methyl nitrite from the 5 position as one of the reaction products. 4,6-Dimethoxy-5-nitropyrimidine reacts with pyridine (in the absence of methylhydrazine) to yield an insoluble methylpyridium salt which is not a precursor of 4-hydrazino-6-hydroxypyrimidine. The mother liquor from this reaction on acid hydrolysis yields 4-hydroxy-6-methoxy-5-nitropyrimidine and reacts with methylhydrazine to yield 4-hydroxy-6-hydrazinopyrimidine. Both 4-chloro-6-hydroxy-5-nitropyrimidine and 4,6-dichloro-5-nitropyrimidine react with methylhydrazine in ethanol to yield the corresponding methylhydrazino derivatives.

In previous work,[1] the reaction of methylhydrazine with 4,6-dimethoxy-5-nitropyrimidine (1) in an alcoholic solvent was found to be unexpectedly complex. We have continued the investigations of the reactions of 1 and the 2-methyl and 2-phenyl analogs (2 and 3) and 4,6-diethoxy-5-nitropyrimidine (4) and have established that the products are the 4-hydrazino-6-hydroxypyrimidines 5–7.

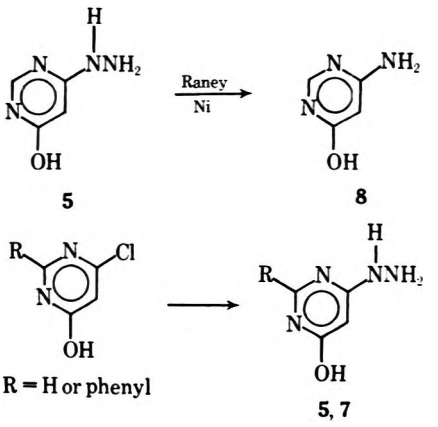


1, R = H
2, R = CH_3
3, R = C_6H_5

5, R = H
6, R = CH_3
7, R = C_6H_5

The structures were initially inferred from the spectral data which showed the probable presence of either a hydrazino, amino, or hydroxyl substituent and the absence of the methoxy and nitro substituents of the original starting material 1. High-resolution mass spectral measurements gave apparent molecular formulas $RC_4H_5N_4O$, R = H or phenyl.

The hydrazino structures were finally established by hydrogenolysis of 5 to give 4-amino-6-hydroxypyrimidine[2] (8) and by the synthesis of 5 and 7 from the reac-



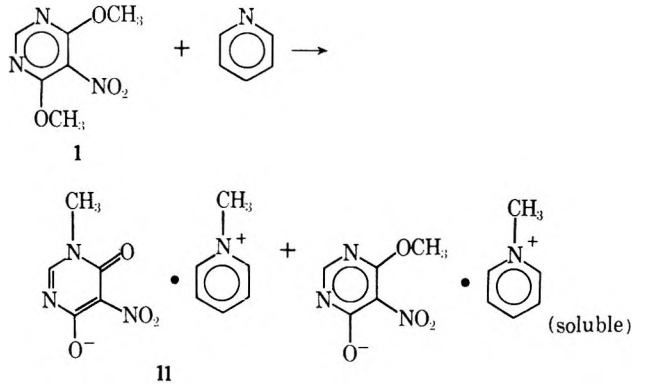
(1) M. H. Krackov and B. E. Christensen, *J. Org. Chem.*, **28**, 2677 (1963).

(2) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).

tions of the respective 6-chloropyrimidines[3,4] with hydrazine.

In an effort to ascertain the mechanism of this unusual reaction, 4,6-di(1-methylhydrazino)-5-nitropyrimidine (**9**), 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (**10**), and 5-amino-4,6-dimethoxypyrimidine were synthesized and subjected to the same reaction conditions with methylhydrazine in refluxing pyridine as **1**. No evidence for the formation of **5** was observed in these experiments, indicating that these compounds could not have served as an intermediate in the course of this reaction.

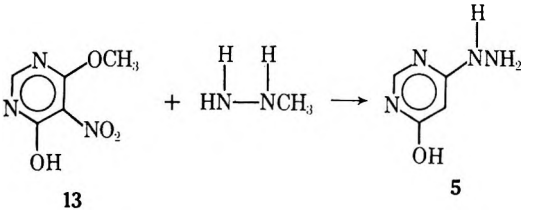
Since neither **9** or **10** was a precursor of **5**, the behavior of **1** in refluxing pyridine was investigated to determine if the initial step involved a reaction with the solvent. This reaction gave an insoluble crystalline salt in 25% yield which was shown to be the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (**11**).



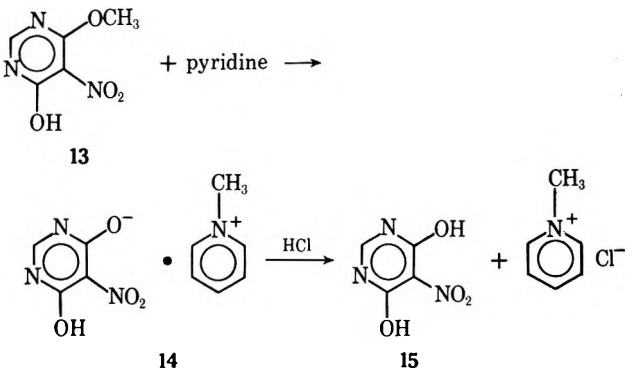
The nmr spectrum of **11** showed that the two equivalent methoxyl groups of **1** absorbing at δ 4.12 ($DCCl_3$) had split into two 3-proton singlets absorbing at δ 3.42 and 4.42 (D_2O), corresponding to those of the *N*-methyl groups in *N*-methylpyridinium iodide (δ 4.46) and 1,3-dimethyluracil (δ 3.30 and 3.43[5]). These changes were accompanied by the disappearance of the strong absorption band in the 1125-cm^{-1} region of the ir spectrum which is attributed to the methoxyl groups of **1** and the appearance of an absorption band at about 1650 cm^{-1}, indicative[6] of a conjugated amide carbonyl group in **11**. Hydrolysis of **11** gave 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (**12**) [δ 9.07 (1 H) and 3.62 (3 H)].

As expected, **11** was not a precursor of 4-hydrazino-6-hydroxypyrimidine but the mother liquor from the crystallization of **11**, when treated with methylhydrazine, did yield **5** in substantial amounts. After removal of pyridine, 4-hydroxy-6-methoxy-5-nitropyrimidine[7] (**13**) was isolated from the acidified residue in approximately 30% yield.

The isolation of **13** suggested that the first reaction in the sequence leading to **5** involved the methylation of pyridine followed by reaction of the methyl pyridinium salt of **13** with methylhydrazine. The compound **13** was synthesized[7] and treated with methylhydrazine in refluxing pyridine; this gave **5** in an 87% yield as contrasted to 65% in the original reaction.



The demethylation reaction observed with **1** in refluxing pyridine also occurred with the monomethoxy compound **13**. The resulting methylpyridinium salt obtained in 65% yield gave 5-nitro-4,6-dihydroxypyrimidine (**15**) in 86% yield. The mother liquor from the experiments yielding **14** gave **5** in much smaller yield when treated with methylhydrazine. This confirmed the presence of some unreacted **13** in the mother liquor.



The volatile products from the reaction which yielded **5** were isolated and investigated. The alkalinity of volatile vapors which were not removed by a cold water condensor was substantial, indicating the presence of ammonia or methylamine. Examination of the volatile products after trapping out the amines revealed the presence of methyl nitrite and another compound which may have been cyanic acid. Gas–liquid chromatography detected methanol in the mother liquor.

The first step in the sequence of reactions leading to **5** must therefore involve the methylation of the solvent by **1**. A plausible sequence of reactions that will account for the loss of the nitro substituent by **1** are shown in Scheme I.

Additional support for this mechanism stems from the following considerations: (1) the failure of 4-chloro-6-hydroxy-5-nitropyrimidine to behave in the same manner as 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methylhydrazine and ethanol; (2) the work of Kauffmann[8] which predicts the presence of hydrazide ions in basic solution of hydrazine which are essential for this mechanism to proceed.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra with the exception of the methyl nitrite spectra were obtained with a Beckman Model IR-8 spectrophotometer with the samples in the form of potassium bromide pellets. The methyl nitrite spectra were obtained through the use of a Beckman Model IR-7

(3) J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, 328 (1952).

(4) D. J. Brown and J. S. Harper, *ibid.*, 1298 (1961).

(5) Varian Associates, "High Resolution NMR Spectra Catalog," Vol. 2, 1963.

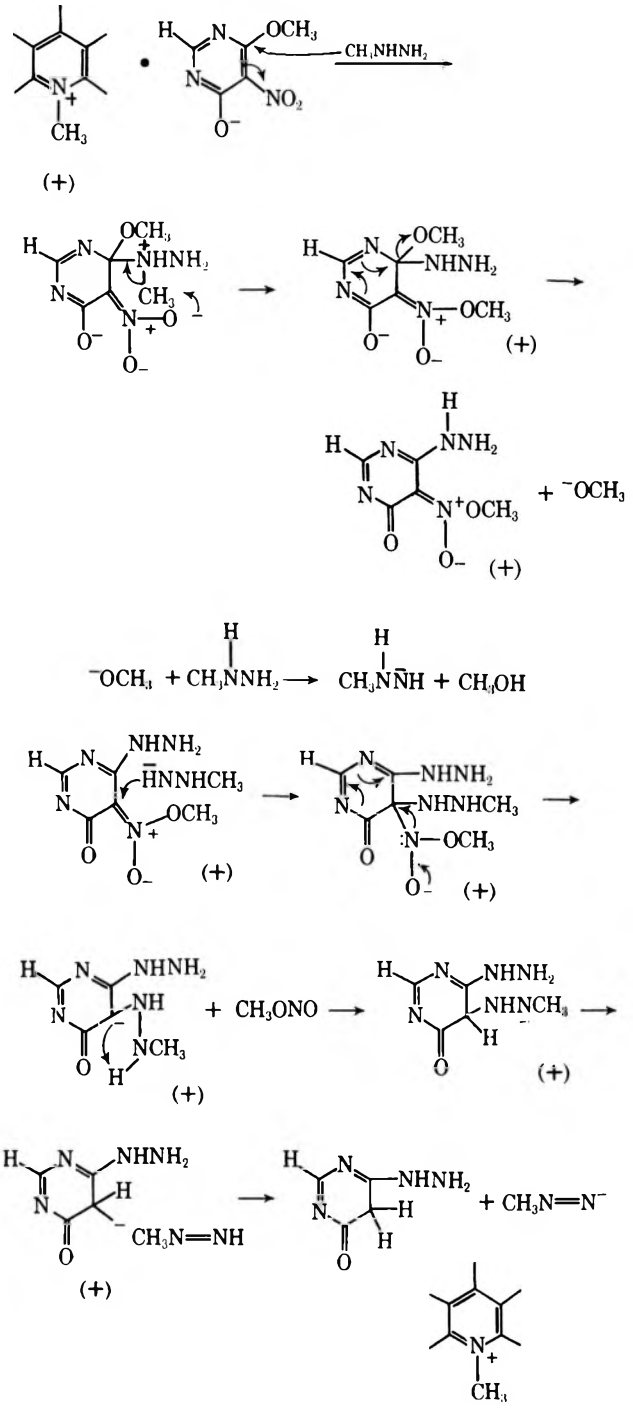
(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 233.

(7) G. M. Kheijets and N. V. Khromov-Borisov, *J. Org. Chem. USSR*, **2**, 1492 (1966).

(8) T. H. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **3**, 342 (1964); T. H. Kauffman, *et al.*, *Angew. Chem.*, **79**, 918 (1960).

SCHEME I

1 + pyridine ⟶ methylpyridinium salt of 13



spectrophotometer using a gas cell with sodium chloride windows. The nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. An external standard of 10% tetramethylsilane in deuteriochloroform was used for the samples run in deuterium oxide solutions. The carbon–hydrogen analyses were obtained through the use of a Coleman Model 33 carbon–hydrogen analyzer. A Coleman Model 29 nitrogen analyzer was used to obtain the nitrogen analyses. Mass spectra were determined with a Varian M-66 mass spectrometer and an AEI MS-9 (high-resolution spectra) with a 200° probe temperature and 70-eV energy.

4,6-Dimethoxy-2-methyl-5-nitropyrimidine (2).—To a rapidly stirred solution of sodium methoxide [prepared by adding 4.8 g (0.21 g-atom) of sodium to 150 ml of reagent grade methanol] was added dropwise over a period of 30 min 100 ml of a methanolic solution containing 11.0 g (0.053 mol) of 4,6-dichloro-2-methyl-5-nitropyrimidine. The pale red mixture was allowed to reflux for 1 hr and then the methanol was removed by distillation leaving a thick paste. An ice–water slurry (approximately 400 ml) was added and the mixture brought to neutrality (litmus) with 6 *N* hydrochloric acid. The precipitate was collected, washed well with cold water, and dried to yield 10.2 g (97%) of the cream-colored product, mp 123–124° (Urban and Schnider[9] reported an 86% yield, mp 116–117°). A small amount was recrystallized from methanol, mp 124.0–124.5°.

4,6-Dimethoxy-5-nitro-2-phenylpyrimidine (3).—Finely powdered 4,6-dichloro-5-nitro-2-phenylpyrimidine[10] (40.5 g, 0.15 mol) was suspended in 200 ml of anhydrous methanol and the mixture then cooled in an ice bath. A solution of sodium methoxide, prepared by adding 13.8 g (0.60 g-atom) of sodium to 300 ml of anhydrous methanol, was introduced dropwise into the stirred suspension at a rate which did not allow the temperature to rise above 20°. After the addition was complete, the mixture was refluxed for 1 hr, whereupon on cooling it was poured with vigorous stirring into 400 ml of ice-cold water. The precipitate was collected, washed well with cold water, and dried to yield 36.9 g (94.4%) of a yellow material. Recrystallization from ligroin (bp 90–120°) gave pale yellow needles: mp 122.5–123°; nmr (TFA) δ 7.77 (m, 2), 7.04 (m, 3), 3.75 ppm (s, 1).

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.3; H, 4.2; N, 15.8.

4,6-Diethoxy-5-nitropyrimidine (4).—A solution consisting of sodium ethoxide [4.6 g of sodium (0.2 g-atom) in 100 ml of ethanol] was added to 19.4 g (0.1 mol) of 4,6-dichloro-5-nitropyrimidine in 160 ml of absolute ethanol. The sodium ethoxide solution was added slowly so as to keep the temperature between 28–32°. After addition of the sodium ethoxide, the mixture was stirred 2 hr and then poured over ice. The precipitate was filtered, dried, and recrystallized from petroleum ether to yield needles (15.5 g, 73%), mp 62–63°.

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.1; H, 5.2. Found: C, 45.0; H, 5.3.

4-Hydrazino-6-hydroxypyrimidine (5). A.—Into a refluxing solution containing 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of reagent grade pyridine was pipetted 1.84 ml of methylhydrazine causing an immediate yellow coloration; the solution was allowed to reflux for 1 hr. During the first 5 min of the reflux period, a fine white material began to precipitate. After cooling in the refrigerator, the solution was filtered and the product filter cake washed with cold methanol to yield 0.71–0.82 g (56–65%) of crude cream-colored product, mp 245–255° dec. Evaporation of the filtrate yielded only unidentified products which exhibited mainly end absorption in its ultraviolet spectra. Recrystallization of the solid product twice from an ethanol–water solvent (1:1) produced fine long white crystals which decomposed on heating at 237°: uv max (H_2O pH 1) 212 (21,400), 258 mμ (5040); ir (Nujol) 3320, 3257, 3186 (hydrazino NH), 1667 (cyclic amide CO), 1626 (hydrazino NH_2); nmr (TFA) δ 8.11 (s, 1), 6.06 ppm (s, 1) [on standing peaks shift to 8.3 (s, 1), 5.75 ppm (s, 1)]; mass spectrum 70 eV *m/e* (rel intensity) 126 (100), 110 (40), 99 (43), 96 (17), 83 (9), 69 (28), 68 (60), 41 (19), 40 (28), 28 (41); peaks measured by high-resolution $C_4H_6N_4O$ (126.0547), $C_3H_5N_3O$ (99.0432), $C_4H_4N_2O$ (96.0321), $C_3H_4N_2$ (68.0136).

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.1; H, 4.7.

B.—To a refluxing solution of 2.13 g (0.01 mol) of 4,6-diethoxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 1 hr, cooled, and filtered. The product was washed with cold methanol and dried. The yield was 0.259 g (20.6%), mp 235–255° dec. The product was shown by infrared spectral analysis to be identical with the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

C.—Compound 13 (1.71 g, 0.01 mol) in refluxing pyridine was treated with 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 30 min, cooled, and filtered. The product was washed with cold methanol and dried. The yield was 1.10 g (87%), mp 235–255° dec. The product was shown by infrared spectral analysis to be identical with the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

(9) R. Urban and Schneider, *Helv. Chim. Acta*, **41**, 1806 (1958).

(10) H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1858 (1955).

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.0; H, 4.7.

D.—To 1.71 g (0.01 mol) of compound **13** in 50 ml of dry benzene was added 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 30 min. The product was isolated by filtration, washed with cold methanol, and dried, yield 0.64 g (50.8%), mp 235–255° dec. An infrared spectrum of the compound was identical with that obtained for an authentic sample of 4-hydrazino-6-hydroxypyrimidine.

4-Hydrazino-6-hydroxy-2-methylpyrimidine (6).—The procedure was essentially the same as for **5**. Recrystallization twice from ethanol–water (1:2) gave a 51% yield of long white crystals of **6**, mp 155–156° dec. This product also gave a positive blue color test with ferric chloride: uv max (H_2O pH 1) 261 mμ (6810); ir (Nujol) 3335, 3265, 3142 (hydrazino NH), 1671 (cyclic amide CO), 1621 (hydrazino NH_2); nmr (TFA) δ 5.75 (s, 1), 2.17 ppm (s, 3) [on standing peaks shift to δ 5.40 (s, 1), 2.47 (s, 3) ppm]; mass spectrum 70 eV *m/e* (rel intensity) 141 (33), 140 (90), 125 (21), 124 (33), 110 (25), 99 (100), 82 (28), 69 (28), 68 (83), 55 (24), 43 (33), 42 (73), 41 (54), 40 (55), 32 (37), 28 (54).

4-Hydrazino-6-hydroxy-2-phenylpyrimidine (7).—The 4,6-dimethoxy-5-nitro-2-phenylpyrimidine in hot pyridine did not react with methylhydrazine to give **7** in an isolable yield but instead yielded other products most likely from the cleavage of the pyrimidine ring. By the use of 1-butanol (dried with calcium sulfate and freshly distilled) as solvent, a small amount of **7** was formed.

A solution of 10.4 g consisting of (0.04 mol) of 4,6-dimethoxy-5-nitro-2-phenylpyrimidine and 600 ml of refluxing 1-butanol was added dropwise to a solution of 7.4 ml (0.16 mol) of methylhydrazine in 100 ml of 1-butanol over a period of 45 min. The deep yellow solution was refluxed over 2 hr becoming orange (no precipitation). On cooling in a deep freeze overnight, 2.5 g (31%) of the crude yellow-tan crystals were obtained, mp 210–230° dec. Recrystallization from 1-butanol gave pale yellow crystals: mp 227–228° dec; uv (H_2O pH 1) 206 (34,000), 239 (16,400), 287.5 mμ (8080); ir (Nujol) 3367, 3289, 3252 (hydrazine NH), 1668 (cyclic amide CO), 1618 (hydrazino NH_2), 1568 (aromatic ring); nmr (TFA) δ 7.72 (m, 2), 7.23 (m, 3), 6.02 ppm (s, 1); nmr (DMSO-d_6) 8.39 (m, 3), 7.80 (m, 3), 5.66 (s, 1), 3.65 ppm (s, broad, 2.7); mass spectrum 70 eV *m/e* 202, 187, 186, 173, 172, 160, 159, 144, 124, 104, 99, 75, 74, 69, 56, 43, 42, 32, 31, 28; peaks measured at high resolution $C_{10}H_{10}N_4O$ (202.0851), $C_{10}H_9N_3O$ (187.0746), $C_{10}H_8N_2O$ (172.0641), $C_9H_8N_2$ (144.0689), $C_4H_4N_4O$ (124.0387), C_7H_6N (104.0500), $C_3H_5N_3O$ (99.0433), C_3H_3NO (69.0215). The ir and nmr spectra of the samples were identical with those prepared from authentic compounds.

Anal. Calcd for $C_9H_{10}N_4O$: C, 59.5; H, 5.0. Found: C, 59.4; H, 4.8.

4-Amino-6-hydroxypyrimidine (8).—The procedure of Ainsworth[11] was modified to prevent the reduction of the pyrimidine ring. To a gently boiling solution of 0.50 g (0.004 mol) of 4-hydrazino-6-hydroxypyrimidine in 10 ml of water and 3 ml of 28% aqueous ammonium hydroxide was added in small portions 2 g of Raney nickel, prepared according to Brown.[2] After completing the addition, the mixture was gently refluxed, with stirring, for 30 min; upon evaporation to dryness 400 mg of crude product was obtained. Recrystallization from water or sublimation yielded 350 mg (79%), mp 264–265°.

Anal. Calcd for $C_4H_5N_3O$: C, 43.2; H, 4.5; N, 37.8. Found: C, 43.1; H, 4.3; N, 37.6.

4-Hydrazino-6-hydroxypyrimidine from 4-Chloro-6-hydroxypyrimidine.—To 2.6 g (0.02 mol) of 4-chloro-6-hydroxypyrimidine[4] dissolved in 100 ml of absolute ethanol heated to approximately 70° was added 1.35 ml (0.04 mol) of 95% anhydrous hydrazine, and the resultant mixture was refluxed for 30 min; within 5 min crystals were observed. Upon cooling, the solution was diluted with 50 ml of water and allowed to stir for an additional 5 min. The precipitate was collected and washed with cold water to yield 1.26 g (50%) of the white product, mp 235–245° dec. Concentration of the mother liquor to about 10 ml gave another 1.0 g (40%) of crude product.

Recrystallization of a small portion from ethanol–water (1:1) solvent gave long white needles which decomposed at *ca.* 237°; its melting point was *ca.* 310° when inserted at 305°.

This compound gives a positive Tollens test, a positive reaction with sodium pentacyanoamineferrate, and (unexpected) positive test (a deep blue color) with ferric chloride solution.

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.1; H, 4.9.

4-Chloro-6-hydroxy-2-phenylpyrimidine.—A mixture of 5 g (0.22 mol) of 4,6-dichloro-2-phenylpyrimidine[3] and 50 ml of 3 *N* sodium hydroxide was refluxed vigorously until only a clear solution remained (approximately 8 hr). The solution cooled in an ice bath was carefully acidified to pH 2–4 with concentrated hydrochloric acid.

After filtering and thoroughly washing with water, the product was pressed and then dried *in vacuo* over phosphorus pentoxide, yield 4.5 g. Recrystallization from isopropyl alcohol yielded fine white needles (92%): mp 226–227°; uv max (H_2O pH 1) 242 (11,500), 289 mμ (9760); nmr (DMSO-d_6) δ 8.17 (m, 2), 7.60 (m, 3), 6.55 (s, 1), 4.20 ppm (s, broad, 1).

Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.1; H, 3.5; N, 13.6. Found: C, 58.0; H, 3.5; N, 13.3.

4-Hydrazino-6-hydroxy-2-phenylpyrimidine.—The addition of 0.67 ml (0.02 mol) of 95% anhydrous hydrazine to a gently refluxing suspension of 2.1 g (0.01 mol) of 4-chloro-6-hydroxy-2-phenylpyrimidine in 50 ml of absolute ethanol gave a clear colorless solution. This solution was refluxed for 30 min before the product began to precipitate. After refluxing for an additional 30 min, the mixture was cooled and diluted with 25 ml of cold water, and the product was isolated by filtration to yield 1.2 g (59%) of white crystals, mp 239–241° dec. Concentration of the mother liquor to 10 ml gave 0.7 g (35%) more of the crude product. A small portion was recrystallized for analysis from 1-butanol as fine white crystals, mp 239–240° dec.

The product gave a weakly positive test (blue color) with ferric chloride solution. The compound also gave a positive reaction with Tollens reagent and with sodium pentacyanoamineferrate solution.

Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.5; H, 5.0. Found: C, 59.6; H, 4.9.

4,6-Di(1-methylhydrazino)-5-nitropyrimidine (9).—A 250-ml standard taper erlenmeyer flask containing a solution of 1.94 g (0.01 mol) of 4,6-dichloro-5-nitropyrimidine in 200 ml of absolute methanol was cooled to −10°. On addition of 1.85 ml (0.04 mol) of methylhydrazine the solution turned to a yellow color. The solution in the stoppered flask was stirred for 1 hr while allowing the temperature to rise to 20–25°. During this period the product precipitated as a yellow powder. After removing the product by filtration and drying, the yield was 1.85 g (84.5%), mp 175–177° dec. Recrystallization from dioxane gave fine yellow crystals, mp 183.5–184.5° dec.

Anal. Calcd for $C_6H_{11}N_7O_2$: C, 33.8; H, 5.2; N, 46.0. Found: C, 33.9; H, 5.2; N, 45.8.

4-Methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (10).—A solution containing 9.48 g (0.05 mol) of 4-chloro-6-methoxy-5-nitropyrimidine[12] in 400 ml of absolute methanol was cooled below 0°. Then 4.6 ml (0.1 mol) of methylhydrazine was pipetted into the solution, producing a yellow color. The solution in a stoppered flask was stirred for 30 min while allowing it to warm to room temperature. Evaporation of the solution to approximately 150 ml, followed by filtration and washing of the filter cake with cold water, yielded 8.3 g (83.5%) of yellow product, mp 196–198°. Purification by either crystallization from absolute ethanol or by sublimation gives a yield of 6.8 g (68%), mp 201–202°.

Anal. Calcd for $C_6H_9N_5O_3$: C, 36.2; H, 4.5; N, 35.2. Found: C, 36.1; H, 4.6; N, 35.1.

Methylpyridinium Salt of 1,6-Dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (11).—In a 100-ml round-bottom flask were placed 1.027 g (0.0056 mol) of 4,6-dimethoxy-5-nitropyrimidine and 50 ml of anhydrous pyridine. The flask was fitted with a reflux condensor and heated in an oil bath maintained at 135–140°, for about 40 min, with stirring. On cooling overnight in a refrigerator, the salt precipitated as a brown crystalline solid. The mixture was filtered with suction, and the solid was washed with fresh pyridine and dried *in vacuo* at about 80° for 24 hr, yielding 0.379 g (25.8%) of the light brown salt: mp 155–157°; ir (Nujol) 3067 (aromatic hydrogen), 1655 (cyclic amide CO), 1618 (aromatic ring), 1595, 1330 (nitro); nmr (D_2O) δ 3.45 (s, 3), 4.51 (s, 3), 8.10 (m, 3), 8.53 (m, 1), 8.87 ppm (m, 2).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 49.99; H, 4.59. Found: C, 49.81; H, 4.56.

(11) C. Ainsworth, *J. Amer. Chem. Soc.*, **78**, 1636 (1956).

(12) J. W. Barton and W. W. Pauler, *J. Org. Chem.*, **26**, 4961 (1961).

1,6-Dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (12).—To 0.379 g of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine was added 5 ml of dilute hydrochloric acid, whereupon a tan precipitate formed immediately. The mixture was refrigerated for several hours and then filtered with suction. Recrystallization of the solid from water yielded 0.118 g (43.3%) of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine: mp 265–269° dec; ir (Nujol) 3085 (hydrogen bonded OH), 1684 (cyclic amide CO), 1513, 1340 (nitro); nmr (D_2O) δ 9.03 (s, 1), 3.62 ppm (s, 3).

Anal. Calcd for $C_5H_5N_3O_4$: C, 35.09; H, 2.95. Found: C, 34.83; H, 2.89.

4-Hydroxy-6-methoxy-5-nitropyrimidine (13).—A solution of 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine was refluxed for 30 min. After filtration of the insoluble salt (the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxcpyrimidine), 1.03 g (38.8%), the pyridine was removed by vacuum distillation. The resulting dark oil was dissolved in 15 ml of cold water and acidified with glacial acetic acid. The light yellow precipitate was isolated by filtration, washed with cold water, and dried to yield 0.47 g (27.4% yield based on the 4,6-dimethoxy-5-nitropyrimidine not accounted for by the insoluble salt), mp 242–243°. An infrared spectrum of the material was identical with the infrared spectrum of an authentic sample of 4-hydroxy-6-methoxy-5-nitropyrimidine.[7] The two compounds accounted for 66.2% of the starting material.

Anal. Calcd for $C_5H_5N_3O_4$: C, 35.1; H, 2.9. Found: C, 35.0; H, 2.9.

Methylpyridinium Salt of 4,6-Dihydroxy-5-nitropyrimidine.—To 50 ml of refluxing pyridine was added 1.71 g (0.01 mol) of 4-hydroxy-6-methoxy-5-nitropyrimidine. After 1 hr two immiscible layers separated which were then cooled in an ice bath. Upon being stirred the lower layer crystallized, yielding light brown crystals. The mixture was separated by filtration and the crystalline product was washed with fresh pyridine, yielding 1.62 g (65%) of the light brown salt, mp 147–148°.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.0; H, 4.0; N, 22.4. Found: C, 47.8; H, 3.9; N, 22.2.

The methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine (1 g) in 15 ml of cold water was acidified with dilute hydrochloric acid until the solution was acidic to litmus paper, whereupon a white precipitate formed. Isolation of the precipitate yielded 0.54 g (86.3%) which was identified from infrared spectra and C, H, and N analysis as 4,6-dihydroxy-5-nitropyrimidine, mp <300°.

Anal. Calcd for $C_4H_3N_3O_4$: C, 30.6; H, 1.9; N, 26.8. Found: C, 30.5; H, 1.9; N, 26.7.

To the mother liquor from the preparation of the methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine was added 0.64 ml (0.04 mol) of methylhydrazine. The solution was refluxed for 30 min and isolation yielded 0.076 g (17.3% based on the 4-hydroxy-6-methoxy-5-nitropyrimidine not accounted for by the salt) of 4-hydrazino-6-hydroxypyrimidine as judged by comparison of infrared spectra.

Volatile By-products Evolved from Reaction of Methylhydrazine, 4,6-Dimethoxy-5-nitropyrimidine, and Pyridine and Butanol Solvents. A. Amines.—To 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine heated under reflux was added 1.84 ml (0.04 mol) of methylhydrazine. The system was flushed with nitrogen gas. The volatiles from the reaction system were first passed through a salt–ice cold trap and then into 100 ml of 0.1 *N* hydrochloric acid. The acid was back titrated with 0.1 *N* sodium hydroxide; 33.60 ml of sodium hydroxide were required. This accounts for 0.00664 mol of amine vapors. The yield of 4-hydrazino-6-hydroxypyrimidine was 0.708 g (56.2%).

B. Methyl Nitrite. 1.—The 4,6-dimethoxy-5-nitropyrimidine–methylhydrazine reaction in pyridine was carried out as described previously. The volatiles from the reaction were passed through a double U-tube. In the first U-tube was placed a strip of starch–iodide test paper wetted with distilled water; in the second was placed a strip of starch–iodide test paper wetted with dilute hydrochloric acid. During the reaction the first strip of test paper remained white while the second strip started turning dark purple after about 5 min of reflux (simultaneous with the first appearance of precipitation in the reaction vessel).

2.—A reaction was carried out with methylhydrazine and 4,6-dimethoxy-5-nitropyrimidine in pyridine. The system was first flushed with nitrogen gas and then the reactants were added. The usual scale of 0.01 mol of 4,6-dimethoxy-5-nitropyrimidine was used. To ensure the removal of any amines or pyridine vapors, the gaseous products were passed through a calcium chloride tube and two U-tubes cooled in salt–ice bath prior to trapping in the Schwartz tube. A soda–lime tube and a drierite tube were used to prevent carbon dioxide or water from condensing into the Schwartz tube. After the reflux period the Schwartz tube was sealed off and attached to a vacuum line. The material in the tube was then transferred by normal techniques to a gas infrared cell. The spectrum was then obtained using a Beckman IR-7 spectrophotometer. This spectrum accounted for the presence of methyl nitrite as well as another extremely volatile compound, possibly cyanic acid.

C. Methanol and Methyl-*n*-butyl Ether.—To 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 100 ml of 1-butanol was added 1.84 ml (0.04 mol) of methylhydrazine. The solution was refluxed for 3 hr and then cooled in an ice bath. The 4-hydrazino-6-hydroxypyrimidine, 0.24 g (19% yield), was removed by filtration. The mother liquor was analyzed by gas chromatographic techniques which revealed the presence of methanol, methyl *n*-butyl ether, methylhydrazine, and 1-butanol.

Registry No.—1, 15846-14-7; 2, 29939-34-2; 3, 29939-35-3; 4, 29939-36-4; 5, 29939-37-5; 6, 29939-38-6; 7, 29939-39-7; 8, 1193-22-2; 9, 29939-41-1; 10, 29954-19-6; 11, 29954-20-9; 12, 29954-21-0; 13, 14341-20-9; 14, 29954-23-2; 15, 2164-83-2; 4-chloro-6-hydroxy-2-phenylpyrimidine, 29954-25-4; methylhydrazine, 60-34-4.

Acknowledgment.—The authors wish to express their appreciation to Standard Oil of California and Varian Associates for mass spectrographic data and to Richard Harper for his assistance in the elucidation of the structure of methylpyridium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine.

Pyrolysis of 1-Methyl-2-phenylpiperidine-1-acylimides

S. WAWZONEK*[1] AND J. G. STEPHANIE[2]

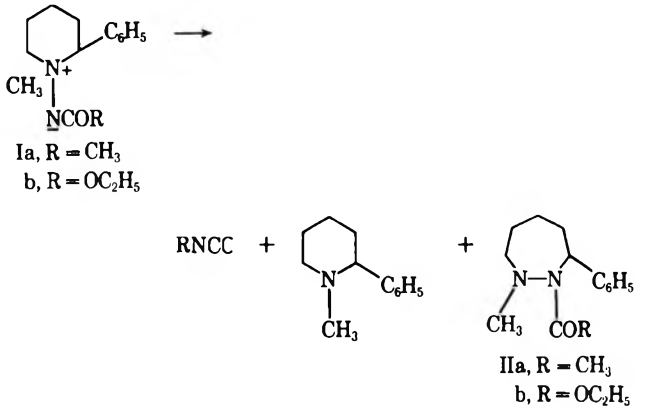
Department of Chemistry, University of Iowa, Iowa City, Iowa 52240

Received September 25, 1970

1-Methyl-2-phenylpiperidine-1-acetylimide upon pyrolysis formed methyl isocyanate, 1-methyl-2-phenylpiperidine, and 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine. The corresponding carbethoximide gave ethyl carbamate and 1-methyl-2-carbethoxy-3-phenylhexahydro-1,2-diazepine. The structures of the diazepines were demonstrated by spectra and an independent synthesis from ethyl 4-benzoylbutyrate.

The successful rearrangement of 1-methyl-2-phenylpyrrolidine-1-acetylimide to 1-methyl-2-acetyl-3-phenylhexahydropyridazine[3] suggested a study of the rearrangement of the related piperidine derivatives as a possible method for preparing hexahydrodiazepines.

In this work the rearrangement of 1-methyl-2-phenylpiperidine-1-acetylimide (Ia) and 1-methyl-2-phenylpiperidine-1-carbethoxyimide (Ib) is described. The aminimides were prepared from 2-phenylpiperidine by reactions described earlier.[4] The yield of aminimide



Ia was comparable to that obtained from 2-phenylpyrrolidine[3] but the yield of the carbethoxy analog (Ib) was low; alkylation of 1-carbethoxyamino-2-phenylpiperidine with methyl iodide gave low yields of the corresponding hydrazinium salt.

The alternate method[5] for preparing aminimides using the base-catalyzed condensation of 1-amino-1-methyl-2-phenylpiperidinium iodide and ethyl carbonate gave a 28% yield of Ib based on the iodide.

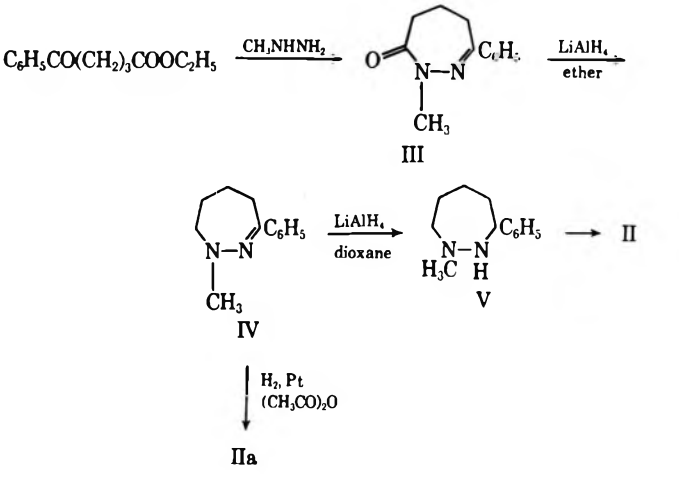
The structure of Ia was supported by a band at 1560–1580 cm^{-1} in the infrared, the nmr spectrum, and the formation of 1-acetamino-1-methyl-2-phenylpiperidinium iodide upon treatment with hydriodic acid in acetonitrile.

The carbethoxyaminimide (Ib) as expected showed a band at longer wavelength, 1630 cm^{-1}, in the infrared. Further evidence for the structure was the nmr spectrum and the facile hydrolysis with hydriodic acid in water to 1-methyl-1-amino-2-phenylpiperidinium iodide.

Pyrolysis of the aminimide (Ia) at 150–200° under reduced pressure gave a 15.5% yield of 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa). The major products in this reaction were methyl isocyanate and 1-methyl-2-phenylpiperidine.

The same reaction with the carbethoxy derivative (Ib), which cannot form an isocyanate, gave the hexahydro-1,2-diazepine derivative IIb (22.4%), ethyl carbamate, 1-methyl-2-phenylpiperidine, and tarry materials (50%).

The structures of the diazepines (II) was established by the following independent synthesis from ethyl 4-benzoylbutyrate and by the nmr spectra which were temperature dependent.



Condensation of ethyl 4-benzoylbutyrate with methylhydrazine at 200–210° gave 1-methyl-3-phenyl-Δ^2-tetrahydro-1,2-diazepin-7-one (III). The structure was supported by bands at 1680 and 1660 cm^{-1} in the infrared spectrum and by the characteristic splitting of the aromatic hydrogen peaks observed in the nmr spectrum for the benzylidene system. Reduction of this compound III with lithium aluminum hydride in ether gave 1-methyl-3-phenyl-Δ^2-tetrahydro-1,2-diazepine (IV). This compound had the same splitting for the protons of the phenyl group in the nmr spectrum as III.

Reduction of IV with lithium aluminum hydride in dioxane gave 1-methyl-3-phenylhexahydro-1,2-diazepine (V). This compound could not be obtained in a pure condition since it is easily oxidized by air to IV. A similar sensitivity to air has been reported for 3,7-diphenylhexahydro-1,2-diazepine.[6]

The hexahydrodiazepine V when treated with acetic anhydride gave 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa). This product was also obtained by the catalytic reduction of IV in acetic anhydride and was identical with the product obtained by pyrolysis. The acetyldiazepine (IIa) was resistant to basic hydrolysis and was obtained unchanged after refluxing in glycerol with potassium hydroxide at 200° for 9 hr.

(1) To whom inquiries should be addressed.

(2) Abstracted in part from the Ph.D. thesis of J. G. S., June 1969.

(3) S. Wawzonek and R. C. Gueldner, *J. Org. Chem.*, **30**, 3031 (1965).

(4) S. Wawzonek, J. Chua, E. L. Yeakey, and W. J. McKillip, *ibid.*, **28**, 2376 (1963).

(5) W. J. McKillip and R. C. Slagel, *Can. J. Chem.*, **45**, 2620 (1967).

(6) C. G. Overberger and J. G. Lombardino, *J. Amer. Chem. Soc.*, **80**, 2317 (1958).

The hexahydrodiazepine (V) when treated with ethyl chloroformate in the presence of triethylamine gave the carbethoxy derivative IIb which was identical with the product obtained by the pyrolysis of Ib.

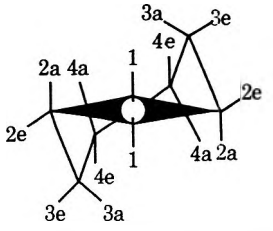
Diazepine IIa in deuteriochloroform showed at −48° three singlets of unequal size at δ 2.08, 2.12, and 2.20 for the CH_3CO protons and three singlets of unequal size at δ 2.71, 2.93, and 2.95 for the NCH_3 protons. On raising the temperature to 0° the methyl singlet for CH_3CO at δ 2.20 disappeared and the NCH_3 singlets appeared at δ 2.70, 2.86, and 2.92. At 35° the two acetyl methyl singlets were at δ 2.04 and 2.13 and the three *N*-methyl singlets were at δ 2.68, 2.81, and 2.90. Raising the temperature to 68° coalesced these peaks to one singlet for each group.

The nmr behavior in carbon tetrachloride was quite similar and gave singlets for these groups at 71°.

The carbethoxy compound IIb showed two singlets at δ 2.67 and 2.78 for the NCH_3 protons between −40 and +15° in deuteriochloroform. At temperatures of +23.5–29° a broad singlet was observed at δ 2.73 with a shoulder at δ 2.71. This combination coalesced to a singlet at 33°. The nmr behavior in carbon tetrachloride was approximately the same.

These data indicate that three conformations exist for the acetyl compound IIa and two for the carbethoxy compound IIb at ordinary temperatures. Since C-3 is an asymmetric carbon, eight different optically active conformers are possible or four different *dl* modifications. Only three of these possibilities contribute to the nmr spectrum for the acetyl derivative IIa.

Assuming that the diazepine ring system will not differ greatly from cycloheptane, a twisted chair form[7] would be the preferred arrangement over other alternatives. In such an arrangement the relative steric hindrance encountered by substituents is qualitatively 2e, 3e, 4e < 1 < 4a < 2a, 3a.[7] This formulation would predict the following conformations.



VI, trans-2,3; trans-3,4; 2e, 3e, 4e
VII, cis-1,2; trans-2,3; 1, 2e, 3e
VIII, trans-2,3; cis-3,4; 2e, 3e, 4a
IX, cis-2,3; cis-3,4; 2e, 3a, 4e

The least sterically hindered configuration would be VI since all three substituents are in an equatorial position. Among the remaining three structures IX would be the most sterically hindered form and would not exist since the acetyl group is axial and causes more crowding than when the methyl is in the 1 (VII) and the phenyl is in the 4a (VIII) positions.

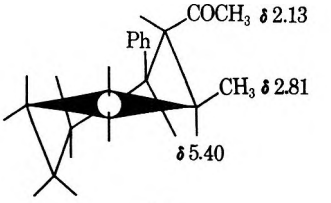
The relative strength of the singlets at δ 2.68, 2.81, and 2.90 at room temperature is approximately 1.2:1.8:1 and is relatively constant up to 49°. At this temperature broadening of the singlet at δ 2.9 occurs without a change in its intensity. At 62° the singlets at δ 2.81 and 2.90 coalesce into a singlet at δ 2.80 which is twice as large in area as the singlet at δ 2.71.

(7) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).

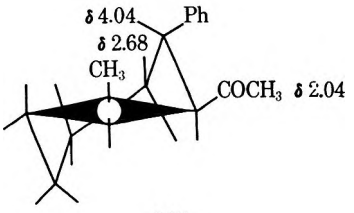
On the basis of Dreiding models the singlets at δ 2.68, 2.81, and 2.90 are assigned to conformation VII, VI, and VIII, respectively. The shielding of the methyl group by the acetyl is slightly larger when these groups are equatorial than when the methyl is in the 1 position of the twisted chair conformer VII.

The singlets for the acetyl methyls, which overlap with the broad multiplet for the 4,5,6-methylene hydrogens, have approximately the same intensities (1:1.1). The smaller singlet at δ 2.13 would correspond to conformer VI and the larger one at δ 2.04 would include both VII and VIII; the shielding would be slightly greater when the three groups are equatorial.

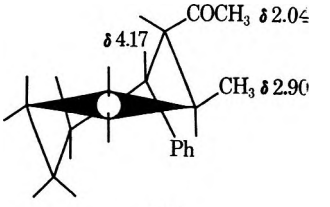
The benzylic proton appears at 35° as three poorly defined multiplets centered at δ 4.17, 4.40, and 5.40 with approximate relative intensities of 1:1:1.8, respectively. The multiplet at δ 5.40 in agreement with the assignments for the NCH_3 would correspond to conformer VI. The marked downfield shift for the axial



IV



VII



VIII

hydrogen is similar to that shown in substituted oxazoles.[8] The multiplet at δ 4.40 is ascribed to conformer VII which also has an axial hydrogen. The reason for the smaller downfield shift observed may be less long-range shielding by the electron pair on the NCH_3.

The carbethoxy group is less bulky than the acetyl group and the barrier to inversion is lower. This compound IIb would therefore exist as the conformer VI with a small amount of conformer VII at lower temperatures.

The yield of 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa) obtained by the pyrolysis of Ia was similar to that (16.4%) obtained for the pyridazine.[3] This behavior indicates that the rearrangement of heterocyclic aminimides incorporating a benzyl group in the ring is more general than when alkyl groups are involved.[9]

(8) F. G. Riddell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968).
(9) W. S. Wadsworth, Jr., and W. Bruxwoort, *Chem. Commun.*, 542 (1968).

The pyrolysis of the carbethoxyimide Ib which cannot form an isocyanate gave a slightly better yield of the diazepine IIb. This reaction is complicated by the formation of carbethoxynitrene which can abstract hydrogen from the starting material Ib and the product IIb and form ethyl carbamate.

Experimental Section

Melting points are corrected and boiling points are not. Infrared spectra were determined with a Perkin-Elmer spectrophotometer. Nmr spectra were determined using a Varian A-60 spectrometer. Gas chromatography was performed on F & M Models 500, 720, and 5750. Mass spectra were obtained on a Hitachi RMUGE mass spectrometer.

1-Acetamino-2-phenylpiperidine.—1-Amino-2-phenylpiperidine (10 g)[10] in benzene (40 ml) was treated with acetic anhydride (5.8 g) in benzene (20 ml), and the resulting solution was stirred for 12 hr at room temperature. The benzene solution after washing with sodium bicarbonate solution and water gave an oil which was recrystallized from ether, yield 10.8 g, mp 52–57°. This melting point did not change upon further recrystallization from ether: ir (KBr) 2.93, 3.10, 3.27, 6.00 μ; nmr ($CDCl_3$) δ 1.5 (m, CH_3 and 3,4,5 methylenes), 3.1 (m, C_6H_5CH, NH, and NCH_2), 7.25 (s, C_6H_5).

Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.56; H, 8.26; N, 12.84. Found: C, 71.50; H, 8.50; N, 12.64.

1-Acetamino-1-methyl-2-phenylpiperidinium Iodide.—A solution of 1-acetamino-2-phenylpiperidine (30 g) in methyl iodide (100 ml) was refluxed for 4 days. Removal of the excess methyl iodide gave a brown syrup which was recrystallized from a mixture of acetonitrile and ether, yield 26.4 g. The filtrate upon further refluxing with methyl iodide (55 ml) for 5 days gave an additional 5.6 g of product. Recrystallization from an acetonitrile–ether mixture gave a melting point of 151–152° dec; ir (Nujol) 3.13, 3.35, 5.92 μ; nmr ($CDCl_3$) δ 2.04 (m, 4,5,6 methylenes), 2.2 (s, CH_3CO), 3.70 (s, NCH_3), 4.28 (m, NCH_3), 6.10 (m, C_6H_5CH), 7.50 (m, C_6H_5), 10.24 (m, NH).

Anal. Calcd for $C_{14}H_{21}N_2OI$: C, 46.68; H, 5.83; N, 7.78. Found: C, 46.76; H, 5.88; N, 7.99.

1-Methyl-2-phenylpiperidine-1-acetimide (Ia).—A solution of the methiodide (58.8 g) in water (50 ml) was titrated with 10% sodium hydroxide using phenolphthalein as an indicator. Removal of the water and extraction of the residue with chloroform (100 ml) gave an oil (37 g) which solidified on standing. Recrystallization from ethyl acetate gave a pale yellow solid: mp 150.5–152° dec; ir (Nujol) 6.31, 6.39 μ; nmr ($CDCl_3$) δ 1.78 (s, CH_3CO), 1.94 (m, 3,4,5 CH_2), 2.92 (s, NCH_3), 3.50 (m, NCH_2), 6.12 (m, C_6H_5CH), 7.42 (m, C_6H_5).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.20; H, 8.51; N, 11.95.

Pyrolysis of 1-Methyl-2-phenylpiperidine-1-acetimide.—The aminimide Ia (20 g) when distilled at 150–200° under reduced pressure gave three products. Methyl isocyanate was collected at −45° and converted with aniline into *N*-methyl-*N'*-phenylurea (3.1 g), mp 150–151.5°. A mixture with an authentic sample[11] melted at the same point.

Distillation at reduced pressure gave 1-methyl-2-phenylpiperidine (7.0 g), bp 62–64° (0.15 mm). The infrared spectrum was identical with that of an authentic sample.[12]

The residue (8.1 g) consisted of 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa) (3.1 g) and 1-methyl-2-phenylpiperidine (5 g). This composition was established by vpc analysis using a 0.25 in. by 10 ft SE-30 column at 235° with a flow rate of 65 ml of helium per minute. The piperidine had a retention time of 3.4 min and the diazepine 13.6 min. Separation of the two compounds was accomplished by chromatography on silica gel with benzene as a solvent. The diazepine IIa had a boiling point of 310–312° using the Siwoloboff method[13] and benzophenone as a standard; $n^{21}D$ 1.5490; ir (film) 5.98–6.02, 6.20 μ; nmr (CCl_4) (30°) δ 1.65 (m, 4,5,6 CH_2), 1.94, 2.02 (s, CH_3CO), 2.65–2.84 (3 s, NCH_3 and NCH_2), 4.30, 5.30 (m, C_6H_5CH), 7.22 (m, C_6H_5); nmr (70°) δ 1.65 (m, 4,5,6 CH_2), 1.96 (s, CH_3CO), 2.75 (s, NCH_3 and NCH_2), 7.21 (m, C_6H_5).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.07; mol wt, 232. Found: C, 72.61; H, 8.78; N, 12.35; mol wt, 232 (mass spectrum).

The hydrochloride was obtained by treating the diazepine IIa with dry hydrogen chloride in benzene: mp 111–112°; ir (Nujol) 3.35, 5.90, 6.20 μ; nmr (CCl_4) δ 1.76 (s, CH_3CO), 1.94 (m, 5,6 CH_2), 2.34 (m, 4 CH_2), 3.36 (s, NCH_3), 3.74 (m, NCH_2), 5.80 (m, C_6H_5CH) 7.20 (m, C_6H_5), 12.54 (broad singlet, NH).

Anal. Calcd for $C_{14}H_{21}N_2OCl$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.91; H, 8.03; N, 10.49.

1-Carbethoxyamino-2-phenylpiperidine.—A solution of 1-amino-2-phenylpiperidine (26.3 g) in benzene was treated dropwise simultaneously with ethyl chloroformate (23.9 g) and with triethylamine (22.2 g). The addition of the last two compounds was carried out separately and regulated so that the temperature remained between 10 and 20°. The resulting mixture was stirred an additional 2.5 hr and the triethylamine hydrochloride was filtered. Removal of the solvent gave a yellow oil (41.0 g) which was purified by chromatography on silica gel. Elution with a 1:3 ethyl acetate–benzene mixture gave 1-carbethoxyamino-2-phenylpiperidine (31.4 g) which after crystallization from hexane melted at 56–57.5°: ir (film) 2.95, 5.80 μ; nmr ($CDCl_3$) δ 1.08 (t, CH_3), 2.75 (m, 3,4,5 CH_2), 3.23 (m, NCH_2, C_6H_5CH), 3.99 (q, CH_2CH_3), 6.85 (s, NH), 7.40 (m, C_6H_5).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.45. Found: C, 67.92; H, 8.17; N, 11.66.

1-Carbethoxyamino-1-methyl-2-phenylpiperidinium Iodide.—A solution of 1-carbethoxyamino-2-phenylpiperidine (23.5 g) in methyl iodide (75 ml) was refluxed for 3 days. Removal of the methyl iodide gave a solid which was recrystallized from a mixture of acetonitrile and other. The salt (8.2 g) melted at 131.5–132°. Further refluxing of the filtrate with methyl iodide for 2 weeks gave an additional 4.8 g. A second recrystallization from an acetonitrile–ether mixture gave a sample melting at 134.0–134.5°: ir (Nujol) 3.15, 5.71 μ; nmr (DMSO-d_6) δ 1.08 (t, CH_2CH_3), 1.84 (m, 3,4,5 methylenes), 4.08 (s and m, NCH_2, NCH_3, and CH_3CH_2), 5.54 (m, C_6H_5CH), 7.62 (s, C_6H_5).

Anal. Calcd for $C_{15}H_{23}N_2OI$: C, 46.17; H, 5.90; N, 7.21. Found: C, 46.13; H, 5.76; N, 6.96.

1-Methyl-2-phenylpiperidine-1-carbethoxyimide (Ib).—A solution of 1-methyl-1-carbethoxyamino-2-phenylpiperidinium iodide (4.24 g) in water (25 ml) was neutralized exactly with 1.186 *N* sodium hydroxide. Removal of the water and extraction of the resulting residue with chloroform gave an oil (3.3 g) which was purified by chromatography on silica gel using methanol as a solvent. The product obtained upon recrystallization from ethyl acetate melted at 104–106°: ir (Nujol) 6.10 μ; nmr ($CDCl_3$) δ 1.30 (t, CH_2CH_3), 2.10 (m, 3,4 and 5 CH_2), 3.04 (s, NCH_3), 4.15 (s and m, CO_2CH_2 and NCH_2), 6.07 (m, C_6H_5CH), 7.60 (m, C_6H_5).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: C, 68.70; H, 8.63; N, 10.74.

1-Methyl-1-amino-2-phenylpiperidinium iodide (1.0 g) was stirred with potassium *tert*-butoxide (0.36 g) and ethyl carbonate (0.50 g) in dimethyl sulfoxide (15 ml) for 2 days at room temperature. The resulting gelatinous mixture was treated with dimethyl sulfoxide until clear and the resulting potassium iodide was filtered. Removal of the solvent gave a residue which was treated with benzene. Unchanged iodide (0.61 g) was removed by filtration and the filtrate was chromatographed on alumina using benzene, 10% ethyl acetate–benzene, and 25% ethyl acetate–benzene as solvents. The aminimide Ib (0.21 g) was obtained in three of the fractions.

Pyrolysis of 1-Methyl-2-phenylpiperidine-1-carbethoxyimide (Ib).—The aminimide Ib (2.92 g) was heated under nitrogen at 100–200°; a volatile product (0.24 g) was obtained which gave an identical ir spectrum with that of ethyl carbamate. No other volatile products were found in the Dry Ice–acetone and aniline traps attached to the system.

The residue (2.49 g) when chromatographed on silica gel using benzene, 10% ethyl acetate–benzene, 25% ethyl acetate–benzene, and 10% methanol–benzene as solvents gave 1-methyl-2-carbethoxy-3-phenylhexahydro-1,2-diazepine (IIb) (0.8 g) in the first four fractions and 1-methyl-2-phenylpiperidine (0.42 g) in fractions 7–12. The remaining eluents gave a tarry material which was not characterized further.

(10) C. G. Overberger and L. P. Herrin, *J. Org. Chem.*, **27**, 417 (1962).

(11) R. Scholl and K. Holdermann, *Justus Liebigs Ann. Chem.*, **345**, 382 (1906).

(12) R. Lukes and M. Cerney, *Collect. Czech. Chem. Commun.*, **24**, 1287 (1959).

(13) A. I. Vogel, "Elementary Practical Organic Chemistry," part I, Wiley, New York, N. Y., 1966, p 86.

The diazepine had a boiling point of 306–308° dec; n^{21}D 1.5202; ir (film) 5.85 μ; nmr ($CDCl_3$) δ 1.30 (t, CH_2CH_3), 2.0 (m, 4,5,6-CH_2), 2.83 (s, NCH_3), 3.30 (m, NCH_2), 4.35 (q, OCH_2), 5.17 (broad s, C_6H_5CH), 7.60 (m, C_6H_5).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: C, 68.70; H, 8.35; N, 10.52.

1-Amino-1-methyl-2-phenylpiperidinium Iodide.—A solution of 1-amino-2-phenylpiperidine (10 g) and methyl iodide (10 ml) in acetonitrile (25 ml) was refluxed for 12 hr and cooled. The resulting solid (3.25 g) upon recrystallization from methanol gave white granules melting at 167–168.5°: ir (Nujol) 3.01, 3.11, and 6.12 μ; nmr (DMSO-d_6) δ 1.80 (m, 3,4,5-CH_2), 2.95 (s, NCH_3), 3.72 (m, NCH_2), 4.70 (m, C_6H_5CH), 5.71 (m, NH_2), 7.38 (m, C_6H_5).

Anal. Calcd for $C_{12}H_{19}N_2I$: C, 45.30; H, 5.97; N, 8.81. Found: C, 45.09; H, 5.79; N, 8.65.

1-Methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepin-7-one (III).—A solution of ethyl 4-benzoylbutyrate (45.2 g)[14] and methylhydrazine (10 g) in benzene (90 ml) was heated in a 500-ml Parr bomb at 200–210° for 70 hr. The resulting brown oil after removal of the solvent was chromatographed on silica gel using benzene, 15% ethyl acetate–benzene, and ethyl acetate as solvents and gave ethyl 4-benzoylbutyrate (4.2 g), 1-methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepin-7-one (16.1 g), and *N*-methyl-4-benzoylbutyramide (6.0 g). (This compound was formed from methylamine present as an impurity in methylhydrazine.) Recrystallization of the diazepinone III from hexane gave a white solid melting at 69–69.5°: ir (Nujol) 5.97, 6.05 μ; nmr ($CDCl_3$) δ 2.35 (m, CH_2CH_2CO), 2.81 (t, 4-CH_2), 3.31 (s, NCH_3), 7.40 (m, meta and para aromatic H), 7.78 (m, ortho aromatic H).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.84. Found: C, 70.94; H, 7.00; N, 13.95.

N-Methyl-4-benzoylbutyramide was recrystallized from benzene and melted at 93–94°: ir (Nujol) 2.93, 5.94, 6.04 μ; nmr ($CDCl_3$) 2.20 (m, CH_2CH_2CO), 2.79 (d, CH_3N), 3.02 (t, $C_6H_5COCH_2$), 6.80 (broad s, NH), 7.40 (m, meta and para aromatic H), 7.90 μ (m, ortho aromatic H).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.22; N, 6.87.

1-Methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepine (IV).—To a refluxing solution of lithium aluminum hydride (8.0 g) in ether (400 ml), a solution of 1-methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepine-7-one (III) (12.4 g) in benzene (100 ml) was added dropwise and the resulting solution was refluxed for 20 hr. Decomposition of the excess lithium aluminum hydride was followed by removal of the ether and gave an oil (11 g). Distillation at 80–82° (0.13 mm) gave a pale yellow liquid (9.2 g) which showed two minor impurities on a tlc silica gel plate using 1:1 ethyl acetate–benzene as an eluent. Purification was accomplished by chromatography on a silica gel column using 1:5 ethyl acetate–benzene as the solvent: n^{21}D 1.5202; ir (film) 6.23, 6.30 μ; nmr (neat) δ 1.45 (m, 5,6 CH_2), 2.53 (m, 4,7 CH_2), 2.79 (s, NCH_3), 7.05 (m, meta and para aromatic H), 7.48 (m, ortho aromatic H).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.60; H, 8.51; N, 14.89. Found: C, 77.00; H, 8.51; N, 15.18.

The picrate was prepared by refluxing the diazepine with picric acid in methanol for 15 min and melted at 128–129.5°.

Anal. Calcd for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.74; H, 4.83; N, 16.26.

Reduction of 1-Methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepine (V). A.—The unsaturated diazepine IV (2.65 g) in dioxane (25 ml) was added dropwise to lithium aluminum hydride (2.5 g) in dioxane (100 ml) and the resulting solution was refluxed for 24 hr. Destruction of the lithium aluminum hydride followed by removal of the solvent gave a pale yellow oil (2.45 g). Analysis by vpc on a 1/8 in. × 6 ft silicon rubber W98 column programmed at 100–250° at a rate of 10° per minute showed that the major component (retention time 11.2 min) (>95%) was 1-methyl-3-phenylhexahydro-1,2-diazepine (V). The minor component was starting material and had a retention time of 12.2 min. The saturated diazepine air oxidized so rapidly that it was not characterized by elemental analysis but used immediately: ir (film) 3.00, 3.35, 6.20 μ; nmr (CCl_4) δ 1.59 (m, 4,5,6-CH_2), 2.38 (s, NCH_3), 2.67 (m, NCH_2, NH), 3.75 (m, C_6H_5CH), 7.18 (m, C_6H_5).

A sample of the hexahydro-1,2-diazepine V (0.75 g) in benzene (20 ml) was stirred with acetic anhydride (2 ml) for 13 hr at room temperature and 10 min at 100°. Neutralization of the resulting solution was followed by removal of the solvent and gave a viscous oil (0.6 g). Analysis of vpc on a silicone rubber W98 column 1/8 in. × 6 ft programmed at 100–250° at a rate of 10° per minute indicated that the oil consisted of 92% 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa) and 8% of the tetrahydro derivative IV. Chromatography on silica gel using benzene and 1:10 ethyl acetate–benzene as solvents gave a sample of the hexahydro derivative which had identical ir and nmr spectra with those of the product obtained from the rearrangement of the piperidine derivative Ia.

A sample of the impure hexahydro-1,2-diazepine V (4.9 g) in benzene (50 ml) was added to a mixture of ethyl chloroformate (20 ml) and triethylamine (15 ml) and the resulting mixture was stirred at room temperature for 11 hr and at 100° for 3 hr. Filtration of the insoluble triethylamine hydrochloride was followed by removal of the solvent and excess reagent. The resulting brown oil (5.2 g) was chromatographed on silica gel using benzene and 1:3 ethyl acetate–benzene as solvents. The benzene eluents gave 1-methyl-2-carbethoxy-3-phenylhexahydro-1,2-diazepine (3.3 g). The ir and nmr spectra were identical with those of the product IIb obtained by pyrolysis.

B.—A solution of 1-methyl-3-phenyl-Δ²-tetrahydro-1,2-diazepine (18 g) in a mixture of acetic acid (21 ml), acetic anhydride (100 ml), and benzene (80 ml) was reduced catalytically at 30–50 psi of hydrogen in the presence of 1.3 g of platinum oxide. After the consumption of 0.1 mol of hydrogen, the solution was filtered out and the solvent was removed under reduced pressure. The resulting oil was dissolved in ether and washed with sodium bicarbonate solution and water. Removal of the ether gave a yellow oil (18.1 g) which was chromatographed on silica gel using benzene and 1:10 ethyl acetate–benzene as solvents. The products consisted of starting material IV (1 g) and 1-methyl-2-acetyl-3-phenylhexahydro-1,2-diazepine (IIa) (11.5 g).

The acetylhexahydrodiazepine was resistant to basic hydrolysis. The hydrochloride (0.49 g) was heated with 10 ml of 20% potassium hydroxide in glycerol for 9 hr at 200°. Dilution with water and extraction with ether gave the acetylhexahydrodiazepine IIa (0.31 g).

Registry No.—Ia, 29953-87-5; Ib, 29953-88-6; IIa, 29953-89-7; IIa HCl, 30102-40-0; IIb, 29953-90-0; III, 29953-91-1; IV, 29953-92-2; IV picrate, 29953-93-3; V, 29953-94-4; 1-acetamino-2-phenylpiperidine, 29953-95-5; 1-acetamino-1-methyl-2-phenylpiperidinium iodide, 29953-96-6; 1-carbethoxyamino-2-phenylpiperidine, 29953-97-7; 1-carbethoxyamino-1-methyl-2-phenylpiperidinium iodide, 29953-98-8; 1-amino-1-methyl-2-phenylpiperidinium iodide, 29953-99-9; *N*-methyl-4-benzoylbutyramide, 29954-00-5.

(14) M. Yu Lure, I. S. Trubnikov, N. P. Susherina, and R. Ya Levina, *Zh. Obshch. Khim.*, **28**, 1351 (1958).

The Synthesis and Gramine Alkylation of Some 3-Piperidones. A Synthetic Route to 2-(3-Indolylmethyl)-4-piperidineacetic Acid Derivatives

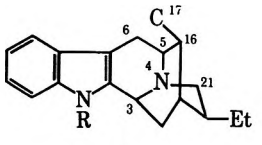
RICHARD J. SUNDBERG,* WOODFIN V. LIGON, JR., AND LONG-SU LIN

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

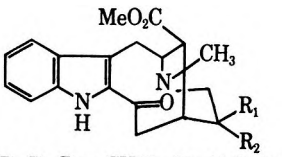
Received January 11, 1971

Syntheses of ethyl 1-benzoyl-3-oxo-4-piperidineacetate and methyl 1-benzoyl-5-ethyl-3-oxo-4-piperidineacetate starting with ethyl 1-benzoyl-1,2,3,6-tetrahydro-4-pyridineacetate and ethyl 1-benzoyl-3-ethyl-1,2,3,6-tetrahydro-4-pyridineacetate are described. Both of these 3-piperidones can be alkylated in fair yield by gramine *via* their pyrrolidine enamines to 2-(3-indolylmethyl)-3-piperidones. Stereochemical assignments for the 2-(3-indolylmethyl)-3-piperidones are made on the basis of stability relationships and analogy with prior stereochemical assignments to 2-substituted *N*-acylpiperidines. Two stereoisomeric ethyl 1-benzoyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetates, two stereoisomeric 1-benzoyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetic acid lactones, two stereoisomeric methyl 1-benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetates, and three stereoisomeric 1-benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetic acid lactones are described. Several other miscellaneous compounds are reported as a result of unsuccessful alternative approaches to these 3-piperidones.

The 2-(3-indolylmethyl)-4-piperidineacetic acid system constitutes a major portion of the skeleton of such indole alkaloids as the sarpagine–ajmaline group A[1] and the 2-acylindoles vobasine, dregamine, and tabernaemontanine (B).[2] The sarpagine–ajmaline skeleton



A



B, R_1, R_2 = CHMe; Et, H; H, Et

is not accessible by the Mannich-type cyclizations which have been so successful in the synthesis of other types of indole alkaloids, especially those containing the tetrahydro-β-carboline ring,[3] because of the prohibition against a bridgehead double bond. Successful syntheses of the ajmaline–sarpagine ring system and close structural relatives have therefore involved closure of the C-5–C-16[4] or C-21–N-4 bonds[5] for construction of the quinuclidine ring in the latter stages of the syntheses. It would appear that the sarpagine–ajmaline skeleton might also be approached *via* 2-acylindoles having the N_b-demethyl vobasine skeleton (B) by a transannular ring closure involving C-3 and N-4.[6] The closest approach to the vobasine skeleton is that of Yamada and Shioiri who have described the synthesis of 1-methyl-16-demethoxycarbonyl-20-deethylidene vobasine.[7] We record here our efforts to develop a synthesis of intermediates suitable for subsequent conversion to the vobasine and sarpagine type ring systems.

We decided to approach these systems by a gramine alkylation[8] of the pyrrolidine enamine of a 4-substituted 3-piperidone. Syntheses of the tetrahydropyridines **3b** and **3d** from 1-benzoyl-4-piperidones have been reported[9] and modifications described herein have made these compounds reasonably accessible. An initial approach commencing with hydroboration of the tetrahydropyridine ring failed for reasons discussed below. An alternative route outlined in Scheme I has provided the desired piperidones **9b** and **9c** in good overall yield from **3b** and **3d**.

The epoxidation can be carried out on pure **3** or **3** can be selectively epoxidized in the presence of the less reactive exocyclic esters **1** which are by-products in the synthesis of **3**.[9] Stereoisomers arbitrarily designated **4d**A and **4d**B are formed in the case of **4d** but separation is not required since the stereoisomers are equilibrated at a subsequent stage.

The epoxide ring in **4** is readily opened by bases *via* a β-elimination mechanism. For **4b** this reaction is most efficiently effected by adsorbing the epoxide on a column of basic alumina. Subsequent elution gives **5b** (60% yield) and **6a** (30% yield). Ring opening is rapid using potassium *tert*-butoxide at room temperature but total recovery of products is substantially lower (36% **5b**, 6% **6a**). For **4d** ring opening was effected using DABCO[10] in refluxing xylene or with alumina. A mixture containing **5d** and **6c** is generated. Separation of the various components (including stereoisomers) at this point is inefficient. Catalytic hydrogenation, hydrolysis, and diazomethane esterification provides **7c** in good overall yield.

Spectral data for the isolated intermediates in this scheme are reported in the Experimental Section. In general, the data are in accord with expectation and confirm each of the expected functional group changes. The nmr signals for the piperidine ring protons are diffuse multiplets which provide no direct insight into the stereochemistry of the various intermediates.

The piperidones **9a–d** were obtained by oxidation with Jones reagent of the corresponding hydroxy esters.

(1) W. I. Taylor in "The Alkaloids," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, pp 785–814; Vol. XI, 1968, pp 41–72.

(2) U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, **46**, 2186 (1963).

(3) For some typical examples, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 256–269.

(4) E. E. van Tamelen and L. K. Oliver, *J. Amer. Chem. Soc.*, **92**, 2136 (1970).

(5) S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar, and Y. Yasunari, *ibid.*, **89**, 2506 (1967); K. Mashimo and Y. Sato, *Tetrahedron Lett.*, 901, 905 (1969).

(6) G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **86**, 4631 (1964).

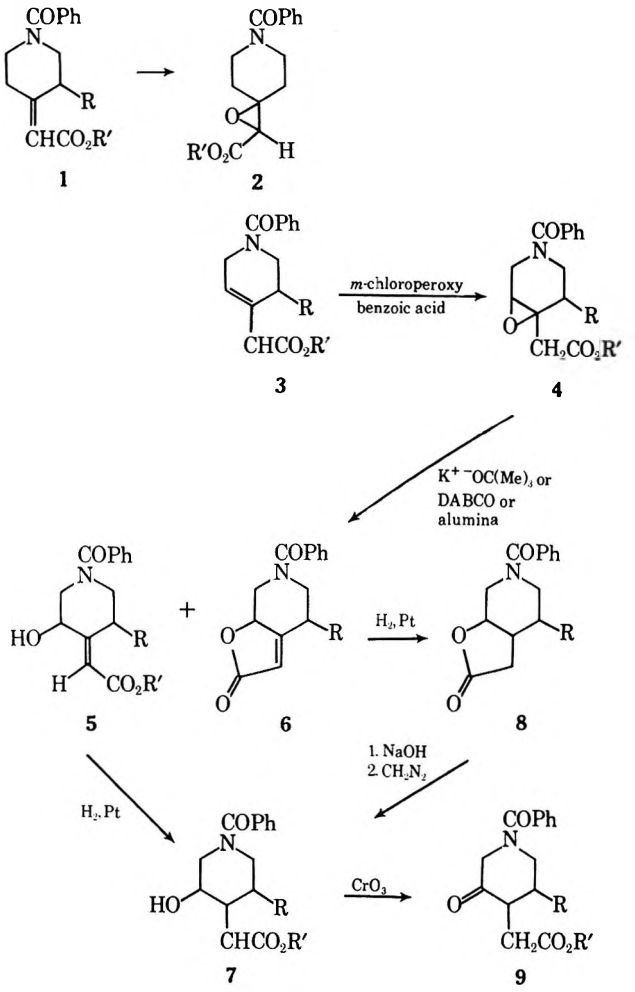
(7) T. Shioiri and S. Yamada, *Tetrahedron*, **24**, 4159 (1968).

(8) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 3240 (1965). A. A. Semenov and I. V. Terent'eva, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 235 (1965); *Chem. Abstr.*, **63**, 11478 (1965).

(9) R. J. Sundberg and F. O. Holcombe, Jr., *J. Org. Chem.*, **34**, 3273 (1969).

(10) 1,4-Diazabicyclooctane.

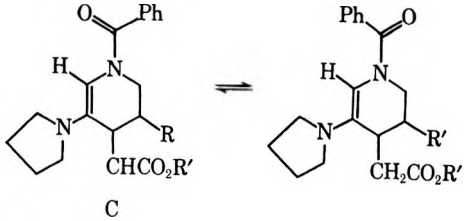
SCHEME I



a, R = H; R' = Me or none
b, R = H; R' = Et
c, R = Et; R' = Me or none
d, R = Et; R' = Et

These piperidones were not stable to extended storage and satisfactory analytical data were not obtained. Nevertheless, spectral data, including mass spectral data, left no doubt that the required piperidones were in hand.

When refluxed in benzene with pyrrolidine, enamine formation occurred as evidenced in particular by sharp nmr signals at 5.7 and 6.6 ppm in the case of **9b** and similar, slightly less well-defined signals for **9c**. These are assigned to the vinyl protons in the enamine. The occurrence of two singlets (total integration one

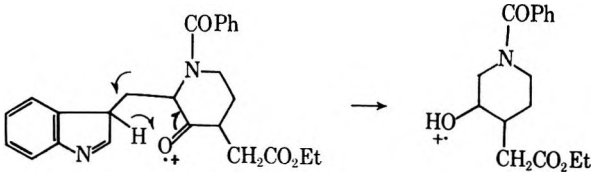


C

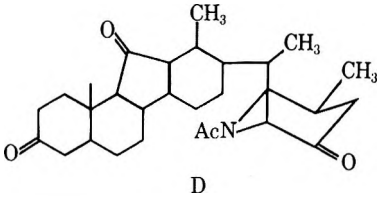
proton) is attributed to the presence of two conformational isomers resulting from slow (nmr time scale) rotation of the *N*-benzoyl group. Solutions of the enamines when refluxed with gramine and hydrolzyed gave product mixtures best processed by chromatography.

After alkylation of **9b**, chromatography gave diindolylmethane, cis and trans stereoisomers of the desired ketone **10b**, the pyrrolidine amide **10e**, and a byproduct assigned the structure **11b**.

The stereoisomeric ketones **10b** can be separated by fractional crystallization. The higher melting isomer *t*-**10b**, mp 174–176°, is the major product, predominating over *c*-**10b**, mp 163–165°, by roughly 3:1 in most runs. The infrared and nmr spectral data confirm the presence of the expected functional groups in both *c*-**10b** and *t*-**10b** but fail to provide stereochemical information. The mass spectral data for *c*-**10b** and *t*-**10b** are virtually identical and confirm the expected molecular weight. Besides strong peaks at 105 and 130 corresponding to the benzoyl and indolylmethyl substituents, the mass spectra show prominent peaks at M, M − 129, and M − 175. The M − 129 peak indicates the loss of the indolylmethyl substituent with hydrogen atom transfer to the piperidine ring perhaps by a McLafferty rearrangement *via* the 3H tautomer.



Although spectral data provided no basis for a stereochemical assignment, demonstration that the isomer of mp 174–176° is stable relative to that of mp 163–165° permits stereochemical assignment by analogy with other *N*-acylpiperidines. Conventional alkoxide ion catalyzed equilibration led to substantial losses of material but equilibration could be effected by heating the ketones in ethanolic potassium fluoride.[11] Johnson and coworkers[11] have investigated the stereochemistry of the piperidone D derived from jervine and concluded that the more stable configuration is the cis isomer depicted in the formula. The large 2 substituent



D

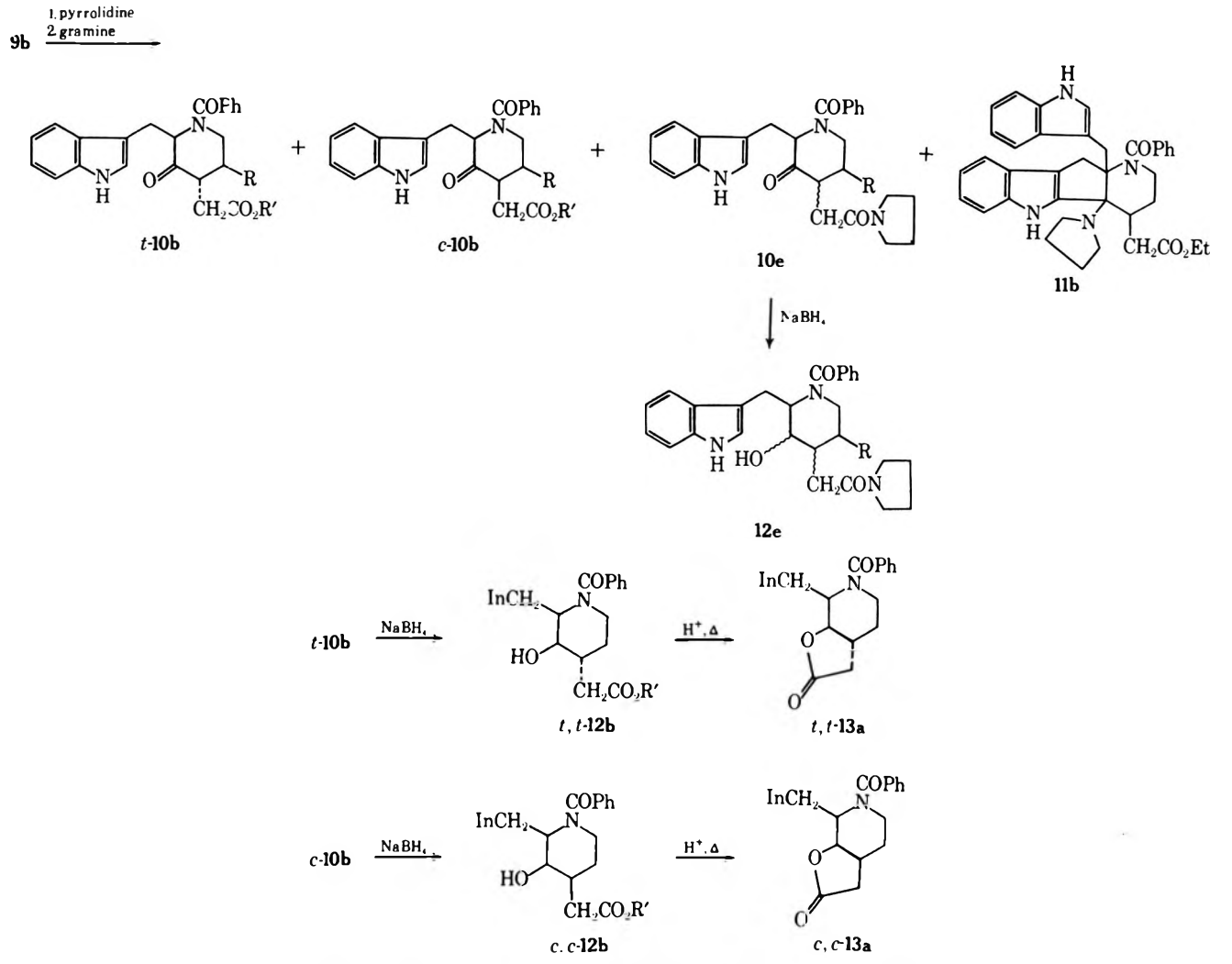
thus occupies an axial position in the preferred conformation. This stereochemistry is favored because of $A^{(1,3)}$ strain which develops between the amide group and a 2 substituent in the equatorial position.[12]

In the case of the stereoisomers of **10b**, the axial–equatorial isomer *t*-**10b** is therefore expected to be more stable than the cis isomer *c*-**10b** which must suffer either $A^{(1,3)}$ strain, a 1,3-diaxial interaction, or adopt a nonchair conformation. Equilibration of the ketones gave mixtures in which the ketone of mp, 174–176° now designated *t*-**10b**, dominates by roughly 4:1.

(11) J. W. Scott, L. J. Durham, H. A. P. de Jongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Lett.*, 2381 (1967).

(12) (a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); (b) H. Paulsen and K. Todt, *Angew. Chem., Int. Ed. Engl.*, **5**, 899 (1966); (c) H. Paulsen and F. Leupold, *Carbohyd. Res.*, **3**, 47 (1966); (d) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3585 (1967); (e) G. Büchi, S. J. Gould, and F. Näf, *J. Amer. Chem. Soc.*, **93**, 2492 (1971).

SCHEME II[a]



a, R = H; R′ = Me or none **c**, R = Et; R′ = Me or none **e**, R = H
b, R = H; R′ = Et **d**, R = Et; R′ = Et **f**, R = Et

[a] Prefixes *c* and *t* designate stereochemistry of substituents relative to the 4-acetic acid residue.

By-product **10e** has not been isolated in crystalline form but it gives a crystalline dihydro derivative **12e** on sodium borohydride reduction. Spectral and analytical data are in accord with the structure assigned to **12e** in Scheme II. The structural assignment for **11b** is more tenuous. The mass spectrum shows an apparent parent ion at 600 corresponding to the molecular weight of a bisindolylmethyl derivative of the intermediate enamine. Analytical data are also consistent with this molecular composition. Ultraviolet data is in accord with structure **11b**. Structure **11b** could arise by dialkylation of enamine C followed by cyclization of the resulting iminium salt.[13]

The ketones *t*-**10b** and *c*-**10b** show divergent behavior on sodium borohydride reduction. *t*-**10b** gives a single alcohol in excellent yield. It is assigned the structure and stereochemistry *t,t*-**12b** (Scheme II) on the basis of the normal preference for formation of equatorial alcohols on reduction of six-membered cyclic ketones in the absence of strong steric effects. Neither an axial nor an equatorial substituent α to the carbonyl strongly perturb the axial–equatorial isomer ratio in hydride reductions.[14] Alcohol *t,t*-12b gives the corresponding lactone *t,t*-**13a** on heating with a trace of acid in toluene. In contrast, sodium borohydride reduction of *c*-**10b** gives approximately equal amounts of an alcohol and lactone assigned structures *c,c*-**12b** and *c,c*-**13a**, respectively. Lactonization of *c,c*-**12b** gives c,*c*-**13a**, demonstrating that the alcohol and lactone are of the same stereochemical family. The all cis configuration is assigned on the basis of the facile partial lactonization which accompanies reduction and the fact that *c,c*-**13a** has lower carbonyl frequency (1780 cm^{-1}) than the lactone *t,t*-**13a** (1810 cm^{-1}). The mass spectra of the stereoisomeric lactones are shown in Figure 1. The most significant difference in the spectra of the isomeric lactones is the strong M − 129 peak in *c,c*-**13a**. In addition, *t,t*-**13a** shows peaks at M − 105 and M − 121 which are not prominent in *c,c*-**13a**. A sample of *c,c*-**13a** deuterated (50%) at the indole nitrogen showed shift of the 374, 245, and 130 peaks to 375, 246, and 131, respectively, but the 186 peak was not shifted. This shows that the indole *N*–*H* hydrogen atom is transferred in formation of the M −

(13) The data in hand cannot rule out an alternative formulation of **11** in which the indolylmethyl substituent shown at the 2 position of the piperidine ring is placed on the 4 position.

(14) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968); A. V. Kameritzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

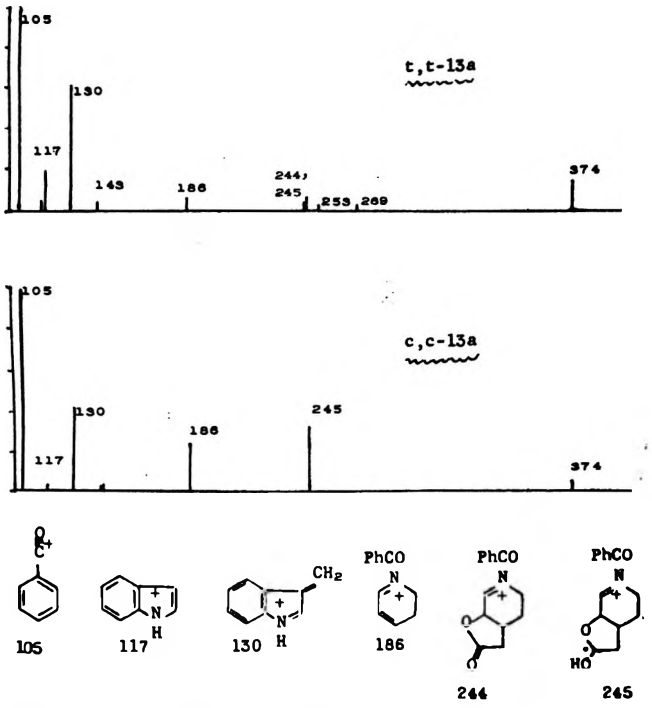
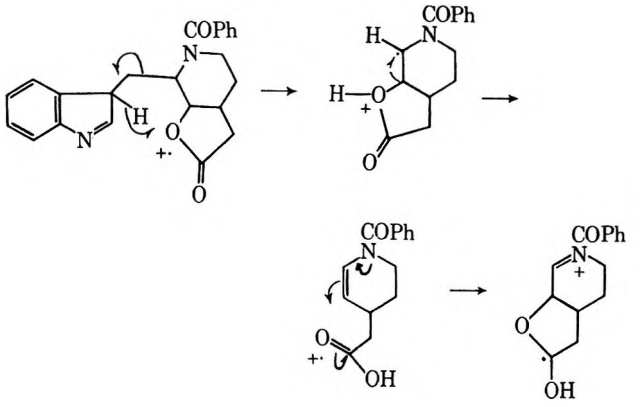
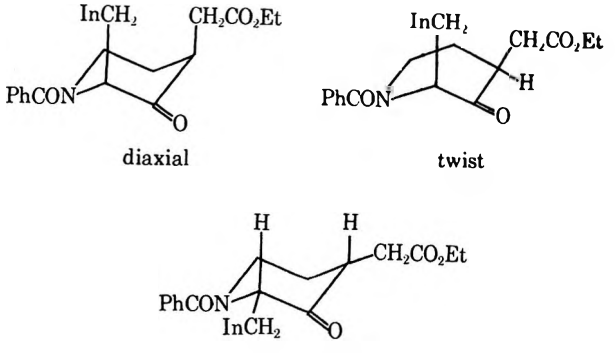


Figure 1.—Principal mass spectral fragments for *t,t*-**13a** and *c,c*-**13a**.

129 peak. A possible fragmentation mechanism is outlined below.



Of the conformations available to *c*-**10b**, the diaxial and twist conformations appear likely to give *c,c*-**12b** on reduction, but the diequatorial conformation would be expected to give the unobserved *c,t*-**12b**.

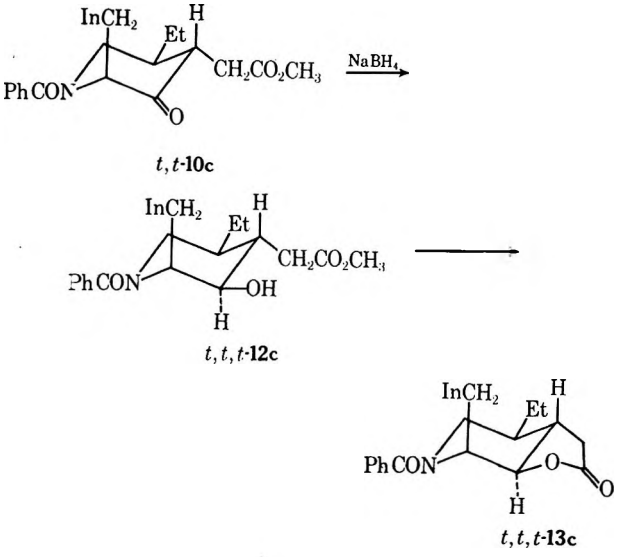


There is little quantitative information on the magnitude of the $A^{(1,3)}$ interaction in *N*-acylpiperidines.[12] However, it is known to be sufficiently large to cause 1-benzoyl-2,6-dimethylpiperidine to adopt the conformation with diaxial methyl groups.[15] It is known that cyclohexanone derivatives are more prone to adopt twist conformations than are cyclohexanes,[16] but the diaxial methyl interactions in 3,3,5,5-tetramethylcyclohexanone is apparently not sufficiently large to force this ketone to adopt a nonchair conformation.[17] It would appear therefore that *c*-**10b** probably exists predominantly in the diaxial conformation.

Independent evidence for the stereochemical assignments shown in Scheme II was obtained by examination of the nmr spectra of the lactones *t,t*-**13a** and *c,c*-**13a**. The nmr spectra in the region δ 3.5–5 are shown along with those of the 3-d_1 analogs in Figure 2.

These spectra permit identification of the 3 proton in *t,t*-**13a** as a doublet of doublets, J = 10, 5 Hz, whereas the corresponding signal in *c,c*-**13a** is a skewed triplet, J = 6.5 Hz. These coupling constants are consistent with the axial–axial and axial–equatorial couplings present in *t,t*-**13a** and the two axial–equatorial couplings present in *c,c*-**13a**.[12b–d,15]

Two ketones were also isolated by chromatography of the product mixture from gramine alkylation of **9c**. The major ketone gave a single alcohol on reduction which can be lactonized. These products are assigned structures *t,t,t*-**12c** and *t,t,t*-**13c** on arguments analogous to those in the desethyl series. The nmr spectrum of *t,t,t*-**13c** is reminiscent of *t,t*-**13a** in that it shows a doublet of doublets, J = 10, 5 Hz at δ 4.3. It is assumed that the C-5 ethyl group is in the more stable equatorial position. The major ketone is therefore assigned the stereochemistry *t,t*-**10c**. The mass spec-



trum of *t,t,t*-**13c** is analogous to that of *t,t*-**13a** and shows all of the expected shifts due to the added ethyl group.

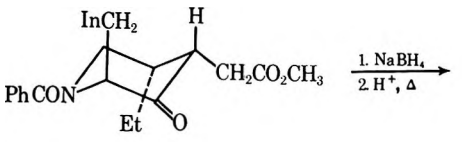
The minor ketone is converted largely to *t,t*-**10c** on refluxing in methanolic potassium fluoride. The minor ketone gives a stereoisomeric mixture of alcohols which can be converted to two lactones. The mass spectrum of one is similar to that of *c,c*-**13a** in showing no M − 130 peak; the second gives a mass spec-

(15) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); Y. L. Chow, C. J. Colón, and J. N. S. Tam, *Can. J. Chem.*, **46**, 2821 (1968).

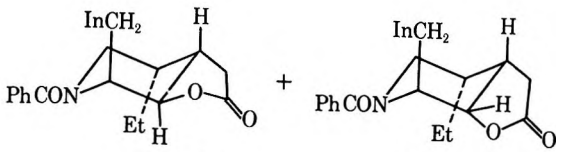
(16) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 472–480.

(17) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

trum which is very similar to that of *t,t,t*-**13c**. The minor ketone, on the basis of this data, might be stereoisomeric with *t,t*-**13c** at C-3 or C-5. The latter possibility is favored by the nmr spectra of the derived lactones. The major lactone shows a doublet of doublets, J = 11, 5 Hz, indicating one axial–axial coupling of the C-3 proton. Only stereoisomer *t,t,c*-**13c** is consistent with this coupling pattern. The minor ketone is therefore apparently stereoisomeric with *t,t*-**10c** at C-5 and has structure *t,c*-**10c**. The second lactone derived from *t,c*-**10c** is assigned structure *t,c,c*-**13c**.



t,c-**10c**



t,t,c-**13c** *t,c,c*-**13c**

The nmr of the lactones *t,t*-**13a**, *t,t,t*-**13c**, *t,t,c*-**13c**, and *t,c,c*-**13c** are all temperature dependent because of the slow rotation of the benzoyl group.[15,18] The signals associated with piperidine ring protons are quite broad at room temperature but considerable fine structure is evident at 90–120° except for the 2 and 6 protons which remain broad even at this temperature. Similar broad signals are typical of the equatorial protons of simple *N*-benzoylpiperidines.[15,18] In contrast, *c,c*-**13a** shows fine structure in the signals near 5.0, even at room temperature. This observation suggests that *c,c*-**13a** is conformationally unique when compared with the other four lactones. The chair conformation of *c,c*-**13a** suffers from a diaxial interaction, as well as from the strain associated with fusion of the lactone ring. Both of these interactions can be relieved in a twist conformation without introducing $A^{(1,3)}$ strain. The combined energy of the 1,3-diaxial interaction (3–4 kcal) and the strain associated with the ring fusion (~4 kcal)[19] may be sufficient to cause adoption of a nonchair conformation.

Various modified conditions failed to increase the proportion of *c*-**10b** in the gramine alkylation product. Since a cis relationship is required for our ultimate synthetic goal, it is clear that a system in which the stereochemistry at C-2 is not governed by $A^{(1,3)}$ strain is needed. Nevertheless, the present work has established that gramine alkylation of 3-alkylamino-1,4,5,6-tetrahydropyridines is a feasible approach to the desired ring system.

Our initial efforts to obtain **7b** involved hydroboration of **3b**. Since reduction of tertiary amide groups by diborane is relatively rapid,[20] the benzoyl group in **3** was replaced by the less easily reduced carbobenzyloxy group[21] by hydrolysis followed by acylation to give **14**. Starting material and the diol **15**, a reduction product, were the major products from several hydroboration attempts. Hydroboration must occur but is followed by intramolecular reduction of the ester group. There are prior examples of such intramolecular reductions in hydroboration and sodium borohydride reduction.[22]

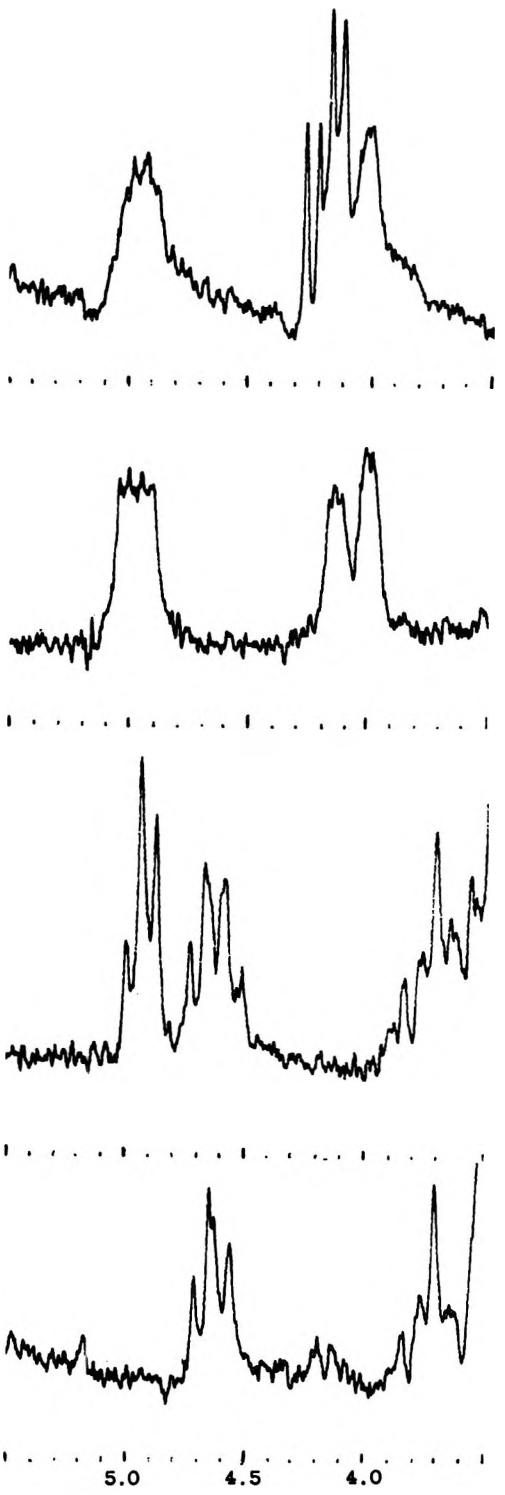


Figure 2.—100-MHz nmr spectra of *t,t*-**13a** and *t,t*-**13a**-3-d_1 at 120° (upper spectra) and *c,c*-**13a** and *c,c*-**13a**-3-d_1 at 35° (lower spectra) in DMSO-d_6.

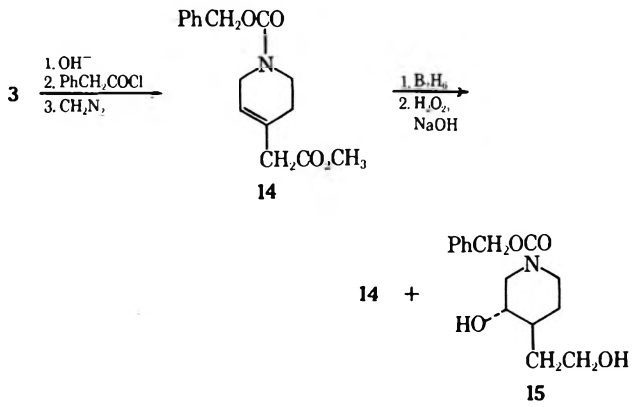
(18) H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966).

(19) W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.*, **83**, 1671 (1961); ref 16, p 230; W. Herz and L. A. Glick, *J. Org. Chem.*, **28**, 2970 (1963).

(20) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 1637 (1970).

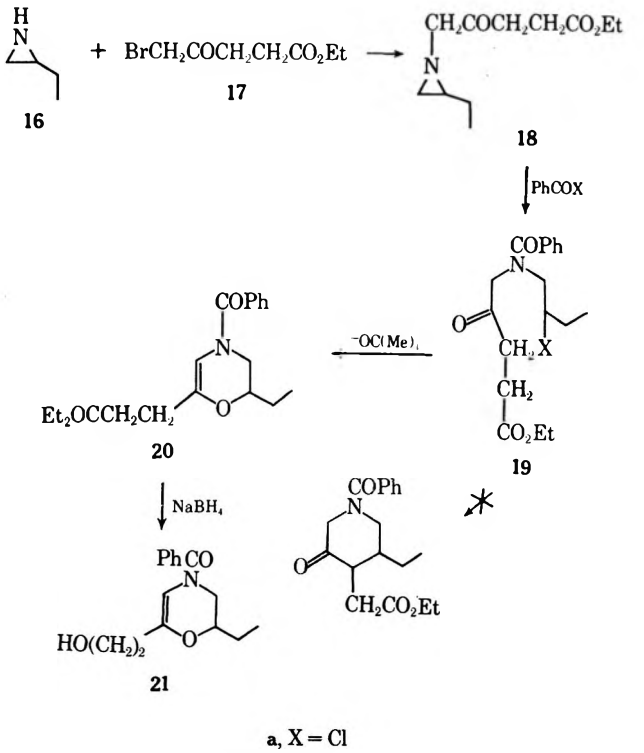
(21) F. Irreverre, K. Morita, A. V. Robertson, and B. Witkop, *ibid.*, **85**, 2824 (1963); Y. Fujita, F. Irreverre, and B. Witkop, *ibid.*, **86**, 1844 (1964).

(22) H. C. Brown and K. A. Keblys, *ibid.*, **86**, 1795 (1964); U. T. Bhalerao, J. J. Plattner, and H. Rapoport, *ibid.*, **92**, 3429 (1970); J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).



This difficulty could probably be overcome by use of a dialkylborane but this possibility was not investigated in view of the general success encountered with the route described in Scheme I.

Although 1-benzoyl-3-ethyl-4-piperidone, the starting material required for **3d**, can be reliably prepared in 100-g quantities by the procedure of Stork and McElvain,[23] this preparation is sufficiently time consuming to make an alternative route to the 3-piperidone **9d** highly desirable. With this goal in mind we prepared the β-haloamide **19** from 2-ethylaziridine and ethyl 5-bromolevulinate.[24] Both the bromo and chloro compounds were easily prepared. Attempts to obtain **9d** by intramolecular C-alkylation following a route



utilized by Dolfini[25] for 3-acylpyrrolidines gave instead the O-alkylation product **20**. This structure is deduced from the slow reduction of **20** to the primary alcohol **21** and from spectral data. Both **20** and **21** show two sharp singlets in the vinyl proton region integrating for a total of one proton. The two singlets are ascribed to slowly interconverted conformers having the two possible orientations of the *N*-benzoyl group. The haloamides **19**, especially the bromide, are sensitive toward hydrolysis by mechanisms involving participation of the amide group.[26,27]

Experimental Section

Ethyl 1-Benzoyl-$\Delta^{4,\alpha}$-piperidineacetate (1b) and Ethyl 1-Benzoyl-1,2,3,6-tetrahydropyridine-4-acetate (3b).—Sodium hydride (7.6 g of 50% mineral oil dispersion) was rinsed with hexane and covered with anhydrous ether (300 ml). A solution of triethyl phosphonoacetate (39.0 g, 0.182 mol) in ether (200 ml) was added slowly. When hydrogen evolution had ceased, a solution prepared from 1-benzoyl-4-piperidone (Aldrich, 30.0 g, 0.148 mol), dry benzene (200 ml), and ether (700 ml) was added in one portion. The resulting reaction mixture was refluxed under nitrogen for 20 hr. The organic solution was decanted and the gummy precipitate was washed with additional ether. The combined organic layers were filtered and washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, and saturated sodium chloride. The solution was dried over magnesium sulfate. Evaporation of the solvent gave 35.5 g of a mixture of **1b** (8.9 g, 0.033 mol, 22%) and **3b** (26.6 g, 0.097 mol, 66%). Separation and characterization of **1b** and **3b** have been reported previously.[9]

Ethyl 1-Benzoyl-3-ethyl-$\Delta^{4,\alpha}$-piperidineacetate (1d) and Ethyl 1-Benzoyl-3-ethyl-1,2,3,6-tetrahydropyridine-4-acetate (3d).—Sodium hydride (11 g of 50% dispersion in mineral oil) was washed with hexane and then covered with anhydrous ether (1300 ml). A solution of triethyl phosphonoacetate (52.0 g, 0.220 mol) in ether was added cautiously. When hydrogen evolution was complete, a solution prepared from crude 1-benzoyl-3-ethyl-4-piperidone[23] (40 g, ~0.16 mol) and ether (600 ml) was added. The resulting solution was refluxed under nitrogen for 20 hr. Work-up as described for **1b** and **3b** gave an oil (42.5 g, ~88%) containing **1d** and **3d** in the ratio 0.8:1.0. The pure components could be separated and characterized as described previously,[9] but normally the mixture was used directly in the epoxidation.

3-Benzoyl-6-carbethoxymethyl-7-oxa-3-azabicyclo[4.1.0]heptane (4b). A. From Pure 3b.—A solution of chromatographically purified **3b** (2.0 g, 7.3 mmol) and *m*-chloroperoxybenzoic acid (2.0 g, 85% peroxide content) in chloroform (50 ml) was stirred at room temperature for 5 hr. The resulting solution was washed successively with sodium sulfite and sodium carbonate solutions, dried over sodium sulfate, and evaporated. The residual oil (1.9 g, 6.6 mmol, 90%) was pure **4b** according to tlc. An analytical sample was prepared by chromatography on silicic acid using 1:4 ether–benzene for elution. Subsequent samples crystallized and could be recrystallized from ether–hexane: mp 79–80°; ν_{CO} 1725, 1620 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t) 2.05 (2 H, broad quartet), 2.35 (1 H, d, J = 16 Hz), 2.27 (1 H, d, J = 16 Hz), 3.0–3.9 (5 H, m), 4.15 (2 H, q), 7.35 (5 H, s); mass spectrum m/e (relative intensity), 289 (8), 271 (8), 202 (17), 105 (100), 77 (30).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.19; H, 6.85; N, 5.06.

B. From a 1b–3b Mixture.—A mixture of **1b** and **3b** (35.5 g, **1b**:**3b** ratio 1:3, 97 mmol of **3b**) was dissolved in chloroform (200 ml) and treated with a solution of *m*-chloroperoxybenzoic acid (21 g, 85% peroxide content) in chloroform (300 ml). The solution was stirred at room temperature for 5 hr and then washed successively with sodium sulfite, sodium bicarbonate, and sodium chloride solutions. The solution was dried and evaporated. Crystallization of the oily residue from ether (60 ml) by addition of hexane (40 ml) gave **4b** (15.8 g), mp 73–76°. Chromatography of the mother liquors on silicic acid using 30% ether in benzene as eluent afforded recovered **2b** (5.8 g), recovered **3b** (3.5 g), and additional **4b** (3.0 g, total yield 67%).

3-Benzoyl-5-ethyl-6-carbethoxymethyl-7-oxa-3-azabicyclo-[4.1.0]heptane (4dA and 4dB).—A 1:1 mixture of crude **1d** and **3d** prepared as described above (45 g, 22.5 g of **3d**, 75 mmol) was dissolved in chloroform (300 ml) and a solution of *m*-chloroperoxybenzoic acid (25 g, 85% peroxide content) in chloroform (500 ml) was added. The solution was stirred at room temperature for 6 hr and then washed successively with sodium sulfite,

(23) G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).
(24) H. Dannenberg and S. Läufer, *Chem. Ber.*, **89**, 2242 (1956).
(25) J. E. Dolfini and D. M. Dolfini, *Tetrahedron Lett.*, 2053 (1965).
(26) W. C. J. Ross and J. G. Wilson, *J. Chem. Soc.*, 3616 (1959).
(27) Consult the Ph.D. Thesis of W. V. Ligon, Jr., University of Virginia, 1970, for characterization of some hydrolysis products.

sodium bicarbonate, and sodium chloride solutions. The solution was dried and evaporated. The residue was chromatographed on 1500 g of silicic acid using 20% ether in benzene as eluent. There was successively eluted 1d (13.0 g), a mixture of 1d and 3d (3.2 g), a mixture of 3d and 4dA (3.8 g), 4dA (4.0 g, 12 mmol, 17%), a mixture of 4dA and 4dB (10.2 g, 32 mmol), 43%) and 4dB (1.9 g, 6 mmol, 8%). Analytical samples of the stereoisomeric epoxides were prepared by bulb-to-bulb distillation. The less polar stereoisomer 4dA showed ν_{CO} 1740, 1640 cm^{-1} (CCl_4); nmr peaks ($CDCl_3$) at δ 1.30 (t) and 0.5–2.0 (m), total integration ~7 H, 2.22 (1 H, d, J = 16 Hz), 4.18 (q) and 3.2–4.5 (m), total integration ~6 H, 7.40 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11 H, 7.30. Found: C, 68.25; H, 7.35.

The more polar stereoisomer 4dB showed ν_{CO} 1740, 1640 cm^{-1} (CCl_4); nmr peaks ($CDCl_3$) at δ 1.32 (t) and 0.5–2.3 (m), total integration ~7 H, 2.45 (1 H, d, J = 15 Hz), 2.95 (1 H, d, J = 15 Hz), 4.25 (q) and 3.0–4.7 (m), total integration ~6 H, 7.50 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30. Found: C, 68.19; H, 7.41.

4-Benzoyl-8-carbethoxy-7-oxa-4-azaspiro[5.2]octane (2b).—Crystalline 1b (2.0 g, 7.3 mmol) was stirred with *m*-chloroperoxybenzoic acid (2.0 g, 85% peroxide content) in chloroform for 5 days. Tlc indicated quantitative conversion to 2b. The chloroform solution was washed successively with sodium sulfite and sodium carbonate solutions, dried, and evaporated. The residue was crystallized from ether–hexane: mp 97–98°; ν_{CO} 1745, 1625 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.32 (3 H, t), 1.5–2 (3 H, m), 3.3–4.2 (~5 H, m with singlet at 3.5), 4.3 (2 H, q), 7.52 (5 H, s); mass spectrum m/e (rel intensity) 289 (30), 288 (28), 276–272 (each 1–2), 271 (3), 244 (2), 242 (1), 216 (20), 186 (8), 184 (4), 105 (100), 77 (60).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.33; H, 6.73; N, 4.94.

Ethyl 1-Benzoyl-3-hydroxy-$\Delta^{4,\alpha}$-piperidineacetate (5b) and 1-Benzoyl-3-hydroxy-$\Delta^{4,\alpha}$-piperidineacetate Acid Lactone (6a).

A. Ring Opening with Potassium *tert*-Butoxide.—To a solution of 4b (14.5 g, 50 mmol) in dry *tert*-butyl alcohol (200 ml) was added a potassium *tert*-butoxide solution prepared by dissolving 0.5 g of potassium metal in 50 ml of dry *tert*-butyl alcohol. After addition of the base (5 min), the reaction solution was poured into a separatory funnel containing 500 ml of 5% hydrochloric acid and 500 ml of chloroform. The combined chloroform extracts were washed with aqueous sodium carbonate and sodium chloride. Drying and evaporation of the solvent gave 15 g of a viscous residue which was dissolved in hot benzene. Addition of ether caused the precipitation of a gum. The resulting solution was decanted and cooled, resulting in crystallization of 5b (1.0 g). The mother liquors were chromatographed on 300 g of silicic acid using 30% ether in benzene as eluent. Additional 5b (4.3 g, total yield 5.3 g, 18 mmol, 36%) and 6a (0.7 g, 3 mmol, 6%) were obtained. Recrystallization of 5b from chloroform–hexane gave crystalline material: mp 146–148°; ν_{OH} 3330 cm^{-1}; ν_{CO} 1720, 1625 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t), 1.50–4.0 (7 H, m), 4.15 (2 H, q), 6.10 (1 H, s), and 7.45 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.26; H, 6.64; N, 4.79.

Recrystallization of 6a from hexane gave crystals: mp 160–165°; ν_{CO} 1745, 1630 cm^{-1}; nmr peaks ($CDCl_3$) at 2.4–3.1 (4 H, m), 4.0–5.0 (3 H, m), 5.85 (1 H, s), and 7.45 (5 H, s).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.39; H, 5.26; N, 5.70.

B. Ring Opening on Basic Alumina.—A solution of 4b (4.8 g, 17 mmol) in benzene was run onto a column of Fisher Basic Alumina, Activity I, (125 g) packed in benzene. After standing for 3 hr the column was eluted with 40% ether in benzene. The lactone 6a (1.3 g, 5.3 mmol, 31%) was eluted rapidly followed by 5b. Elution of 5b was slow and it proved to be convenient to remove the alumina from the column after removal of 6a. The alumina was thoroughly washed with 1:1 ethanol–chloroform. Evaporation of the solvent gave 5b (2.9 g, 10 mmol, 60%).

1-Benzoyl-3-hydroxy-4-piperidineacetic Acid Lactone (8a).—Hydrogenation of 6a (0.60 g) over platinum oxide in ethanol effected quantitative conversion to a single new material. An analytical sample was prepared by eluting the compound through acidic alumina (activity II) with 1:1 ether–benzene. Compound 8a was obtained as a very viscous oil: ν_{CO} 1790, 1640 cm^{-1} (CCl_4); nmr (DMSO-d_6) peaks at δ 1.0–4.4 (9 H, m), 4.55 (1 H, s, $W_{1/2}$ = 10 Hz), and 7.50 (5 H, s).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.49; H, 6.36; N, 5.67.

Methyl 1-Benzoyl-3-oxo-4-piperidineacetate (9a).—A solution of 8a (4.0 g) in methanol (30 ml) was stirred 1 hr at room temperature with 10 ml of 10% sodium hydroxide solution. The solution was diluted with brine and extracted with ether. The aqueous phase was cooled, acidified, and rapidly extracted with chloroform. The chloroform solution was washed with brine, dried briefly over sodium sulfate, and treated with diazomethane to give 3.1 g of methyl 1-benzoyl-3-hydroxy-4-piperidineacetate (7a). Oxidation was carried out as for 9b. The nmr spectrum closely resembled that of 9b except for the expected differences in the signals of the alkoxy groups.

Ethyl 1-Benzoyl-3-oxo-4-piperidineacetate (9b).—A solution of 5b (6.0 g, 21 mmol) in ethanol (150 ml) containing platinum oxide catalyst (300 mg) was hydrogenated at 30 psi for 40 min. The reaction mixture was filtered and concentrated at reduced pressure. Excessive heating was avoided to minimize lactonization. The alcohol was freed of residual ethanol using vacuum and then dissolved in acetone (150 ml). The resulting solution was treated with Jones reagent (11 ml)[28] and stirred for 20 min. The acetone layer was poured into a brine–chloroform mixture and the precipitate dissolved in water. The combined water layers were extracted with additional chloroform. The chloroform solution was washed with sodium chloride, dried, and evaporated leaving 9b as an oil: ν_{CO} 1730, 1630 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t), 1.7–3.8 (series of multiplets), 4.15 (2 H, q), and 7.40 (5 H, s); mass spectrum m/e (rel intensity) 289 (12), 275 (15), 274 (18), 244 (6), 243 (6), 230 (4), 228 (2), 202 (12), 200 (3), 188 (2), 186 (6), 184 (4), 174 (10), 170 (14), 122 (6), 121 (2), 120 (1), 105 (100), 77 (60). The ketone was unstable to storage (color development, new tlc spots) and several attempts to prepare satisfactory analytical samples failed. Subsequently, the ketone was used directly in the next step.

Ethyl 1-Benzoyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (*c*-10b and *t*-10b).—A solution of 9b (2.7 g, 9.3 mmol) in benzene (40 ml) was heated with pyrrolidine (1.6 ml) and *p*-toluenesulfonic acid (12 mg) for 18 hr. The reaction flask was equipped with a Dean-Stark trap partially filled with type 4A molecular sieve and a nitrogen atmosphere was maintained throughout the reflux period. The benzene was removed at reduced pressure and the residue was dissolved in dry toluene (40 ml). Gramine (2.5 g) was added and the solution was refluxed for 3 hr. The solution was cooled briefly and additional gramine (1.5 g) was added followed by 3-hr additional reflux. The toluene was removed at reduced pressure and the residue was dissolved in ethanol (30 ml). To the resulting solution there was added a solution prepared from ethanol (10 ml), water (2 ml), and concentrated hydrochloric acid (1 ml). This slightly acidic solution (pH 5–6) was stirred at room temperature for 20 min, poured into brine, and extracted thoroughly with chloroform. The chloroform solution was washed with sodium bicarbonate and sodium chloride solutions, dried, and evaporated. The residue was dissolved in benzene, treated with charcoal, and filtered and the filtrate evaporated. The residue was dissolved in ethanol (12 ml). On cooling it deposited a mixture (1.60 g) of *c*-10b and *t*-10b (mainly *t*-10b). The mother liquors were evaporated, dissolved in benzene, and chromatographed on silicic acid using 1:1.5:7.5 chloroform–ether–benzene as solvent. There was eluted diindolylmethane, the crystalline by-product 11b, mp 151–155°, and then *t*-10b (0.15 g) and *c*-10b (0.18 g). Fractional crystallization of the original crystalline product using ethanol gave 1.0 g of pure *t*-10b, mp 173–175° (total yield 1.15 g, 2.7 mmol, 30%) and 0.35 g of *c*-10b, mp 163–165° (total yield 0.53 g, 1.2 mmol, 14%).

An analytical sample of *t*-10b was prepared by recrystallization from ethanol: mp 174–176°; ν_{NH} 3450, 3220 cm^{-1}; ν_{CO} 1740, 1610 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 70°) at δ 1.1 (3 H, t), 1.3–2.0 (~2 H, broad) 2.2 (d, portion of d of d partially obscured by DMSO-d_5), 2.6 (1 H, d of d, J = 16, 6 Hz), 3.3 (~2 H broad d), 3.5 (broad d, J = 10 Hz), 4.0 (~3 H, q superimposed on broad signal), 4.8 (1 H, broad); mass spectrum m/e (rel intensity) 418 (3), 373 (1), 372 (1), 289 (27), 243 (18), 170 (2), 144 (2), 143 (3), 130 (100), 117 (2), 115 (2), 105 (53).

(28) Prepared as described by A. C. Cope and W. D. Burrows, *J. Org. Chem.*, **31**, 3099 (1966).

Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.64; H, 6.28; N, 6.60.

An analytical sample of *c*-**10b** was prepared by recrystallization from ethanol: mp 163–165°; ν_{NH} 3250 cm^{-1}; ν_{CO} 1745, 1740, 1620 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 70°) at δ 1.1 (3 H, t), 1.3–2.0 (~2 H, broad), 2.3 (d, portion of d of d partially obscured by DMSO-d_5), 2.6 (1 H, d of d, J = 16, 6 Hz), 3.2 (~2 H, broad d), 3.6 (1 H, broad d, J = 10 Hz), 4.0 (2 H, q), 4.1 (1 H, broad); mass spectrum *m/e* (rel intensity) 418 (3), 373 (1), 372 (1), 289 (17), 243 (13), 144 (2), (143) (2), 130 (100), 117 (1), 115 (1), 105 (57).

Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.83; H, 6.43; N, 6.65.

The crude reaction mixture also contained several components more polar than *c*-**10b** and *t*-**10b**. These could be eluted from silicic acid with 5:10:30:55 ethanol–chloroform–ether–benzene. Attempts to crystallize these materials failed but reduction with sodium borohydride gave **10e**, mp 243–248°. An analytical sample was prepared by recrystallization from ethanol–benzene: mp 255–257°; $\nu_{OH,NH}$ 3450, 3250 cm^{-1}; ν_{CO} 1635, 1620 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 72.78; H, 7.01; N, 9.43. Found: C, 72.49; H, 7.28; N, 9.37.

An analytical sample of **11b** was prepared by recrystallization from ethanol: mp 227–228°; ν_{NH} 3470, 3270 cm^{-1}; ν_{CO} 1740, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 601 (6), 600 (10), 471 (21), 470 (32), 342 (21), 341 (27), 131 (22), 130 (61), 129 (41), 105 (100), 102 (27), 77 (45), 69 (20); $\lambda_{95\%\ EtOH}^{max}$ (log ϵ) 223 (5.02), 277 (4.34), 283 (4.35), 292 (4.30).

Anal. Calcd for $C_{38}H_{40}N_4O_3$: C, 75.97; H, 6.71; N, 9.33. Found: C, 76.28; H, 6.98; N, 8.91.

Equilibration of *c*-10b and *t*-10b.—Identical experiments were carried out with each ketone. A solution of the ketone (100 mg) and potassium fluoride (300 mg) in ethanol (20 ml) was refluxed for 31 hr. The ethanol was removed at reduced pressure and the residue was dissolved in chloroform and washed with water. Tlc on silica gel (three elutions using 1:1:0.3:0.7 methylene chloride–ether–hexane–benzene) indicated that the product from both *c*-**10b** and *t*-**10b** had identical composition favoring *t*-**10b** by ~4:1. The chloroform was evaporated and the residue was crystallized from ethanol. *t*-**10b** gave 69.6 mg of crystalline product having an infrared identical with pure *t*-**10b**. *c*-**10b** gave 63.1 mg of crystalline product, having an infrared spectrum identical with that of pure *t*-**10b**.

Methyl 1-Benzoyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (10a).—The ketone **9d** (3.0 g, 11 mmol) was converted to the enamine and alkylated by a procedure analogous to that used for **10b**. The crude product was hydrolyzed as for **10b** except that methanol was used instead of ethanol. Chromatography of the product gave **10a** (0.365 g, 0.95 mmol, 8%): mp 114–116° after recrystallization from methanol; ν_{NH} 3300 cm^{-1}; ν_{CO} 1720, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 404 (5), 373 (2), 372 (3), 355 (1), 276 (5), 275 (33), 243 (18), 174 (1), 170 (2), 144 (1), 143 (2), 142 (1), 130 (100), 105 (64).

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; 5.98; N, 6.93. Found: C, 71.34; H, 6.14; N, 7.01.

Ethyl 1-Benzoyl-3-hydroxy-2-(3-indolylmethyl)piperidine-4-acetate (*t,t*-12b).—A solution of *t*-**10b** (0.120 g, 0.29 mmol) in ethanol (20 ml) was stirred for 0.5 hr with sodium borohydride (50 mg). Acetone (2 ml) was added and after 5 min the solution was poured into dilute hydrochloric acid and extracted thoroughly with chloroform. The chloroform was washed with sodium bicarbonate solution, dried, and evaporated. The residue was dissolved in chloroform. Addition of a small amount of hexane induced crystallization of **12b**, (0.108 g, 0.26 mmol, 90%), mp 165°. Recrystallization from chloroform–hexane gave the analytical sample: mp 167–168°; $\nu_{OH,NH}$ 3340 cm^{-1}; ν_{CO} 1745, 1620 cm^{-1}; nmr peaks ($CDCl_3$–DMSO-d_6) at δ 1.22 (3 H, t), 1.5–3.5 (m), 4.1 (2 H, q), 5.2 (d, 1 H exchanged by D_2O), 6.2 (d, 1 H), and 6.5–7.8 (9 H, m); mass spectrum *m/e* (rel intensity) 420 (2), 375 (2), 374 (6), 290 (13), 269 (2), 245 (3), 244 (5), 186 (3), 168 (2), 144 (2), 143 (3), 130 (35), 117 (8), 105 (100).

Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.40; H, 6.69; N, 6.73.

The 3-d_1 analog was prepared similarly using sodium borodeuteride: mass spectrum *m/e* (rel intensity) 421 (8), 376 (6), 375 (12), 291 (40), 246 (8), 245 (12), 187 (5), 130 (36), 117 (8), 105 (100).

1-Benzoyl-3-hydroxy-2-(3-indolylmethyl)piperidine-4-acetic Acid Lactone (*t,t*-13a).—A mixture of *t,t*-**12b** (1.20 g, 2.9 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (50 ml) was refluxed for 12 hr. The toluene was removed by distillation at reduced pressure and the residue was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried, and evaporated. The residue crystallized from chloroform–hexane to give *t,t*-**13a** (0.65 g, 1.7 mmol, 60%), mp 193–198°. Recrystallization from chloroform–hexane gave the analytical sample: mp 202–204°; ν_{NH} 3250 cm^{-1}; ν_{CO} 1810, 1620 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 90°) at 1.2–2.0 (~3 H, m), 2.8–3.4 (~3 H, m), 4.2 (2 H, d of d, J = 10, 5 Hz superimposed on broad singlet), 4.9 (1 H, broad); mass spectrum *m/e* (rel intensity) 374 (15), 269 (4), 253 (4), 245 (7), 244 (6), 240 (2), 230 (2), 226 (2), 186 (7), 172 (2), 171 (2), 170 (2), 169 (2), 168 (2), 167 (2), 157 (2), 156 (2), 155 (2), 143 (7), 144 (2), 142 (2), 141 (2), 130 (62), 117 (20), 115 (4), 105 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.58; H, 5.92; N, 7.46.

The 3-d_1 analog was prepared similarly from *t,t*-**12b**-d_1: nmr spectrum identical with *t,t*-**13a**'s except lacking d of d at δ 4.2; mass spectrum *m/e* (rel intensity) 375 (75), 270 (7), 253 (8), 246 (15), 245 (11), 187 (14), 170 (4), 169 (6), 168 (10), 167 (6), 165 (6), 130 (60), 117 (18), 105 (100).

Reduction of *c*-10b.—A solution of *c*-**10b** (200 mg, 0.48 mmol) was reduced with sodium borohydride (100 mg) in ethanol and the product mixture obtained as described for *t*-**10b**. Tlc showed two major components which were isolated by preparative tlc. The more readily eluted component was an alcohol, *c,c*-**12b**: mp 217–218° (95 mg, 47%); $\nu_{NH,OH}$ 3360, 3250 cm^{-1}; ν_{CO} 1730, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 420 (1), 374 (3), 290 (4), 245 (18), 186 (11), 144 (1), 143 (1), 130 (31), 117 (2), 105 (100).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 72.14; H, 6.87; N, 6.42.

The less readily eluted component (85 mg, 47%) was recrystallized from methylene chloride–ether–hexane to give *c,c*-**13a**: mp 154–156°; ν_{NH} 3410, 3270 cm^{-1}; ν_{CO} 1780, 1605 cm^{-1}; nmr (DMSO-d_6, 35°) δ 1.9 (2 H, broad q), 2.8 (2 H, d), 3.2 (? H, m), 3.7 (2 H, q), 4.5–5 (2 H, 6 line m), 7.0–7.5 (10 H, m); (DMSO-d_6, 90°) δ 1.8 (2 H, septet), 2.5–2.8 (2 H, m), 3.1 (2 H, unsym q), 3.2–3.8 (2 H, 12 line m), 4.6 (1 H, q), 4.8 (1 H, t); mass spectrum *m/e* (rel intensity) 374 (5), 245 (32), 186 (24), 181 (3), 169 (5), 168 (3), 155 (3), 144 (3), 143 (5), 130 (42), 119 (3), 117 (3), 115 (3), 105 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.53; H, 6.00; N, 7.49.

Lactonization of the alcohol *c,c*-**12b** as described for *t,t*-**12b** gave only *c,c*-**13a**. Reduction of *c*-**10b** with sodium borodeuteride gave *c,c*-**13a**-3-d_1, having an nmr identical with *c,c*-**13a**'s except that the t at 4.8 is missing and the signal at 4.6 is a t: mass spectrum *m/e* (rel intensity) 375 (19), 246 (75), 187 (35), 169 (5), 168 (7), 130 (45), 117 (3), 115 (3), 105 (100).

Methyl 1-Benzoyl-5-ethyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (*t,t*-10c and *t,c*-10c).—A mixture of **4dA** and **4dB** (8.0 g, 2.5 mmol) was dissolved in xylene (300 ml) and refluxed for 4 hr with diazabicyclooctane (8.0 g). The xylene was removed by distillation at reduced pressure and the residue was dissolved in chloroform and washed with dilute hydrochloric acid solution and brine. The chloroform was dried, leaving a mixture of the stereoisomers of **5d** and **6c**. The mixture was dissolved in ethanol (200 ml) and hydrogenated over platinum oxide (250 mg) for 2 hr at 35 psi. The solution was filtered and evaporated leaving 7 g of an oil. This was dissolved in ethanol (60 ml) and stirred at room temperature for 45 min with 20 ml of 10% aqueous sodium hydroxide solution. The reaction mixture was poured into brine and extracted with ether which removed 0.5 g of unhydrolyzed material. The aqueous layer was cooled and carefully acidified to pH 2–3 with cold hydrochloric acid. The acidic aqueous solution was extracted with chloroform. The chloroform was washed with brine, dried briefly over sodium sulfate, and then treated with excess diazomethane. The acidification, extraction, and methylation were carried out as quickly as possible to minimize relactonization of the hydroxy acid. The methyl ester was isolated after excess diazomethane was destroyed with acetic acid by washing the chloroform solution with sodium bicarbonate solution and brine. Evaporation of the dried chloroform solution gave 7.5 g of hydroxy ester. Oxidation with Jones reagent was carried out as for **9b**. The resulting ketone **9c** (7.0 g) was dissolved in benzene (100 ml) and refluxed for 30 hr with pyrrolidine (5 cc) and *p*-toluenesulfonic acid (40 mg) using a Dean-Stark water separator filled with molecular

sieve. After removal of the benzene, alkylation with gramine was accomplished as for **10b**. Hydrolysis of the reaction product was carried out using methanol. Chromatography of the product on silicic acid (200 g) using 1:1.5:7.5 chloroform–ether–benzene gave *t,t*-**10c** (1.01 g, 0.23 mmol, 9%), mp 173–175° after crystallization from benzene–hexane, and *t,c*-**10c** (0.433 g, 0.10 mmol, 4%), mp 203–205° after crystallization from ethanol.

An analytical sample of *t,t*-**10c** was prepared by recrystallization from ethanol–hexane: mp 174–175°; ν_{NH} 3200 cm^{-1}; ν_{CO} 1730, 1720, 1620 cm^{-1}; nonaromatic nmr peaks at δ (DMSO-d_6, 70°), 1.8 (3 H, t), 1.0–2.0 (~4 H, very broad), 2.6 (2 H, d), 2.7–3.0 (2 H, m), 3.3 (~3 H, broad doublet), 3.55 (3 H, s), 4.0 (1 H, very broad), 4.8 (1 H, very broad); mass spectrum *m/e* (rel intensity) 432 (3), 400 (1), 303 (25), 271 (17), 198 (1), 171 (1), 170 (1), 144 (2), 143 (3), 130 (100), 117 (2), 115 (2), 105 (67).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.01; H, 6.58; N, 6.60.

An analytical sample of *t,c*-**10c** was prepared by recrystallization from ethanol: mp 210–212°; ν_{NH} 3280 cm^{-1}; ν_{CO} 1740, 1720, 1610 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 70°) at δ 0.7–1.8 (~6 H, very broad), 2.3 (1 H, d of d, J = 17, 8 Hz), 3.4 (2 H, broad d), 3.6 (3 H, s), 3.6–3.8 (~2 H, broad); mass spectrum *m/e* (rel intensity) 432 (3), 401 (0.5), 400 (1), 303 (25), 271 (17), 244 (1.5), 243 (2), 231 (1), 230 (1), 219 (1), 198 (1), 181 (2), 171 (1), 170 (1), 169 (1), 167 (1), 166 (1), 157 (1), 156 (1), 155 (1), 144 (2), 143 (2), 130 (100), 119 (2), 117 (2), 115 (2), 105 (83).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.22; H, 6.70; N, 6.61.

Elution of the column with 5:10:30:55 methanol–chloroform–ether–benzene gave several more polar fractions containing pyrrolidine amides **10f**. Two of the fractions gave crystalline sodium borohydride reduction products **12f** which could be recrystallized from ethanol–hexane. One fraction gave an amide: mp 175–177°; ν_{NH} 3400 cm^{-1}; ν_{CO} 1630 cm^{-1}; mass spectrum *m/e* (rel intensity) 473 (6), 454 (2), 402 (6), 343 (58), 272 (11), 221 (6), 214 (3), 130 (26), 117 (4), 105 (100).

Anal. Calcd for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87. Found: C, 73.71; H, 7.57; N, 8.97.

A second fraction gave a second amide as a solvate: mp (with desolvation) 147–152°; ν_{NH} 3400 cm^{-1}; ν_{CO} 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 473 (4), 402 (7), 343 (34), 273 (5), 272 (9), 221 (4), 214 (5), 130 (29), 117 (7), 105 (100).

Anal. Calcd for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87. Found (after drying at 150°): C, 73.64; H, 7.59; N, 8.94.

The 4dA–4dB mixture could also be converted to *t,c*-**10c** and *t,t*-**10c** after ring opening on basic alumina. A mixture of 9.5 g of the epoxides was absorbed onto 200 g of basic alumina and kept for 3 hr. Elution with 20% ether–benzene eluted a mixture containing mainly unsaturated lactone (4.0 g). Ether–benzene–ethanol (30:65:5) eluted a readily crystallized alcohol **5d** (2.4 g): mp 135–136° after recrystallization from methylene chloride–hexane; ν_{OH} 3300 cm^{-1}; ν_{CO} 1700, 1600 cm^{-1}; $\nu_{C=C}$ 1650 cm^{-1}; nmr peaks ($CDCl_3$) at δ 0.6–1.8 (8 H, m and t at 1.25), 2.2–3.4 (m, ~1 H), 3.5–5.1 (7 H, very broad with q at δ 4.15), 6.2 (1 H, s), 7.4 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11, H, 7.30; N, 4.41. Found: C, 68.21; H, 7.35; N, 4.49.

Combination of the alcohol and lactone fractions followed by the same reaction sequence described for the DABCO ring opening product gave *t,c*-**10c** and *t,t*-**10c** in yields similar to those described above.

Ethyl 1-Benzoyl-5-ethyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (10d).—The alcohol **5d** (0.70 g, 2.2 mmol) was hydrogenated and oxidized as in the preparation of **9b**. The spectral properties of the resulting ketone were in accord with expectation. The ketone was dissolved in benzene (40 ml) and refluxed 18 hr with pyrrolidine (1 ml) and a trace of *p*-toluenesulfonic acid. The benzene was removed and alkylation with gramine was carried out in toluene as described for **10b**. The crude product was chromatographed on silicic acid to give **10d** (0.053 g, 0.012 mmol, 5%): mp 174–176° after recrystallization from ethanol; ν_{NH} 3300 cm^{-1}; ν_{CO} 1745, 1735, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 446 (4), 401 (1), 400 (3), 317 (54), 295 (1), 271 (35), 244 (1), 243 (1), 144 (1), 143 (1), 130 (100), 105 (88).

Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.47; H, 6.83; N, 6.24.

Methyl 1-Benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetate (*t,t,t*-12c).—Reduction of *t,t*-**10c** (200 mg) with sodium borohydride in methanol as described for *t*-**10b** gave *t,t,t*-**12c** (180 mg, 90%): mp 215–217° after recrystallization from chloroform–hexane; $\nu_{NH,OH}$ 3400, 3280 cm^{-1}; ν_{CO} 1740, 1600 cm^{-1}; mass spectrum *m/e* (rel intensity) 434 (2), 402 (6), 304 (5), 297 (2), 285 (1), 281 (2), 273 (3), 272 (5), 252 (1), 231 (1), 219 (1), 214 (4), 181 (2), 169 (2), 168 (1), 157 (1), 156 (1), 155 (1), 154 (1), 144 (2), 143 (2), 130 (33), 119 (3), 117 (10), 115 (1), 105 (100).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.60; H, 7.12; N, 6.34.

Lactone of 1-Benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetate Acid (*t,t,t*-13c).—A solution of *t,t,t*-**12c** was lactonized as described for *t,t*-**12b** giving *t,t,t*-**13c** in 78% yield. An analytical sample was prepared by recrystallization from benzene: mp 220–221°; ν_{NH} 3310 cm^{-1}; ν_{CO} 1795, 1635 cm^{-1}; nmr peaks ($CDCl_3$) at 1.0–4.0 (~11 H, diffuse multiplets), 4.15 (1 H, d of d, J = 9, 5 Hz) 4.45 (1 H, m), 4.95 (1 H, d, 14 Hz), 6.3 (1 H, d, 7 Hz), 6.6–7.7 (9 H, m), 8.5 (1 H, s); nonaromatic nmr peaks (DMSO-d_6, 90°) at 1.9 (3 H, t), 1.0–2.0 (~4 H, broad), 2.5–3.4 (? H, m), 4.2 (2 H, d of d, J = 11, 5 Hz on broad signal), 4.8 (1 H, broad); mass spectrum *m/e* (rel intensity) 402 (9), 297 (1), 285 (1), 281 (3), 273 (4), 272 (5), 258 (3), 252 (1), 226 (1), 214 (5), 186 (1), 180 (1), 172 (1), 171 (1), 169 (1), 168 (3), 167 (1), 154 (3), 144 (3), 143 (4), 130 (37), 117 (9), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.88; H, 6.62; N, 6.94.

Reduction of *t,c*-10c.—A solution of *t,c*-**10c** (94 mg) was reduced in the standard manner with sodium borohydride. Tlc indicated a major and a minor product. Some of the major product *t,t,c*-**12c** crystallized from benzene (30 mg, 32%): mp 200–201° after recrystallization from methylene chloride–benzene; $\nu_{NH,OH}$ 3450, 3300 cm^{-1}; ν_{CO} 1740, 1610 cm^{-1}; mass spectrum *m/e* (rel intensity) 434 (1), 402 (8), 304 (10), 297 (2), 281 (1), 273 (5), 272 (7), 226 (1), 214 (5), 154 (2), 144 (2), 143 (2), 130 (37), 117 (8), 105 (100).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.66; H, 7.01; N, 6.53.

The mother liquors from which *t,t,c*-**12c** crystallized contained additional *t,t,c*-**12c** and the minor reduction product. Concentration and lactonization of the residue gave two lactones which were separated by tlc. The more mobile lactone, *t,t,c*-**13c** (23 mg, 26%), was recrystallized from benzene, mp 203–204°, also isolated as a benzene solvate, mp 110–120°, with desolvation: ν_{NH} 3430, 3300 cm^{-1}; ν_{CO} 1780, 1630 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 120°) at 1.8 (3 H, t), 1.0–1.6 (2 H, m), 1.9 (1 H, broad s), 2.5–2.9 (?, obscured by DMSO-d_5, H_2O), 3.0–3.5 (3 H, m), 4.1 (1 H, broad d), 4.4 (1 H, d of d, J = 11, 5 Hz), 4.9 (1 H, broad s); mass spectrum *m/e* (rel intensity) 402 (10), 297 (2), 285 (1), 281 (2), 273 (5), 272 (6), 226 (2), 214 (6), 186 (1), 180 (1), 170 (1), 169 (1), 168 (2), 167 (1), 154 (2), 144 (2), 143 (3), 130 (43), 117 (11), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.74; H, 6.56; N, 6.75.

The less mobile lactone, *t,c,c*-**13c** (21 mg, 24%), was recrystallized from ethanol–hexane: mp 235–236°; ν_{NH} 3420, 3220 cm^{-1}; ν_{CO} 1775, 1620 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 90°) at δ 0.9 (3 H, t), 1.3 (~2 H, q) 2.0–3.0 (? H, obscured by DMSO-d_5, H_2O), 3.5 (2 H, m), 4.0–5.0 (~3 H, very broad with d of d, J = 8, 1 Hz at 4.6); mass spectrum *m/e* (rel intensity) 402 (5), 273 (29), 262 (1), 244 (1), 228 (1), 223 (1), 214 (12), 186 (2), 181 (2), 169 (2), 168 (3), 144 (2), 143 (2), 130 (25), 119 (2), 117 (2), 115 (2), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.63; H, 6.66; N, 6.95.

Separate lactonization of *t,t,c*-**12c** gave *t,t,c*-**13c**.

Methyl 1-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridine-4-acetate (14).—A mixture of **1b** and **3b** (2.3 g, 8.5 mmol) was stirred at room temperature for 5 hr with a solution of 10% aqueous sodium hydroxide (10 ml) in ethanol (20 ml). The solution was then diluted with water and extracted with ether. The aqueous layer was added to 20 ml of 10% sodium hydroxide solution and refluxed for 24 hr. After extraction with ether the reaction mixture was acidified and extracted with chloroform. It was then brought to neutrality and concentrated until precipitation began. Aqueous 15% sodium hydroxide (30 ml) was added and the solution was cooled in an ice bath. Portions (~0.5 ml) of benzyl chloroformate (total 4 ml) were added with shaking and cooling over a period of 20 min. The solution was extracted with ether, acidified, and extracted with chloroform to give 2.2 g of a mix-

ture of the exocyclic and endocyclic acids. The nmr spectrum indicated that the endocyclic isomer predominated over the exocyclic by about 7:1. Esterification of the acid mixture with diazomethane gave **14**: bp 170–185° (0.5 mm); ν_{CO} 1760, 1730 cm^{-1}; nmr peaks ($CDCl_3$) at δ 2.2 (2 H, m), 3.04 (2 H, s), 3.65 (5 H, s superimposed on m), 4.0 (2 H, m), 5.15 (2 H, s), 5.5 (1 H, m), 7.30 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.60; H, 6.72; N, 4.67.

Hydroboration of 14. 1-Benzyloxycarbonyl-3-hydroxy-4-piperidineethanol (15).—A solution of **14** (1.8 g, 6.3 mmol) in glyme (10 ml) at 0° was treated with 1.0 *M* diborane solution in tetrahydrofuran (3 ml, 3 mmol). After 0.5 hr, water (4 ml), 30% hydrogen peroxide (10 ml) and potassium carbonate (10 g) were carefully added, and the solution was stirred at room temperature for 3 days. The reaction mixture was poured into water and extracted with ether. Chromatography of the crude product (1.6 g) on silicic acid using 30% ether–benzene gave recovered **14** (0.8 g, 44%) and **15** (0.45 g, 16 mmol, 45%): nmr peaks ($CDCl_3$) at δ 1.0–2.0 (5 H, m), 2.0–5.0 (7 H, m), 5.1 (2 H, s), and 7.35 (5 H, s).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58. Found: C, 64.77; H, 7.80.

***N*-(2-Oxo-4-carbethoxybutyl)-2-ethylaziridine (18).**—2-Ethylaziridine (1.77 g, 0.025 mol) was dissolved in triethylamine (10 ml) and added dropwise during 10 min to a solution of ethyl 5-bromolevulinate[24] (5.56 g, 0.025 mol) in benzene (50 ml) at 0°. After stirring 2 hr at 0° triethylamine hydrobromide was removed by filtration and the solvent was removed using a rotary evaporator at room temperature. The product, obtained as a clear pale yellow oil (5.0 g, 94%), was used in subsequent experiments within 0.5 hr.

Ethyl *N*-Benzoyl-*N*-(2-chlorobutyl)-5-aminolevulinate (19).—A solution of **18** (5.56 g, 0.025 mol) in benzene (50 ml) was added dropwise to benzoyl chloride (3.5 g, 0.025 mol) in benzene (50 ml) at 0°. After stirring for 20 min the solvent was removed using a rotary evaporation, and the residue was dissolved in chloroform and washed with dilute potassium carbonate, dilute hydrochloric acid, and water. Evaporation of the chloroform gave the crude haloamide: ν_{CO} 1735, 1640 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.23 (3 H, s), 0.6–2.0 (5 H, unresolved m), 2.9–2.3 (4 H, d), 4.1 (2 H, q), 4.38 (2 H, s), 7.39 (5 H, broad s). Attempts to effect complete purification by distillation or silicic acid chromatography failed.

N-Benzoyl-6-(2-carbethoxyethyl)-2-ethyl-3,4-dihydro-2*H*-1,4-oxazine (20).—A solution of **19** (1.0 g, 2.8 mmol) in dry tetrahydrofuran (10 ml) was treated with potassium *tert*-butoxide (0.317 g, 2.8 mmol) and stirred at room temperature for 3 hr. Gaseous hydrochloric acid was passed through the solution. The solvent was removed and the residue was dissolved in a small amount of chloroform and eluted through Florisil with chloroform giving **20** (0.4 g, 1.2 mmol, 44%). Rechromatography gave the analytical sample: ν_{CO} 1740, 1640 cm^{-1}; $\nu_{C=C}$ 1690 cm^{-1}; nmr signals ($CDCl_3$) at 1.21 (3 H, t), 0.7–2.0 (5 H, complex m), 2.2–2.7 (2 H, m), 4.1 (2 H, q), 2.9–4.5 (3 H, unresolved m), 6.6, 5.8, (1 H, singlets in 1:2 ratio), 7.47 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.13; H, 7.25; N, 4.42. Found: C, 67.86; H, 6.98; N, 4.41.

Reduction of this material by $NaBH_4$ slowly (overnight) gave *N*-benzoyl-2-ethyl-6-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,4-oxazine (**21**) as indicated by mass spectral parent ion 275 and infrared absorption data: ν_{OH} 3440 cm^{-1}; ν_{CO} 1640 cm^{-1}; no ester carbonyl; nmr peaks ($CDCl_3$) at δ 0.7–2.5 (9 H, complex m), 2.32 (1 H, s, exchanged by D_2O), 3.9–4.5 (5 H, complex unresolved signal), 6.65, 5.8 (1 H, singlets in 1:2 ratio), 7.52 (5 H, s).

Registry No.—**2b**, 30338-60-4; **4b**, 30338-61-5; **4d**, 30338-62-6; **5b**, 30338-63-7; **5d**, 30338-64-8; **6a**, 30338-65-9; **8a**, 30338-66-0; **9b**, 30338-67-1; **10a**, 30338-68-2; *t*-**10b**, 30338-69-3; *c*-**10b**, 30338-70-6; *t,t*-**10c**, 30338-71-7; *t,c*-**10c**, 30338-72-8; **10d**, 30338-73-9; **10e**, 30338-74-0; **11b**, 30338-75-1; *t,t*-**12b**, 30338-76-2; *c,c*-**12b**, 30338-77-3; *t,t,t*-**12c**, 30409-18-8; *t,t,c*-**12c**, 30338-78-4; **12f**, 30338-79-5; *t,t*-**13a**, 30338-80-8; *c,c*-**13a**, 30338-81-9; *t,t,t*-**13c**, 30338-82-0; *t,t,c*-**13c**, 30338-83-1; *t,c,c*-**13c**, 30338-84-2; **14**, 30338-85-3; **15**, 30338-86-4; **19**, 30338-87-5; **20**, 30409-19-9; **21**, 30344-94-6.

Acknowledgment.—We are grateful for financial support from NSF Grants GP-7951 and GP-19374, an NIH Predoctoral Fellowship (Woodfin V. Ligon, Jr., 1969–1970), and University of Virginia Du Pont Fellowships (Woodfin V. Ligon, Jr., 1968–1969; Long-Su Lin, 1970–1971).

The Synthesis of Polyalkyl-1-tetralones and the Corresponding Naphthalenes[1]

E. J. EISENBRAUN,*[2a] C. W. HINMAN,[2b] J. M. SPRINGER,[2c–e] J. W. BURNHAM,[2f] AND T. S. CHOU[2g]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

P. W. FLANAGAN AND M. C. HAMMING

Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

Received September 15, 1970

The stepwise synthesis of specifically substituted trialkyl-3,4-dihydro-1(2*H*)-naphthalenones (1-tetralones), the corresponding naphthalenes, and partially hydrogenated derivatives, several having the cadalene-type 1,4,6 substitution, has been reexamined. Individual steps have been improved and new approaches with *fewer* steps and higher overall yields have been devised. Syntheses utilizing lactones in Friedel–Crafts reactions were also carried out. These latter Friedel–Crafts reactions are responsible for rearrangements during tetralone syntheses which were previously attributed to polyphosphoric acid during cyclization.

The synthesis of cadalene (**1**) became important to us as a route to pure polyalkylnaphthalenes and as a model to develop new and improved hydrocarbon syntheses.[3,4]

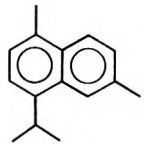
(1) E. J. Eisenbraun and C. W. Hinman, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **10** [1], 33 (1965).

(2) (a) Address correspondence and reprint requests to this author. (b) American Petroleum Institute Graduate Research Assistant, 1962–1965; deceased. (c) API GRA, 1965–1967. (d) NSF Graduate Trainee, 1967–1968. (e) American Chemical Society Petroleum Research Fund Fellow, GB-395, 1968–1969. (f) API GRA, 1969–present. (g) Eli Lilly Co. GRA, 1963–1967.

(3) (a) S. Dev and P. C. Guha, *J. Indian Chem. Soc.*, **25**, 13 (1948); (b) B. A. Nagasampagi, S. Dev, and (in part) C. Rai and K. L. Murthy, *Tetrahedron*, **22**, 1949 (1966); (c) L. Ruzicka and L. Ehmann, *Helv. Chim. Acta*, **15**, 140 (1932).

(4) Correspondence regarding samples of hydrocarbons **6**, **7**, **9a**, 1,2,3,4-tetrahydro-1,4 5-trimethylnaphthalene, and 1,4,5-trimethylnaphthalene should be directed to A. J. Streiff, American Petroleum Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213.

It is of interest that most of the reagents used in an earlier synthesis[3a] which leads to **1** in 18% yield through



1

seven steps have been supplanted and the synthesis is now so drastically modified that comment is required, particularly since some of the reagents and steps remain as textbook favorites. To ensure validity in our comparison, we repeated the preparation of **1** and obtained the reported yields.[3a] This synthesis, however, is impractical for large-scale preparations.

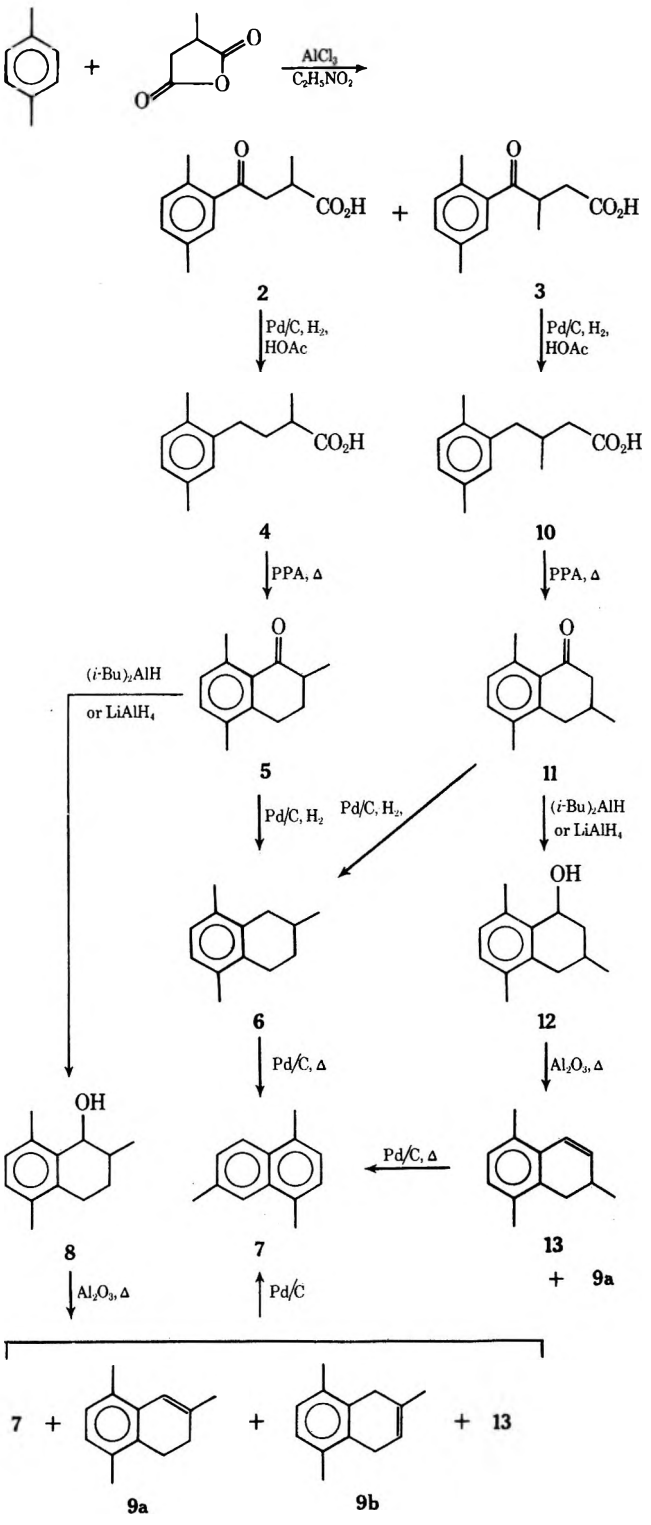
The Friedel–Crafts acylation came under immediate scrutiny because of the difficulty in removing nitrobenzene from the reaction products in large-scale operations. Substitution of the more volatile nitroethane is a major improvement. The reaction of *p*-xylene, methylsuccinic anhydride, and aluminum chloride strongly favors the formation of **2** over **3** when nitroethane is used. This ratio, 61:1 (**2**:**3**), changes to 57:1 with nitromethane and 44:1 with nitrobenzene. The ratio is also altered if excess aromatic hydrocarbon is used as sole solvent since the reaction using methylsuccinic anhydride with excess benzene gave a product ratio of 2.3:1 (α-methyl isomer to β-methyl isomer), whereas in nitroethane this ratio was 7.3:1. We also abandoned the earlier practice[3a] of aging Friedel–Crafts reaction mixtures.[5]

The Clemmensen reaction is a popular method for reducing the ketone carbonyl group of γ-oxo acids[6a] and we have found it to be superior to the Wolff–Kishner procedure. However, low-pressure hydrogenolysis using Pd/C catalyst in acetic acid is even better for the reduction of the benzoyl-type γ-oxo acids of Scheme I to the deoxy acids in 95+% yields.[6b,c] We greatly prefer the use of polyphosphoric acid[6d] (PPA) to the acid chloride–$AlCl_3$ procedure[3a] for cyclization of γ-arylbutyric acids (**4** to **5** or **10** to **11**).

Dehydration of **8** was done with hot alumina.[6e] This procedure is convenient for large-scale reactions but does lead to a mixture of isomeric dihydronaphthalenes, which, however, were readily aromatized with Pd/C to **7**.[6c] Formic acid[3a] dehydration may be preferable since there is less double migration. Dehydration with iodine[3b] gave polymeric products in some cases and hot thoria[6f] also caused formation of isomeric dihydronaphthalenes. Selenium[3a] dehydrogenation was not acceptable because of the expense of the reagent and the inconvenience in disposing of large volumes of H_2Se. Consequently, Pd/C catalyst was used.[6c]

We sought to reduce the number of steps in the synthesis by treating the tetralones **5** and **11** with Pd/C which gave **7** in 43 and 44% yields.[6g] The formation of naphthols which were difficult to remove in some cases dictated other routes.[6g] For 1-tetralone, 2-methyl-1-tetralone, 3-methyl-1-tetralone, and 4-methyl-1-tetralone, the yield of corresponding naphthalenes were 37, 44, 46, and 35%, respectively, and the naphthol impurities were easily removed by extraction with alkali. The best synthesis of **7** was completed in 67% overall yield *via* the sequence [**2**, (82%), **4** (95%), **5** (94%), **6** (93%), **7** (98%)] of Scheme I. The isolation and purification of **3** was accomplished by dis-

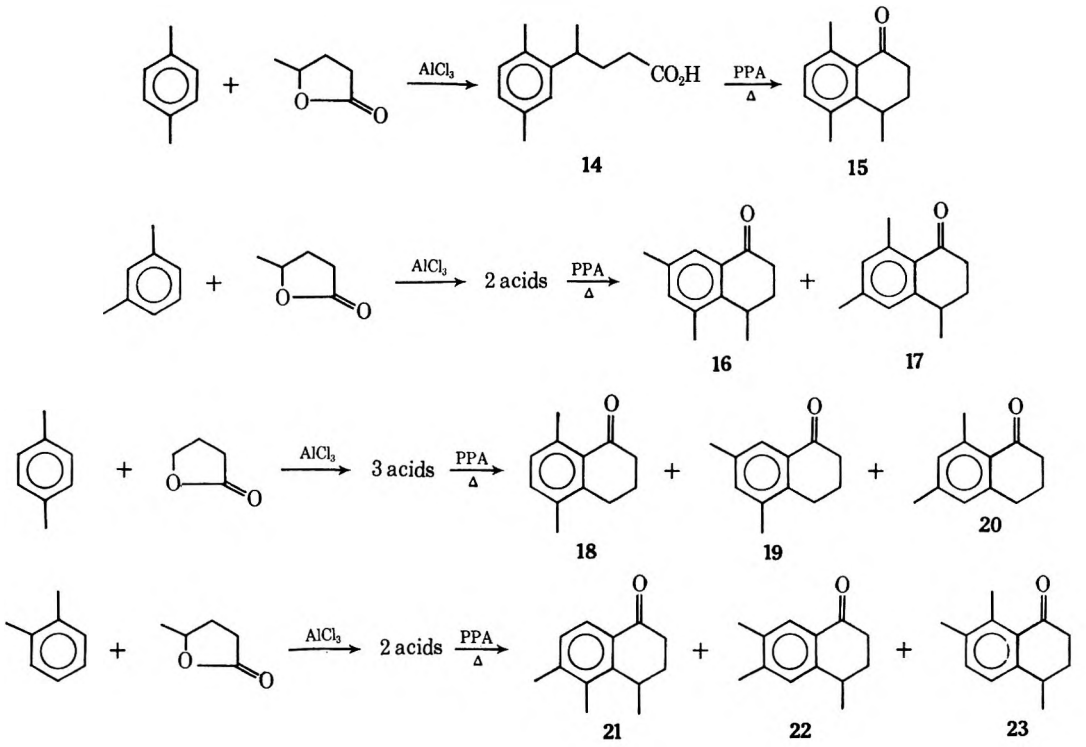
SCHEME I



(5) On standing, gases accumulate in Friedel–Crafts reaction mixtures and once the reaction mixture is disturbed, the release of these gases cause the flask to overflow.

(6) (a) E. L. Martin, *Org. React.*, **1**, 157 (1942); (b) J. W. Burnham and E. J. Eisenbraun, *J. Org. Chem.*, **36**, 737 (1971); (c) R. G. Melton, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *Org. Prep. Proc.*, **2**, 37 (1970); (d) H. R. Snyder and F. X. Werber, "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 798; (e) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **83**, 2847 (1961); (f) A. J. Lundeen and R. Van Hoozer, *ibid.*, **85**, 2180 (1963); (g) J. M. Springer, C. W. Hinman, E. J. Eisenbraun, P. W. Flanagan, M. C. Hamming, and D. E. Linder, *J. Org. Chem.*, **36**, 686 (1971).

SCHEME II



tilling and crystallizing the mother liquors obtained from crude 2.

We also required several di- and trimethyltetralones as precursors to methylated dihydronaphthalenes, tetralins, and naphthalenes not readily prepared using Scheme I. The tetralone **15** was readily obtained[7a] in pure form as shown in Scheme II. However, this procedure, when applied to *m*- and *o*-xylene using γ-valerolactone[7b] or *p*-xylene and γ-butyrolactone,[7c] gave mixtures of the intermediate acids. Since neither these acids nor their methyl esters were cleanly separable by preparative glc, we cannot be specific about their structures. They were cyclized by hot PPA to the corresponding 1-tetralones (Scheme II) and these were separated by preparative glc and identified by instrumental methods. For the 1-tetralones from *m*-xylene and γ-valerolactone, the ratio 77:23 (**16**:**17**) was determined by analytical glc and found to be the same as the ratio of peak areas for the observed methyl esters, which is evidence that rearrangement did not take place during the PPA cyclization. This is contrary to Mosby's observation[7a] that the PPA cyclization of 4-(2,4-dimethylphenyl)-pentanoic acid leads to **17**, whereas another route (acid chloride and $AlCl_3$) gave **16**. Our observations support the earlier work of Vig and Singh[7d] as well as Rao and Dev,[7e] who also cyclized this acid with PPA and obtained **16**. However, it should be noted that rearrangement as well as loss of isopropyl group has recently been reported[7f] for the PPA cyclization of γ-(5-isopropyl-4-methoxy-2-methylphenyl)butyric acid.

Since our results with the γ-butyrolactone and γ-valerolactone were variable, we studied the $AlCl_3$-catalyzed condensation of γ-valerolactone and *p*-xylene under a variety of conditions to obtain the best yield of the acid **14** as a reference point. This procedure involves dropwise addition of γ-valerolactone (1 mol) to a well-stirred mixture of *p*-xylene (2 mol) and $AlCl_3$ (1 mol) at a maximum temperature of 60°. Altering the reaction conditions by adding $AlCl_3$ last[7a] caused the yield of **14** to drop from 81 to 35%. We noted that the crude **14** regardless of method of preparation was accompanied by two acids which appear as small flanking peaks (2–5% total) on the glc trace of the methyl ester mixture of the crude acids including **14** as the major product. Cyclization of this mixture of acids with hot PPA gave mainly **15**. Glc analysis showed the presence of *ca.* 2% of **16** but **17** did not separate from **15** using SE-31 substrate.[8a,b]

Examination of the recovered *p*-xylene, from the preparation of **14**, by glc on a Bentone column[8a,b] revealed that it had been slightly isomerized to *m*-xylene (98:2). Evidently isomerization is occurring before condensation or the product acid, **14** in this case, is formed and then isomerized.

Application of the reaction conditions which gave 81% yield of **14** to γ-butyrolactone and *p*-xylene failed to give more than 23% or less of a combined yield of three acids (analyzed as methyl esters in the ratio 5:82:13 in order of emergence from an SE-31 column).[8b]

(7) (a) W. L. Mosby, *J. Amer. Chem. Soc.*, **74**, 2564 (1952); (b) W. L. Mosby, *J. Org. Chem.*, **18**, 485 (1953); (c) C. S. Kadyrov and D. Z. Lainapov, *Zh. Org. Khim.*, **2**, 1272 (1966); (d) O. P. Vig and S. Singh, *Science and Cult. (Calcutta)*, **22**, 403 (1957); *Chem. Abstr.*, **51**, 12867*d* (1957); (e) G. S. K. Rao and S. Dev, *J. Indian Chem. Soc.*, **36**, 1 (1959); (f) K. Yamada, S. Takada, Y. Hayakawa, and Y. Hirata, *Bull. Chem. Soc. Jap.*, **42**, 3011 (1969).

(8) (a) M. Van der Stricht and J. Van Rysselberge, *J. Gas Chromatogr.*, **1**, No. 8, 29 (1963). (b) A 10 ft × 0.25 in. Bentone column at 70° was used for analysis of xylene mixtures. Other glc analyses were carried out on a 11 ft × 0.25 in. 10% SE-31 on DMCS-treated acid-washed Chromosorb W column with temperatures ranging from 160 to 240°. Preparative separations were made on Carbowax 20M columns. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined on Varian HR-60 and A-60 spectrometers. Mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. Ir and uv spectra were obtained with Beckman IR-5A and Cary 14 spectrometers, respectively. Melting points are corrected. The petroleum ether used for recrystallization boiled at 60–68°. (c) Filtration through Dicalite filter aid improves the separation of layers during ether extraction.

These, in turn, were cyclized to the 1-tetralones **20**:**18**:**19** (5:84:11) in the order of emergence from the SE-31 column.[8b] In addition, the recovered *p*-xylene from the γ-butyrolactone and *p*-xylene reaction contained 7% *m*-xylene.[8a,b] Hence, isomerization is even more pronounced for the γ-butyrolactone case and merely reflects the difference in reactivity and stability of intermediate species generated from these lactones by $AlCl_3$.

The Friedel–Crafts reaction of *o*-xylene and γ-valerolactone (Scheme II) gave two acids which were cyclized to a mixture of three tetralones in the ratio 3:63:34 (**23**:**22**:**21**) in order of emergence from a Carbowax or silicone rubber column. Thus, although the Friedel–Crafts alkylation of an aromatic hydrocarbon with a γ-lactone is a shorter route than the conventional anhydride acylation, the latter, in certain cases, is the preferred procedure.

In addition to hydrocarbons **6**, **7**, **9a**, **9b**, and **13**, the described syntheses provided 1,2,3,4-tetrahydro-1,5,7-trimethylnaphthalene, 1,2,3,4-tetrahydro-1,5,8-trimethylnaphthalene, 1,2,3,4-tetrahydro-1,6,8-trimethylnaphthalene, 1,3,5-trimethylnaphthalene, 1,3,8-trimethylnaphthalene, and 1,4,5-trimethylnaphthalene. Data are given in the Experimental Section.

Experimental Section[8-10]

3-(2,5-Dimethylbenzoyl)-2-methylpropionic Acid (2).—Methylsuccinic anhydride (2109 g, 18.5 mol), *p*-xylene (2162 g, 20.4 mol), and distilled nitroethane (6 l.) were mixed and cooled to 10°. Anhydrous $AlCl_3$ (5435 g, 40.7 mol) was added slowly to the vigorously stirred reaction mixture over a period of 5 hr, at 15°. Approximately 15 min after the final addition, ice and water were drained from the cooling vessel. The reaction mixture was stirred for an additional 90 min[5] and was then poured onto approximately 50 lb of ice and stirred until the red-brown color had disappeared. Concentrated HCl (3 l.) was then added to complete the decomposition. The reaction product was extracted with ether,[8c] washed, dried ($MgSO_4$), filtered, and concentrated until crystals developed on refrigeration. The decanted liquor was further concentrated under aspirator vacuum to give additional **2**, total weight 3322 g (82%). Recrystallization from ether–petroleum ether (bp 60–68°) gave **2**: mp 118–119°; ir ($CHCl_3$) 1695 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 220 (30), 133 (100), 105 (42), 41 (31), 39 (40); nmr ($CDCl_3$) δ 11.75 (s, 1, CO_2H), 7.42 (s, 1, isolated Ar H), 7.10 (AB q, 2, vicinal Ar H), 3.50–2.78 (m, 3, side chain), 2.40 (s, 3, Ar CH_3 ortho to carbonyl), 2.32 (s, 3, Ar CH_3 meta to carbonyl), 1.18 (d, 3, CH_3); uv max (95% C_2H_5OH) 211 mμ (log ε 4.33), 245 (3.95), and 293 (3.18).[9a]

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.90; H, 7.02.

The methyl ester of **2** was prepared with CH_2N_2: mp 22–23°; ir (neat) 1680 (C=O) and 1730 cm^{-1} (ester C=O); mass spectrum (70 eV) *m/e* (rel intensity) 234 (12), 133 (100), 105 (26), 79 (11), 77 (16), 15 (19).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.80; H, 7.56.

Hydrogenolysis of 2 to 4-(2,5-Dimethylphenyl)-2-methylbutyric Acid (4).—The hydrogenolysis of 20 g of **2** at 50 psi in the presence of 0.5 g of 10% Pd/C in 55 ml of acetic acid gave 17.8 g (95%) of **4**: ir ($CHCl_3$) 1695 cm^{-1} (C=O); mp 54–55°; mass spectrum (70 eV) *m/e* (rel intensity) 206 (33), 133 (76), 132 (58), 119 (100), 74 (39), 41 (32); nmr ($CDCl_3$) δ 11.74 (s, 1, CO_2H), 6.94 (AB q, 2, vicinal Ar H), 6 92 (s, 1, isolated Ar H), 2.70–2.36 (m, 3, Ar CH_2 and >$CHCH_3$), 2.20–1.44 (m, 2, ArCH_2CH_2), 1.24 (d, 3, >$CHCH_3$); uv max (95% C_2H_5OH) 215 mμ (log ε 4.03), 268 (2.75), and 276 (2.77).[9a]

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.80; H, 8.59.

A Clemmensen reduction[6a] gave **4** in 89% yield.

The methyl ester of **4** was prepared with CH_2N_2: bp 102° (0.4 mm); ir (neat) 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 220 (16), 133 (19), 132 (21), 119 (41), 88 (100), 15 (21).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.66; H, 9.10.

PPA Cyclization of 4 to 2,5,8-Trimethyl-1-tetralone (5).—To 7248 g of well-stirred PPA[6d] at 90° was added 2126 g (10.3 mol) of solid **4**. The reaction mixture became brown colored and the temperature rose to 115–120° after about 20 min. An identical portion of PPA was added and stirring at 90–100° was continued for an additional 30 min. After cooling to 60°, the reaction mixture was poured into ice water (25 lb of ice and 20 l. of H_2O). Ether was added and the mixture was stirred to hasten decomposition of the heavy dark reaction product. The mixture was extracted with 8 l. of ether which was washed successively with 800 ml of 5% NaOH and with water and then dried ($MgSO_4$). Concentration of the ether solution afforded 1820 g (94%) of **5**: bp 95–100° (0.2 mm); mp 20° from isopropyl alcohol; ir (neat) 1675 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 188 (41), 146 (100), 118 (27), 117 (25), 115 (19); nmr (CCl_4) δ 6.95, 6.79 (AB q, 2, Ar H), 2.46 (s, 3, Ar CH_3 peri to carbonyl), 2.10 (s, 3, Ar CH_3), 2.9–1.2 (envelope, 5, Ar CH_2CH_2CH), 1.08 (d, 3, CH_3); uv max (95% C_2H_5OH) 213 mμ (log ε 4.73), 254 (4.18), and 300 (3.62).[9a]

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.89; H, 8.43.

The red 2,4-dinitrophenylhydrazone of **5** was prepared and recrystallized from 95% ethanol, mp 183–184°.

Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.70; H, 5.67; N, 15.40.

Conversion of 5 to 1,2,3,4-Tetrahydro-2,5,8-trimethylnaphthalene (6).—Hydrogenolysis of 10 g of **5** in the presence of 0.25 g of 10% Pd/C in 50 ml of acetic acid at 55 psi and 65° gave 8.6 g (93%) of **6** as a clear colorless liquid: bp 77° (0.6 mm); mp 3–6°; mass spectrum (70 eV) *m/e* (rel intensity) 174 (91), 159 (100), 132 (85), 119 (42), 115 (25); nmr (CCl_4) δ 6.72 (s, 2, Ar H), 2.59 (m, 3), 2.11 (s, 6, CH_3), 2.00–1.10 (m, 4), 1.08 (d, 3, CH_3); uv max (isooctane) 268 mμ (log ε 2.39) and 273 (2.28).[9a]

Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.68; H, 10.43.

A Clemmensen reduction[6a] of **5** gave **6** in 86% yield.

Dehydrogenation of 6 to 1,4,6-Trimethylnaphthalene (7).—Dehydrogenation of 1097 g (6.3 mol) of **6** in the presence of 12 g of 10% Pd/C for 13 hr at the reflux temperature afforded 1052 g (6.2 mol) of **7** in 98% yield as a clear colorless liquid: bp 90° (0.9 mm) [lit.[3c] 140–142° (15 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 170 (100), 169 (18), 155 (69), 153 (14), 152 (12); nmr (CCl_4) δ 7.38 and 7.52 (d, 2, Ar H), 7.10 and 6.88 (m, 3, Ar H), 2.40 (s, 6, CH_3), 2.32 (s, 3, CH_3); picrate mp 134–135° (lit.[3c] 133°).

3-(2,5-Dimethylbenzoyl)butyric Acid (3).—Distillation and crystallization of the mother liquor remaining from the isolation of **2** afforded **3** as colorless crystals from petroleum ether:[8b] mp 81–82°; mass spectrum (70 eV) *m/e* (rel intensity) 220 (33), 157 (89), 133 (100), 105 (47), 41 (40), 39 (61); nmr ($CDCl_3$) δ 11.40 (s, 1, CO_2H), 7.38 (s, 1, isolated Ar H), 7.08 (AB q, 2, vicinal Ar H), 3.68 (m, 1, >$CHCH_3$), 3.05–2.28 (octet, 2, CH_2CO_2H), 2.32 (two s, 6, two Ar CH_3), 1.11 (d, 3, $CHCH_3$); uv max (95% C_2H_5OH) 211 mμ (log ε 4.34), 245 (3.92), and 290 (3.16).[9a]

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.60; H, 7.56.

The methyl ester of **3** was prepared using CH_2N_2: mp 62–63°; ir (neat) 1680 (C=O) and 1725 cm^{-1} (ester C=O); mass spectrum (70 eV) *m/e* (rel intensity) 234 (8), 133 (100), 105 (24), 79 (10), 77 (13), 39 (8).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.90; H, 7.70.

Hydrogenolysis of 3 to 4-(2,5-Dimethylphenyl)-3-methylbutyric Acid (10).—The γ-oxo acid **3** was hydrogenolyzed as described for **2** and then recrystallized from petroleum ether[8b] to give **10**: mp 68–68.5°; mass spectrum (70 eV) *m/e* (rel intensity) 206 (17), 146 (32), 119 (100), 69 (35), 41 (19); nmr ($CDCl_3$) δ 11.69 (s, 1, CO_2H), 6.98, 6.88 (AB q, 2, vicinal Ar H), 6.90 (s, 1, isolated Ar H), 2.76–2.04 [m, 5, $ArCH_2CH(CH_3)CH_2$], 3.26 and

(9) We thank the following chemists of Continental Oil Co. for their generous assistance: (a) Dr. F. M. Evens; (b) A. B. Carel; (c) Dr. D. E. Linder; and (d) E. Sones.

(10) We thank the following chemists of Oklahoma State University for their generous assistance: (a) Dr. B. C. Gandhi and (b) H. R. Harrison.

3.24 (two s, 6, two Ar CH_3), 0.97 (d, 3, $CHCH_3$); uv max (95% C_2H_5OH) 215 mμ (log ε 4.05), 268 (2.78), and 277 (2.82).[9a]

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.77; H, 8.70.

The methyl ester of **10** was prepared with CH_2N_2: bp 110° (0.3 mm); ir (neat) 1725 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 220 (25), 146 (88), 133 (14), 119 (100), 91 (15), 15 (28).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.46; H, 9.09.

Cyclization of 10 with hot PPA[6d] gave a 91% yield of 3,5,8-trimethyl-1-tetralone (11): mp 71–72° from petroleum ether;[8b] mass spectrum (70 eV) *m/e* (rel intensity) 188 (65), 173 (25), 146 (100), 118 (31), 117 (27); nmr (CCl_4) δ 7.01, 6.81 (AB q, 2, Ar H), 2.49 (s, 3, Ar CH_3 peri to carbonyl), 2.17 (s, 3, Ar CH_3), 3.1–1.7 (envelope, 5, $ArCH_2CHCH_3$), 1.07 (d, 3, CH_3); uv max (95% C_2H_5OH) 213 mμ (log ε 4.67), 254 (4.08), and 306 (3.42).[9a]

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.90; H, 8.65.

The red 2,4-DNP of **11** was prepared and recrystallized from 95% ethanol, mp 249–250°.

Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47. Found: C, 62.13; H, 5.37.

Hydrogenolysis of **11** in the presence of Pd/C catalyst at 50 psi in acetic acid gave **6**.

Reduction of 5 and 11 to the 2,5,8- and 3,5,8-Trimethyl-1-tetralols (8 and 12).—The reduction of 376 g (2 mol) of **5** in dry ether with 30 g (0.8 mol) of $LiAlH_4$ afforded 361 g (1.9 mol) of **8** as a clear, colorless liquid [bp 95° (0.35 mm)] which crystallized as a mixture of cis and trans isomers, mp 79–81°, from petroleum ether in 95% yield: mass spectrum (70 eV) *m/e* (rel intensity) 172 (91), 157 (100), 143 (22), 142 (37), 141 (25); the nmr spectrum in CCl_4 confirmed the structures.

A similar reduction of 1 mol of **11** using 15 g of $LiAlH_4$ in dry ether afforded 182 g of **12** in 96% yield: mp 76–77°, from petroleum ether;[8b] mass spectrum (70 eV) *m/e* (rel intensity) 172 (45), 157 (100), 143 (14), 142 (38), 141 (23); nmr (CCl_4) δ 6.72 (AB q, 2, vicinal Ar H), 4.51 (t, 1, ArCHOH), 2.90 (s, 1, >CHOH), 2.24 (s, 3, Ar CH_3), 2.09 (s, 3, Ar CH_3 peri to hydroxyl) 2.8–1.1 [envelope, 5, $ArCH_2C(CH_3)HCH_2$], 1.02 (d, 3, $>CHCH_3$); uv max (95% C_2H_5OH) 217 mμ (log ε 4.03), 2.70 (2.77), and 279 (2.75).[9a]

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.38; H, 9.61.

Our recent experience in the reduction of 1-tetralones has shown that diisobutylaluminum hydride (dibal H)[11] is superior to $LiAlH_4$ for this series. The latter gave incomplete reduction of **5** and **11**, presumably due to enolization.

Dehydration of 8 and 12 to 1,2-Dihydro-3,5,8-trimethyl- and 1,4-Dihydro-2,5,8-trimethylnaphthalene and 1,2-Dihydro-2,5,8-trimethylnaphthalene (9a, 9b, and 13).—1,2,3,4-Tetrahydro-2,5,8-trimethyl-1-naphthol (**8**) (20 g, 0.105 mol) was dissolved in 100 ml of cyclohexane and passed through a preheated column (30 mm × 38 cm) containing 33 cm of Harshaw alumina (Al-0104, 1/8 in., B901). The temperature of the column was maintained between 250 and 270°.[6e] The alcohol **8**, which vaporized on contact with the alumina, was swept through the column with a gentle flow of N_2 gas. The solution of **8** was metered onto the column by means of a bellows pump over a period of 2 hr. A second 100-ml portion of cyclohexane was passed through the system as a rinse. The collected solution was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), filtered, concentrated, and distilled to give 14.8 g (75%) of a hydrocarbon mixture, bp 81–93° (0.7 mm). A sample of the product was analyzed by glc on a Carbowax column (0.25 in. × 10 ft, acid-washed Chromosorb W, 80–100 mesh) at 200° and found to contain four components, **9a**, **13**, **9b**, and **7**, in the ratio 81:5:5:8 and in the order of emergence from the glc column. Preparative glc[9b] on a 10 ft × 4 in. diameter column of 20% Carbowax on 60–80 mesh Chromosorb W was used to purify **9a**: bp 66° (0.2 mm); mass spectrum (70 eV) *m/e* (rel intensity) 172 (84), 157 (100), 143 (21), 142 (38), 141 (26); nmr (CCl_4) δ 6.68 (s, 2, Ar H), 6.30 (m, 1, Ar CH=C<), 2.80–2.50 (m, 2, Ar CH_2), 2.40–2.00 (m, 2, allylic CH_2), 1.92 (s, 3, allylic CH_3), 2.16, 2.20 (two s, 6, two Ar CH_3).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: 90.71; H, 9.29.

A similar dehydration of **12** gave **9a** and **13** in about equal amounts. A pure sample of **13** was obtained by fractional distillation and showed bp 75° (0.7 mm); mass spectrum (70 eV) *m/e* (rel intensity) 172 (43), 157 (100), 155 (23), 142 (41), 141 (27); nmr (CCl_4) δ 6.75 (s, 2, Ar H), 6.55 (m, 1, Ar CH=), 5.79 (m, 1, ArCH=CH), 3.4–2.2 [envelope, 3, $ArCH(CH_3)CH_2$], 2.21 (s, 6, Ar CH_3), 1.04 (d, 3, $ArCHCH_3$).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.38; H, 9.47.

1,4-Dihydro-2,5,8-trimethylnaphthalene (**9b**) was obtained as a minor component and was purified by crystallization from methanol: bp 96–100° (1.8 mm); mp 38–40°; mass spectrum (70 eV) *m/e* (rel intensity) 172 (54), 157 (100), 155 (22), 144 (25), 142 (40); nmr (CCl_4) δ 6.74 (s, 2, Ar H), 5.49 (m, 1, vinylic), 3.3–2.9 (envelope, 4, Ar CH_2), 2.12 (s, 6, Ar CH_3), 1.76 (m, 3, allylic CH_3).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.71; H, 9.29.

Friedel–Crafts Reaction of γ-Butyrolactone or γ-Valerolactone with *p*-Xylene.—γ-Valerolactone (1 mol, 100 g) was added dropwise to a well-stirred mixture of 2 mol (212 g) of *p*-xylene and 1 mol (140 g) of $AlCl_3$ cooled initially to 10° in an ice bath. The temperature of the reaction mixture was allowed to rise to 60° during addition of the lactone. After addition (10–15 min) was complete, the reaction mixture was stirred 30 min and then poured onto ice. Concentrated hydrochloric acid (100 ml) was added and the mixture was extracted with ether (two 500-ml portions), washed with water, and then extracted with two 500-ml portions of 10% NaOH solution. The ether layer was dried ($MgSO_4$) and distilled at 1 atm to yield 100 g of mainly *p*-xylene. Glc analysis using the Bentone column[8a,b] showed about 2% *m*-xylene to be present.

The alkaline extract was acidified with 200 ml of concentrated hydrochloric acid and then extracted with ether (two 250-ml portions). From this extract was obtained 190 g (92%) of crude **14**. Glc analysis of crude **14**, using the SE-31 column,[8b] of the methyl esters prepared with diazomethane showed 2–5% of two ester impurities as flanking peaks. These impurities were no longer present after recrystallization of **14** from petroleum ether[8b] which gave 166 g (81%) of pure **14**: mp 111–112° (lit.[7a] mp 109–111°). The methyl ester was prepared with CH_2N_2: bp 95° (0.2 mm); ir (neat) 1740 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 220 (20), 146 (24), 145 (10), 133 (100), 91 (11), 15 (22).[10]

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.62; H, 8.89.

A purified sample of **14**, mp 111–112°, was cyclized with hot PPA[6d] to the 1-tetralone **15**: bp 90° (0.5 mm) [lit.[3c] 138° (12 mm)]; ir (neat) 1681 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 188 (100), 173 (75), 160 (89), 117 (41), 115 (35); nmr (CCl_4) δ 7.01, 6.83 (AB q, 2, Ar H), 2.49 (s, 3, Ar CH_3 peri to carbonyl), 2.23 (s, 3, Ar CH_3), 3.5–1.7 [envelope, 5, $ArCH(CH_3)CH_2CH_2$], 1.17 (d, 3, CH_3).

An equivalent run using γ-butyrolactone gave 160 g of recovered *p*-xylene shown to contain 7% *m*-xylene. The acidic fraction, shown by glc of methyl esters to be a mixture of three acids (5:82:13 in order of emergence from the SE-31 column),[8b] weighed 44 g (23%).

A procedure similar to that of Mosby[7a] was used in the preparation of arylbutyric acids obtained from the reactions of *o*-xylene and *m*-xylene with γ-valerolactone. The acids or acid mixtures were then cyclized in high yield with PPA[6d] to the 1-tetralones **16**, **17**, **18**, **19**, **20**, **21**, **22**, and **23**. These 1-tetralones were isolated by preparative glc on a Carbowax column.[9c,d]

16:[12a] bp 180° (1 mm) [lit.[12a] bp 174–176° (20 mm)]; ir (neat) 1678 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 188 (49), 173 (100), 145 (28), 117 (17), 115 (21); nmr (CCl_4) δ 7.56 (s, 1, Ar H peri to carbonyl), 7.02 (s, 1, Ar H), 3.11 [m, 1, $ArCH(CH_3)$], 2.8–1.5 (m, 4, $ArCOCH_2CH_2$), 2.24, 2.19 (two s, 6, Ar CH_3), 1.21 (d, 3, CH_3).

17: bp 120° (1 mm); ir (neat) 1672 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 188 (93), 173 (29), 160 (100), 117 (33), 115 (32); nmr (CCl_4) δ 6.81 (d, 2, Ar H), 2.50 (s, 3, Ar CH_3 peri to carbonyl), 2.26 (s, 3, Ar CH_3), 2.9–1.4 [m, 5, $ArCOCH_2CH_2CH(CH_3)$], 1.29 (d, 3, CH_3).

(11) L. F. Fieser and Mary Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 260.

(12) (a) I. M. Heilbron and D. G. Wilkinson, *J. Chem. Soc.*, 2537 (1930); (b) E. de Barry Barnett and F. G. Sanders, *ibid.*, 434 (1933); (c) W. P. Campbell and M. D. Soffer, *J. Amer. Chem. Soc.*, **64**, 417 (1942); (d) K. M. Baker, K. H. Bell, and B. R. Davis, *Aust. J. Chem.*, **21**, 2945 (1968).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.84; H, 8.59.

18:[12b] bp 98° (0.2 mm); mp 31.5–33.5°, from petroleum ether[8b] (lit.[12b] mp 33°); ir (neat) 1678 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 174 (66), 146 (100), 118 (31), 117 (28), 115 (23); nmr (CCl_4) δ 7.03, 6.84, (AB, q, 2, Ar H), 2.59 (t, 2, Ar CH_2), 2.38 (s, 3, Ar CH_3 peri to carbonyl), 2.08 (s, 3, Ar CH_3), 2.4–1.6 (m, 4, $ArCOCH_2CH_2$).

19:[3c,12b] bp 86–90° (0.2 mm); mp 49–51°, from petroleum ether[8b] (lit.[12b] mp 50°); mass spectrum (70 eV) *m/e* (rel intensity) 174 (85), 146 (100), 118 (71), 117 (30), 115 (28); nmr (CCl_4) δ 7.56 (s, 1, Ar H peri to carbonyl), 7.04 (s, 1, Ar H), 2.73 (t, 2, Ar CH_2), 2.27–2.22 (two s, 6, Ar CH_3), 2.6–1.9 (m, 4, $ArCOCH_2CH_2$). The red 2,4-dinitrophenylhydrazone was recrystallized from 95% ethanol: mp 272° with darkening at 230° (lit.[7b] mp 268.8–269.4° or at 272–273° with preheated bath).

20: bp 105° (0.6 mm); mass spectrum (70 eV) *m/e* (rel intensity) 174 (46), 146 (100), 100 (19), 117 (18), 115 (15); nmr (CCl_4) δ 6.77 (s, 2, Ar H), 2.82 (t, 2, Ar CH_2), 2.52 (s, 3, Ar CH_3 peri to carbonyl), 2.25 (s, 3, Ar CH_3), 2.6–1.8 (m, 4, $ArCOCH_2CH_2$).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.60; H, 7.83.

21: bp 122 (0.4 mm); mass spectrum (70 eV) *m/e* (rel intensity) 188 (62), 173 (100), 160 (37), 145 (32), 117 (28), 115 (27); nmr (CCl_4) δ 7.70, 7.00 (AB q, 2, Ar H), 3.28 [m, 1, $ArCH(CH_3)$], 2.30, 2.24 (two s, 6, Ar CH_3), 2.9–1.8 (m, 4, $ArCOCH_2CH_2$), 1.29 (d, 3, CH_3).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.93; H, 8.70.

22:[12c] bp 112° (0.5 mm) [lit.[12c] bp 111.5° (0.4 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 188 (84), 173 (100), 160 (57), 146 (51), 132 (45), 117 (38); nmr (CCl_4) δ 7.66 (s, 1, Ar H peri to carbonyl), 6.96 (s, 1, Ar H), 2.96 [m, 1, $ArCH(CH_3)$], 2.28 (s, 6, Ar CH_3), 2.8–1.6 (m, 4, $ArCOCH_2CH_2$), 1.36 (d, 3, CH_3).

23: bp 115° (0.5 mm); mass spectrum (70 eV) *m/e* (rel intensity) 188 (93), 173 (57), 160 (100), 132 (47), 117 (44), 115 (38); nmr (CCl_4) δ 7.11–6.88 (AB q, 2, Ar H), 2.45 (s, 3, Ar CH_3 peri to carbonyl), 2.27 (s, 3, Ar CH_3), 3.1–1.5 [m, 5, $ArCOCH_2CH_2CH(CH_3)$], 1.32 (d, 3, CH_3).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.83; H, 8.73.

Glc analyses of reaction mixtures showed the following ratios of products in the order of emergence from a Carbowax 20M[8b] column: 23:77 (17:16), 14:75:11 (20:18:19), 3:63:34 (23:22:21).

Catalytic hydrogenation of **15**, **16**, and **17** as used in the preparation of **6** gave:

1,2,3,4-Tetrahydro-1,5,7-trimethylnaphthalene from **17**: bp 57–59° (0.1 mm) [lit.[12d] 87° (0.5 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 174 (34), 160 (13), 159 (100), 146 (13), 132 (13); nmr (CCl_4) δ 6.67 (d, 2, Ar H), 2.98–2.27 (m, 3, Ar CH_2 and Ar CH<), 2.18 (s, 3, CH_3), 2.07 (s, 3, CH_3), 1.97–1.30 (m, 4, CH_2), 1.22 (d, 3, CH_3).

1,2,3,4-Tetrahydro-1,5,8-trimethylnaphthalene from **15**: bp 89° (0.5 mm) [lit.[12d] 88° (1.0 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 174 (22), 160 (13), 159 (100), 129 (10), 128 (10); nmr (CCl_4) δ 6.70 (s, 2, Ar H), 2.98 (m, 1, Ar CH<), 2.53 (m, 2, Ar CH_2), 2.19 (s, 3, CH_3), 2.06 (s, 3, CH_3), 1.73 (m, 4, CH_2), 1.12 (d, 3, CH_3).

1,2,3,4-Tetrahydro-1,6,8-trimethylnaphthalene from **16**: bp 65° (0.3 mm) [lit.[12a] 133–136° (18.5 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 174 (18), 160 (13), 159 (100), 129 (9), 128 (9); nmr (CCl_4) δ 6.60 (s, 2, Ar H), 2.96 (m, 1, tertiary and Ar CH<), 2.67 (m, 2, Ar CH_2), 2.18 (s, 3, CH_3), 2.15 (s, 3, CH_3), 1.71 (m, 4), 1.09 (d, 3, CH_3).

The following trimethylnaphthalenes were prepared by Pd/C dehydrogenation of tetralins in a manner analogous to the preparation of **7**.

1,3,5-Trimethylnaphthalene from **1,2,3,4-Tetrahydro-1,5,7-trimethylnaphthalene**.—Recrystallization from methanol gave mp 43–45° (lit.[12a] mp 47°); mass spectrum (70 eV) *m/e* (rel intensity) 171 (14), 170 (100), 169 (17), 155 (64), 153 (15); nmr (CCl_4) δ 7.82–7.42 (m, 2, Ar H), 7.23–6.93 (m, 3, Ar H), 2.57 (s, 6, CH_3), 2.42 (s, 3, CH_3).

1,3,8-Trimethylnaphthalene from **1,2,3,4-Tetrahydro-1,6,8-trimethylnaphthalene**.—Recrystallization from methanol gave mp 48–50° (lit.[12a] mp 48°); mass spectrum (70 eV) *m/e* (rel intensity) 170 (84), 155 (57), 153 (14), 32 (22), 28 (100); nmr (CCl_4) δ 7.50–6.93 (m, 5, Ar H), 2.79 (s, 6, CH_3), 2.34 (s, 3, CH_3).

1,4,5-Trimethylnaphthalene from **1,2,3,4-Tetrahydro-1,5,8-trimethylnaphthalene**.—Recrystallization from methanol gave mp 62.5° (lit.[3c] 63°, lit.[7a] 59.6–60.6°); mass spectrum (70 eV) *m/e* (rel intensity) 170 (100), 169 (15), 155 (77), 153 (19), 152 (17); nmr (CCl_4) δ 7.69–6.91 (m, 5, Ar H), 2.73 (s, 3, CH_3), 2.70 (s, 3, CH_3), 2.48 (s, 3, CH_3).

Registry No. –2, 16206-40-9; 2 methyl ester, 30316-11-1; **3**, 16206-39-6; **3** methyl ester, 30316-13-3; **4**, 30316-14-4; **4** methyl ester, 30316-15-5; **5**, 10468-59-4; **5** 2,4-DNP, 30316-40-6; **6**, 30316-17-7; **7**, 2131-42-2; *cis*-**8**, 30318-93-5; *trans*-**8**, 30318-94-6; **9a**, 30316-18-8; **9b**, 30316-19-9; **10**, 30275-76-4; **10** methyl ester, 30316-20-2; **11**, 10468-60-7; **11** 2,4-DNP, 30316-08-6; **12**, 30316-22-4; **13**, 30316-23-5; **14**, 28591-11-9; **14** methyl ester, 30316-09-7; **15**, 10468-61-8; **16**, 27410-97-5; **17**, 27410-98-6; **18**, 5037-63-8; **19**, 13621-25-5; **20**, 30316-30-4; **21**, 30316-31-5; **22**, 30316-32-6; **23**, 30316-33-7; 1,2,3,4-tetrahydro-1,5,7-trimethylnaphthalene, 21693-55-0; 1,2,3,4-tetrahydro-1,5,8-trimethylnaphthalene, 21693-51-6; 1,2,3,4-tetrahydro-1,6,8-trimethylnaphthalene, 30316-36-0; 1,3,5-trimethylnaphthalene, 2131-39-7; 1,3,8-tirmethylnaphthalene ,17057-91-9; 1,4,5-trimethylnaphthalene, 2131-41-1.

Acknowledgments.—We thank the American Petroleum Institute for partial support of this work through API Research Project 58A and the Research Foundation of Oklahoma State University for their assistance. Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a fellowship to J. M. Springer. We thank Dr. O. C. Dermer for having read the manuscript.

Chemistry of Dithienyl Diketones. I. Synthetic Explorations

ROBERT D. SCHUETZ* AND GEORGE P. NILLES[1]

Department of Chemistry and The Institute of Biology and Medicine, Michigan State University, East Lansing, Michigan 48823

Received February 9, 1971

A series of dithienyl diketones (thenils) have been prepared by four routes: *via* the thenoin condensation followed by oxidation; by the reaction of thienyllithiums with dimethyl oxalate; by oxalylation of alkoxythiophenes; and by oxidation of the thenoins resulting from the reaction of thienyl Grignards with thienylglyoxals. All except the alkoxythenils **11**, **12**, and 3,3′-benzo[*b*]thenil (**3**) give the unstable thenilic acids upon treatment with hydroxide.

Dithienyl diketones, or thenils,[2] the thiophene analogs of benzils, have been scarcely investigated. Indeed, of the simple thenils, only 2,2′-thenil[3] (**1**), 3,3′-thenil[4] (**2**), and 3,3′-benzo[*b*]thenil[5] (**3**) have been reported. We were first attracted to this area by our efforts toward the synthesis of some dithienyl isosteres of JB 336, a pharmaceutical with demonstrated antispasmodic and psychotomimetic properties.[6,7] The thenilic acids needed to prepare those amino esters were to be prepared by the base-induced rearrangement of the thenils. Since we wished to have at hand many different substituted thenilic acids, this gave us an excellent opportunity to explore the rather neglected thenilic acid rearrangement on both a qualitative and a quantitative basis. By analogy, a study of this type would have much meaning in terms of the benzilic acid rearrangement as well.[8]

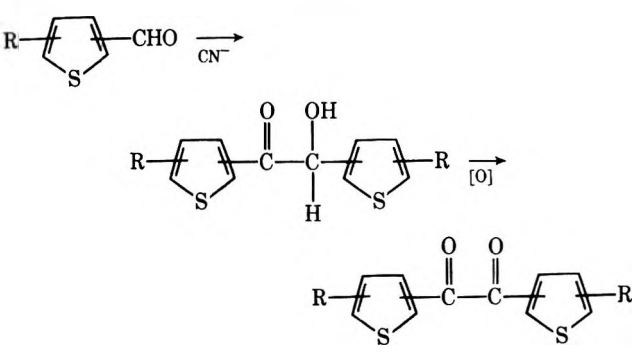
The most obvious means of preparing the thenils was by oxidation of the thenoins and here we could investigate the benzoin condensation of thienyl aldehydes, at least on a qualitative basis.

Discussion

All of the aldehydes needed in Scheme I for the thenil syntheses have been previously described.[9] They were formed either by Wilsmeier–Haack formylation of the appropriate substituted thiophene or by reaction of thienyllithiums with dimethylformamide.

There appears to be no simple method of predicting which aldehydes will undergo the benzoin or mixed benzoin condensation.[10] Present studies involving the thiophene aldehydes certainly supported this contention as well. Of the compounds listed in Table I, only **1**–**6** were accessible by Scheme I in which the intermediate thenoin was isolated. Thenils **7** and **8** were obtained by direct oxidation of the thenoin condensation reaction mixture with cupric sulfate and pyridine.

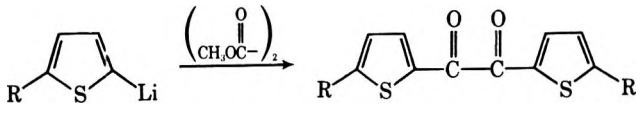
SCHEME I



The remaining aldehydes gave only recovered starting material or intractable tars upon treatment with cyanide and subsequent oxidation.

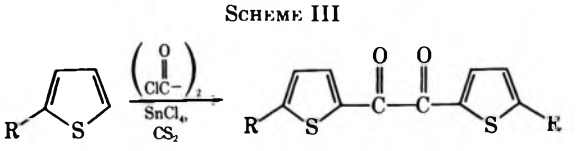
Nyberg[11] has shown that 2- and 3-thienyllithium give the corresponding thenils upon reaction with dimethyl oxalate. Thenils **9** and **10** were synthesized in this manner, thus extending the generality of this procedure (Scheme II).

SCHEME II



Advantage was taken of the strong electron-donating properties of the alkoxy group to obtain thenils **11** and **12** by the reaction of 2-methoxy and 2-isopropoxythiophene with oxalyl chloride. The yield of **12** was especially low since this compound probably suffers protolytic degradation to give the very unstable hydroxythienyl compound during the acylation (Scheme III).

SCHEME III



The H_3–H_4 coupling constant in **11** was 4.4 Hz and this falls outside the range reported for 3–4 coupling constants in thiophenes.[12] However, degradation of the thenil with ammonium cyanide followed by basic hydrolysis and acidification gave only 5-methoxy-2-thenoic acid, thereby confirming 2,5 substitution.

Thenil **13** was obtained by oxidation of the thenoin formed by the reaction of 5-methyl-2-thienylmag-

(1) Abstracted, in part, from the Ph.D. dissertation of G. P. N.

(2) The name thenil for dithienyl diketone is a logical extension of IUPAC rule C 313.4. The name has been used previously for such compounds.[3,4]

(3) S. Z. Cardon and H. P. Lankelma, *J. Amer. Chem. Soc.*, **70**, 4248 (1948).

(4) E. Campaigne and R. C. Bourgeois, *ibid.*, **75**, 2702 (1953).

(5) E. Campaigne and E. S. Neiss, *J. Heterocycl. Chem.*, **3**, 46 (1966).

(6) J. H. Biel, L. G. Abood, W. K. Hoya, H. A. Lesser, and E. P. Kluchesky, *J. Org. Chem.*, **26**, 4096 (1961).

(7) G. P. Nilles and R. D. Schuetz, *J. Med. Chem.*, **13**, 1249 (1970).

(8) G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, **36**, 2489 (1971).

(9) (a) H. D. Hartough, "Thiophene and Its Derivatives," Interscience, New York, N. Y., 1952, Chapter 11; (b) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience, New York, N. Y., 1954, p 109; (c) A. R. Dodson, Ph.D. Thesis, Michigan State University, East Lansing, Mich., 1961; (d) J. Sice, *J. Amer. Chem. Soc.*, **75**, 3697 (1953); (e) W. Hoek, H. Wynberg, and J. Strating, *Recl. Trav. Chem. Pays-Bas*, **85**, 1054 (1966); (f) R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2188 (1971).

(10) W. S. Ide and J. S. Buck, *Org. React.*, **4**, 269 (1948).

(11) K. Nyberg, *Acta Chem. Scand.*, **23**, 1087 (1969).

(12) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 8 (1963).

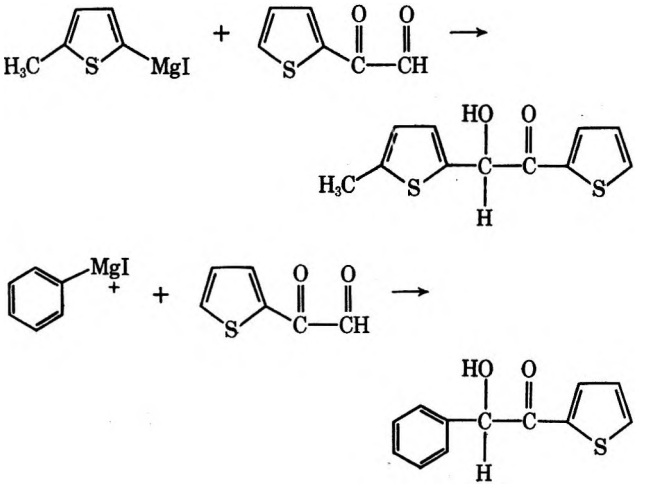
TABLE I
THENILS SYNTHESIZED

Thenil	R_1	R_2[a]	Scheme	% yield[a]	λ_{max} (log ϵ)[b]
1	H	H	I	23	310 (4.236)
2	3,3′-Thenil		I	36	273 (4.261)
3	3,3′-Benzo[*b*]thenil		I	14	316 (4.459)
4	2,2′-Benzo[*b*]thenil		I	83	336 (4.723)
5	2-Thienyl	2-Thienyl	I	64	397 (4.775)
6	2-Thienylphenyl diketone		IV	21	290 (4.014)
7	Cl	Cl	I	41	335 (4.278)
8	CH_3	CH_3	I	30	324 (4.282)
9	F	F	II	34	314 (4.482)
10	1-Adamantyl	1-Adamantyl	II	22	324 (4.577)
11	CH_3O	CH_3O	III	33	350 (4.335)
12	$(CH_3)_2CHO$	$(CH_3)_2CHO$	III	17	354 (4.631)
13	CH_3	H	IV	28	317 (4.236)

[a] Based on the starting material as illustrated in each scheme. [b] Of the principle band responsible for the color of the compound.

nesium iodide with 2-thienylglyoxal (Scheme IV). To our knowledge this is the first report of the reaction of a

SCHEME IV

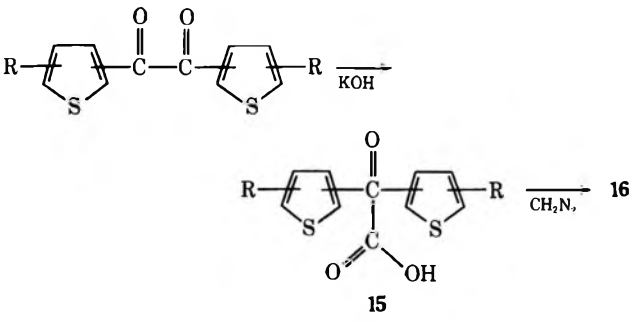


Grignard reagent with an arylglyoxal. While the yields are low, the method should be quite general for the synthesis of symmetrical and unsymmetrical benzoins. In a similar manner, the reaction of phenylmagnesium iodide with 2-thienylglyoxal gave 2-thenoylphenylcarbinol (**14**) which was identical with the compound obtained by cocondensation of benzaldehyde and 2-thenaldehyde. This synthesis serves to confirm the structure originally proposed for this compound.[13]

All of the new thenils were characterized by their satisfactory elemental analyses (see Table II), their low energy carbonyl absorptions $\nu_{C=O} = 1630 \pm 30$ cm^{-1}, visually by their yellow to rust orange color, and by their facile conversion, for the most part, to the corresponding thenilic acid **15** upon treatment with hydroxide.

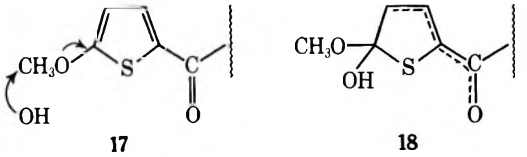
The thenilic acids seem to be stable only in solution or in the solid state below −20°. They were all characterized by conversion to their methyl esters **16** upon treatment with diazomethane. The esters are stable indefinitely. The thenilic acids were the only products discovered upon base-induced rearrangement of the thenils, with three exceptions.

(13) J. H. Biel, E. P. Sprengler, H. L. Leiser, J. Horner, A. Drukker, and H. L. Friedman, *J. Amer. Chem. Soc.*, **77**, 2250 (1955).



Treatment of the methoxythenil **11** with hydroxide failed to yield the corresponding methoxythenilic acid, or its methyl ester after treatment of the rearrangement reaction mixture with diazomethane. In addition, the rate of disappearance of hydroxide was much greater than that predicted on the basis of the substituent effect. Indeed, the rate was greater than for the unsubstituted thenil.[8]

We postulate that either SN2 attack of the hydroxide on either or both of the methoxy carbons occurs, **17**, or direct attack by the hydroxide on the thiophene ring, possibly *via* a Meisenheimer type complex as in **18**, leads to a hydroxythiophene. The hydroxythiophenes are well noted for their instability[14] which could explain our failure to obtain the expected product.



Although insufficient amounts of the isopropoxythenil **12** prevented us from carrying out any synthetic investigations, the kinetics of the rearrangement indicate[8] the same type of behavior as for **11**. The decrease in the rate of disappearance of hydroxide for **12** *vs.* **11** tends to support, by steric arguments, the explanation for the anomolous behavior of the alkoxythenils.

The reaction of **3** with hydroxide yielded methyl 3-thianaphthoate[15] after the usual work-up rather than

(14) C. Frisell and S. O. Lawesson, *Org. Syn.*, **43**, 55 (1963).

(15) Identified on the basis of its mass spectrum. Peaks were found at *m/e* 192 (parent 35%), 161 (P − 31, loss of CH_3O–, 65%) and *m/e* 133 (loss of CO from *m/e* 161, 17%).

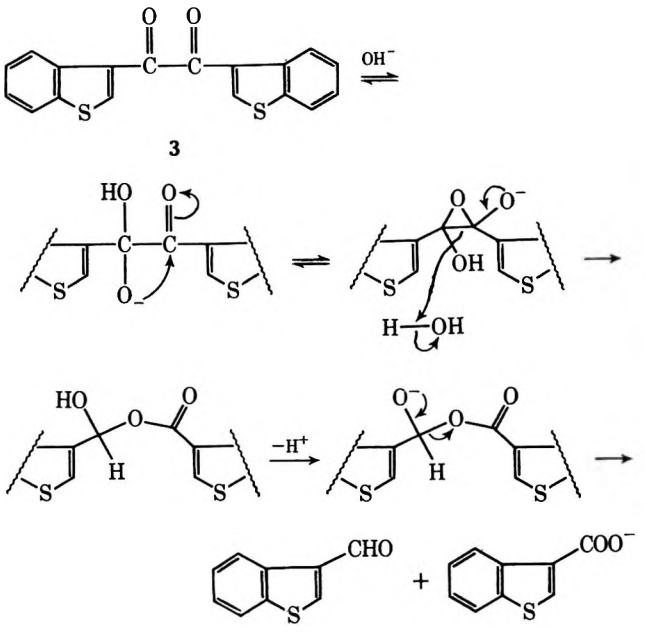
TABLE II

ELEMENTAL ANALYSIS FOR NEW COMPOUNDS

Thenil	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found	Thenilic ester from thenil	Registry no.	% yield[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found
4	239–240	67.06	67.08	3.12	3.08	19.89	19.96	1	26447-85-8	69	93	51.95	51.86	3.96	3.80	25.22	25.02
5	177–179	55.93	55.80	2.61	2.83	33.18	33.04	2	28540-31-0	70	80–81	51.95	52.06	3.96	3.97	25.22	25.18
7	121–122	41.25	41.36	1.38	1.49	22.02	22.00	4	30202-68-7	62	103–104	64.38	64.15	3.98	3.95	18.09	17.98
8	86–87	57.57	57.44	4.03	4.01	25.62	25.60	5	30135-39-8	94	112–113	54.52	54.62	3.37	3.37	30.64	30.70
9	125–127	46.50	46.70	1.56	1.65	24.83	24.62	7	30202-67-6	92	Liquid	40.87	41.05	2.49	2.63	19.84	19.47
10	260–261	73.42	73.17	6.98	6.83	13.07	12.91	8	30135-41-2	80	57–58	55.29	55.60	5.00	4.95	22.71	21.47
11	140–142	51.05	51.08	3.57	3.56	22.72	22.79	9	30135-42-3	78	55–57	45.51	45.74	2.78	2.63	22.09	22.18
12	98–99	56.78	56.80	5.36	5.49	18.95	19.07	13	30226-74-5	56	95–96	53.91	53.71	4.15	4.22	23.99	24.10
13	44–45	55.91	55.74	3.41	3.41	27.14	26.97										

[a] Based on the thenil.

the expected thenilic acid ester. The cleavage of benzils, rather than the rearrangement, has been noted before only in the presence of alcohols.[16] We propose a mechanism to account for this behavior which is analogous to the one by Kwart[17] for the cyanide-catalyzed cleavage of benzils. The intermediate



aldehyde could be converted to 3-thianaphthoic acid and 3-hydroxymethyl thianaphthene by the Cannizzaro reaction.

Experimental Section[18,19]

Thenils 1–6 *via* Scheme I.—Thenils **1**, **2**, and **3** were prepared as described, ref 3–5, respectively. Thenils **4** and **5** were prepared as follows. A 0.100-mol quantity of the appropriate thiophene aldehyde and 3.25 g (0.050 mol) of potassium cyanide in 100 ml of 90% ethanol was refluxed for 30 min. The solution was cooled and neutralized with acetic acid, and 500 ml of water was gradually added. The precipitated thenoin was collected, air-dried, and dissolved in 100 ml of 80% aqueous acetic acid and 8.0 g (0.10 mol) of ammonium nitrate and 0.1 g of cupric acetate was added. After refluxing for 1 hr, the solution was cooled and the thenil crystallized and was collected. Purification was effected by sublimation at 120° (0.1 Torr).

Thenils 7 and 8 *via* Scheme II.—A solution of 14.7 g (0.100 mol) of 5-chloro-2-thenaldehyde and 2.5 g (0.051 mol) of sodium cyanide in 100 ml of dry THF containing 2% (v/v) of dimethyl sulfoxide was stirred under N_2 in a sealed flask for 30 hr. After neutralization with 2.4 ml of acetic acid, 25 g (0.10 mol) of cupric sulfate pentahydrate was added along with 100 ml of dry pyridine. This mixture was stirred 3 hr at room temperature and quenched in 750 ml of water. After standing 12 hr at 0°, the precipitate was collected, washed with water, air-dried, and continuously extracted with 30–50° petroleum ether until the yellow color was exhausted. The solvent was removed and the thenil was collected. Thenil **8** was prepared in the same manner except the reaction solvent was 50 ml of dimethyl sulfoxide instead of the THF–DMSO mixture.

Thenils 9 and 10 *via* Scheme II.—A solution of 0.02 mol of the appropriate substituted thiophene in 30 ml of dry ether under N_2 was stirred and treated in one portion with 0.025 mol of 1.6 *N* *n*-BuLi in hexane. After stirring 15 min, the thienyllithium solution was cooled to −60° and added dropwise to 0.018 mol of dimethyl oxalate in 100 ml of dry ether precooled to −60°. After an additional 1 hr of stirring, the reaction mixture was allowed to warm to room temperature and 50 ml of 2% HCl was added. The layers were separated, and the aqueous layer was extracted with ether (two 50-ml portions). The combined dried (Na_2SO_4) extracts were taken to dryness and the residue was continuously extracted with 30–50° petroleum ether. Further purification was by sublimation at 120° (0.1 Torr).

Thenils 11 and 12 *via* Scheme III.—A solution of 0.100 mol of the alkoxythiophene in 150 ml of carbon disulfide was cooled below 5° and 26.1 g (0.100 mol) of stannic tetrachloride in 30 ml of carbon disulfide was added with stirring. This solution was treated with 6.35 g (0.050 ml) of oxalyl chloride dropwise during 90 min, at 5° or lower. After stirring a further 15 min, the reaction mixture was poured into 100 ml of ice water and stirred well. The bulk of the product was removed by filtration. The ether layer was separated and the aqueous layer was extracted with ether (four 100-ml portions). The combined dried (Na_2SO_4) ether solutions were stripped of solvent, and the residue was combined with the previously isolated product. Further purification was by sublimation at 120° (0.1 Torr).

Thenils 6 and 13 *via* Scheme IV.—A Grignard solution prepared from 2.46 g (0.011 mol) of 5-methyl-2-iodothiophene and 0.267 g (0.011 g-atom) of magnesium in 20 ml of dry ether was added to 1.40 g (0.100 mol) of 2-thienylgyloxal in 25 ml of dry ether precooled to −50° with stirring and at such a rate that the temperature was maintained below −40° during the addition. After a further 1 hr of stirring, 10 ml of saturated ammonium chloride was added and the layers were separated. The aqueous layer was extracted with ether (two 25-ml portions), the combined ether solutions were dried (Na_2SO_4), and the solvent was removed in a rotary evaporator. The thenoin was oxidized to the thenil as in Scheme I. Thenil **6** was prepared in exactly the same manner using phenylmagnesium iodide in place of 2-

(16) S. Selman and J. F. Eastham, *Quart. Rev., Chem. Soc.*, **14**, 221 (1960).

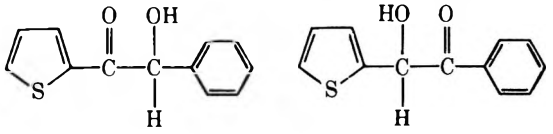
(17) H. Kwart and M. M. Baevsky, *J. Amer. Chem. Soc.*, **80**, 580 (1958).

(18) Infrared spectra were determined as KBr disks on a Perkin-Elmer 237B spectrophotometer. Nmr spectra were recorded on a Varian A-60 instrument with TMS as internal standard. Mass spectra were run by Mrs. L. Guile using a Hitachi Perkin-Elmer RMU-6 instrument at 70 eV. Ultraviolet spectra were taken on a Cary 14 spectrophotometer. Melting points were determined on an Electrothermal melting point apparatus calibrated with furnished standards. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

(19) The melting point reported[5] for 3,3′-benzo[*b*]thenil is in error. It should be as in Table II: E. Campaigne, Indiana University, personal communication, 1968.

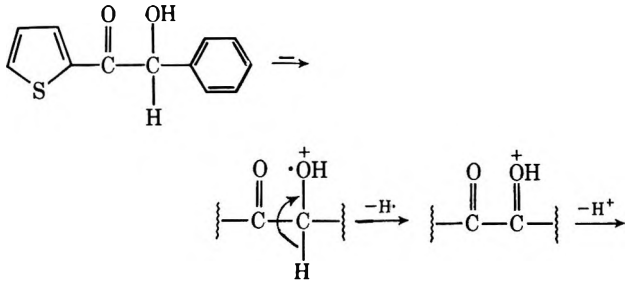
thienylmagnesium iodide, to give **14** which was oxidized[20] to **6** as in Scheme I.

(20) The mass spectrum of **14** deserves further comment. It would appear that of the two possibilities for the condensation product between benzaldehyde and 2-thenaldehyde, namely, **14** and **19**, it should be possible



14 **19**

to distinguish between them on the basis of their mass spectra if cleavage occurred between the acyl and carbinol halves of the molecule. It appears, however, that the initial process upon electron impact is oxidation of the thenil, thus



with peaks observed at *m/e* 216 (P − 2, 5%), 111 (2-thenoyl, 55%), 105 (benzoyl, 100%), and 77 (phenyl, 36%). A literature search failed to uncover any reports concerning the mass spectra of benzoins. A mass spectrum of benzoin taken in these laboratories reveals the same behavior, that is, no apparent peak but only signals at *m/e* 210 (P − 2, 3%), 105 (benzoyl, 100%), and 77 (phenyl, 47%).

General Procedure for the Thenil–Thenilic Acid Rearrangement.—A 0.010-mol quantity of the thenil was suspended in 25 ml of water containing 2 g of potassium hydroxide. The solution was stirred and heated to reflux under N_2 until solution was effected. If solution was not complete in 1 hr, 10 ml of dioxane was added, and heating was continued an additional 2 hr. The cooled solution was acidified to congo red with concentrated HCl and immediately extracted with ether (two 25-ml portions). The combined dried (Na_2SO_4) extracts were treated with an excess of ethereal diazomethane. After stirring 1 hr at room temperature, the solvent was removed under reduced pressure, and the residue was recrystallized from 60–90° petroleum ether.

Registry No.—**1**, 7333-07-5; **2**, 7333-08-6; **3**, 5381-27-1; **4**, 30135-06-9; **5**, 30135-21-8; **6**, 30135-07-0; **7**, 30135-23-0; **8**, 30135-04-7; **9**, 30135-26-3; **10**, 30135-25-2; **11**, 30135-27-4; **12**, 30226-72-3; **13**, 30135-05-8.

Chemistry of Dithienyl Diketones. II. Kinetic Investigations

GEORGE P. NILLES[1] AND ROBERT D. SCHUETZ*

Department of Chemistry and The Institute of Biology and Medicine, Michigan State University, East Lansing, Michigan 48823

Received February 9, 1971

The kinetics and thermodynamic parameters of the thenilic acid rearrangement have been followed as a function of substituent effect in the temperature range of 15–80°. A reevaluation of the ionization constants of nine thenoic acids has been made in water at 49.5°. Improved Hammett type correlations are obtained basing a new set of σ values on these ionization constants. The deviation in the Hammett plot caused by the halo substituents is discussed in terms of the mechanism of the rearrangement.

Some years ago Smith[2] and Clark[3] proposed a mechanism for the benzilic acid rearrangement in which attack by hydroxide, 1,2 migration of the aryl group, and proton transfer all occurred simultaneously. This was in contrast to the earlier concept by Ingold[4] that a complex[5] between the diketone and hydroxide preceded rearrangement to the benzilate skeleton with the temporal location of the proton transfer being unspecified. It appeared to be of interest to investigate the existence of a linear free-energy relationship and whatever bearing this might have on the reaction mechanism.

In our preceding article[6] we have described the synthesis of a number of dithienyl diketones (thenils). It was shown that, with the exception of the alkoxy thenils and 3,3′-benzo[*b*]thenil, these compounds undergo the benzilic acid rearrangement to give the corresponding thenilic acids in good to excellent yields. Thusly, we were able to make a quantitative study of this rearrangement and, in addition, to further elucidate the electromeric nature of the thiophene ring.

Results

The potassium hydroxide induced rearrangement of the nine thenils in Table I was studied in the temperature range of 15–80°. Corrections were made for thenil consumed prior to t_0 and for the nonideality of the solvent, 2:1 (v/v) dioxane–water. The titrimetrically determined loss in hydroxide was used as basis to compute the observed second-order rate constants by the usual equation.[7a] In all cases, a plot of log [thenil/OH^-] *vs.* time was linear to at least 3 half-lives of the thenil, the minor component.[8]

Thermodynamic parameters for each reaction were calculated in the usual manner from the Arrhenius equation and the Eyring equation[9] and are presented in Table II. The entropy of activation, $\Delta S^{\ddagger}_{323°K}$, was

(1) Abstracted, in part, from the Ph.D. dissertation of G. P. N.

(2) D. G. Ott and G. G. Smith, *J. Amer. Chem. Soc.*, **77**, 2325 (1955).

(3) M. T. Clark, E. G. Hendley, and O. K. Neville, *ibid.*, **77**, 3280 (1955).

(4) C. K. Ingold, *Annu. Rep., Chem. Soc. (London)*, 124 (1928).

(5) A claim is made for the isolation of this intermediate complex which, depending on reaction conditions, can give benzilic acid or can be decomposed back to benzil and hydroxide: G. Scheuing, *Chem. Ber.*, **56**, 252 (1923).

(6) R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2486 (1971).

(7) (a) F. H. Westheimer, *J. Amer. Chem. Soc.*, **58**, 2209 (1936), has shown that the rearrangement is first order in base and first order in diketone. Thus, we employed the usual second-order equation as in S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 18; (b) p 91.

(8) It became quite tedious with compounds such as 5,5,-dimethyl-2,2′-thenil to perform rate studies beyond 2 half-lives, since this would have required individual runs lasting longer than 3 days.

(9) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 71.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE THENILIC ACID REARRANGEMENT AT VARIOUS TEMPERATURES

Compd[a]	Registry no.	15°	30°	40°	50°
2,2′-Thenil	7533-07-5	6.07×10^{-5}	2.35×10^{-4}	$5.35 \pm 0.14 \times 10^{-4}$	$1.22 \pm 0.04 \times 10^{-3}$
5,5′-Dimethyl-2,2′-thenil	30135-04-7	1.22×10^{-5}	4.50×10^{-5}	$9.85 \pm 0.73 \times 10^{-5}$	$1.96 \pm 0.30 \times 10^{-4}$
5-Methyl-2,2′-thenil	30135-05-8	3.84×10^{-5}	1.28×10^{-4}	$2.74 \pm 0.13 \times 10^{-4}$	$5.20 \pm 0.31 \times 10^{-4}$
5,5′-Dichloro-2,2′-thenil	30135-23-0	$1.29 \pm 0.04 \times 10^{-2}$	$4.50 \pm 0.33 \times 10^{-2}$	$9.18 \pm 0.14 \times 10^{-2}$	1.86×10^{-1}
5,5′-Difluoro-2,2′-thenil	30135-26-3	$5.11 \pm 0.14 \times 10^{-3}$	$1.81 \pm 0.07 \times 10^{-2}$	3.90×10^{-2}	$8.07 \pm 0.35 \times 10^{-2}$
5,5′-Di(2″-thenyl)-2,2′-thenil	30288-11-0	1.24×10^{-4}	4.88×10^{-4}	1.12×10^{-3}	$2.57 \pm 0.12 \times 10^{-3}$
2,2′-Benzo[*b*]thenil	30135-06-9	8.53×10^{-4}	3.84×10^{-3}	$9.77 \pm 1.23 \times 10^{-3}$	$2.36 \pm 0.07 \times 10^{-2}$
2-Thienylphenyl diketone	30135-07-0	1.99×10^{-5}	3.11×10^{-5}	$1.82 \pm 0.14 \times 10^{-4}$	$3.68 \pm 0.12 \times 10^{-4}$
3,3′-Thenil	30135-08-1	3.61×10^{-5}	7.92×10^{-5}	$1.31 \pm 0.07 \times 10^{-4}$	$1.87 \pm 0.15 \times 10^{-4}$

Compd[a]	60°	70°	80°	r[b]
2,2′-Thenil	$2.46 \pm 0.08 \times 10^{-3}$	$4.96 \pm 0.11 \times 10^{-3}$	$9.36 \pm 0.11 \times 10^{-3}$	0.999+
5,5′-Dimethyl-2,2′-thenil	$3.84 \pm 0.31 \times 10^{-4}$	$7.54 \pm 0.45 \times 10^{-4}$	$1.57 \pm 0.15 \times 10^{-3}$	0.999
5-Methyl-2,2′-thenil	$1.00 \pm 0.02 \times 10^{-3}$	$1.93 \pm 0.07 \times 10^{-3}$	$3.40 \pm 0.07 \times 10^{-3}$	0.999
5,5′-Dichloro-2,2′-thenil	3.60×10^{-1}	6.70×10^{-1}	1.20	0.999+
5,5′-Difluoro-2,2′-thenil	1.60×10^{-1}	3.03×10^{-1}	5.55×10^{-1}	0.999+
5,5′-Di(2″-thienyl)-2,2′-thenil	$5.11 \pm 0.38 \times 10^{-3}$	$1.14 \pm 0.07 \times 10^{-2}$	$2.01 \pm 0.34 \times 10^{-2}$	0.998
2,2′-Benzo[*b*]thenil	$5.46 \pm 0.23 \times 10^{-2}$	$1.12 \pm 0.08 \times 10^{-1}$	2.33×10^{-1}	0.999+
2-Thienylphenyl diketone	$8.79 \pm 0.62 \times 10^{-4}$	$1.48 \pm 0.07 \times 10^{-3}$	$3.65 \pm 0.25 \times 10^{-3}$	0.996
3,3′-Thenil	$3.07 \pm 0.11 \times 10^{-4}$	$4.60 \pm 0.24 \times 10^{-4}$	6.85×10^{-4}	0.997

[a] Rate constants shown without standard deviations are those extrapolated from the Arrhenius plot. [b] Correlation coefficient for the Arrhenius plot.

TABLE II

THERMODYNAMIC CONSTANTS FOR THE THENILIC ACID REARRANGEMENT

Compd[a,b]	$\Delta H^{\ddagger}_{323°K}$	$\Delta S^{\ddagger}_{323°K}$	$\Delta F^{\ddagger}_{323°K}$	Log A[c]
2,2′-Thenil	15.0 ± 0.3	−25.6 ± 1.3	23.3 ± 0.7	7.676
5,5′-Dimethyl-2,2′-thenil	14.5 ± 1.0	−30.8 ± 5.5	24.4 ± 2.8	6.522
5-Methyl-2,2′-thenil	13.3 ± 0.4	−32.5 ± 2.4	23.8 ± 1.2	6.162
5,5′-Dichloro-2,2′-thenil	13.5 ± 0.6	−20.3 ± 1.6	20.0 ± 1.1	8.820
5,5′-Difluoro-2,2′-thenil	14.6 ± 0.4	−20.5 ± 1.5	20.6 ± 0.9	8.773
3,3′-Benzo[*b*]thenil	16.8 ± 1.0	−14.2 ± 1.8	21.4 ± 1.6	10.155
5,5′-Di(2″-thienyl)-2,2′-thenil	15.2 ± 1.3	−23.6 ± 4.0	22.8 ± 2.6	8.104
2-Thienylphenyl diketone	15.6 ± 0.6	−26.1 ± 3.0	24.0 ± 1.6	7.569
3,3′-Thenil	8.40 ± 0.8	−49.5 ± 5.4	24.4 ± 2.5	2.447

[a] $\Delta H^{\ddagger}$ and $\Delta F^{\ddagger}$ are in units of kcal/mol; $\Delta S^{\ddagger}$ is in cal/(°K mol). [b] A plot of $\Delta S^{\ddagger}$ *vs.* $\Delta H^{\ddagger}$, omitting the values for the halothenils, gives an isokinetic temperature of 242 ± 24°K. [c] A is the preexponential factor from the Arrhenius equation.

calculated[10] by eq 1. The uncertainties in the energy of activation and, consequently, the enthalpy of activation were calculated by Benson's method[7b] with the errors due to temperature being assumed negligible. Errors in the entropy of activation were estimated from Wiberg's expression.[11]

$$\Delta S^{\ddagger}_{323} = 4.576 \log A - 60.689 \quad (1)$$

Previous efforts at correlating physical parameters in thiophene compounds with Hammett's σ values based on the ionizations of benzoic acids have been only partially successful.[12]

Accordingly, potentiometric determinations of the ionization constants of nine thenoic acids in Table III were made in water at 49.5°. From these, the corresponding "σ_θ" values were calculated as the log of the ratio of the ionization constants of the unsubstituted *vs.* the substituted acids.

Discussion

The entropies of activation are in agreement with those expected for a reaction involving considerable restricted geometry in the transition state. The entropy of activation of −14.2 eu for the rearrangement of 2,2′-benzo[*b*]thenil indicates that a lesser degree of ordering may be necessary in going from the ground state to the transition state for the reaction. This may be due to steric interactions in the ground state which invoke a specific conformation of the benzo[*b*]thienyl rings. Coincidentally, this geometry may be similar to that required by the transition state and hence shows up as a less negative entropy of activation, relative to the other thenils.

In a similar manner, the high value of $\Delta S^{\ddagger}$ of −49.5 eu for the 3,3′-thenil rearrangement could indicate that the geometry of the transition state bears little resemblance to the geometry of the ground state. It must be kept in mind, however, that according to the Ingold mechanism for the rearrangement the observed thermodynamic data would be a function of either the

(10) A simple combination of the Eyring equation with the Arrhenius equation together with the relationship that $\Delta H^{\ddagger} = E_a - RT$ gives eq 1 which is valid at 323°K, although in the range 293–353°K the maximum error within 30°K of this temperature is only 0.4%.

(11) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 379.

(12) For example, see H. H. Jaffe and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 240 (1964); R. D. Schuetz and D. M. Teller, *J. Org. Chem.*, **37**, 410 (1962); P. A. TenThije and M. J. Janssen, *Recl. Trav. Chem. Pays-Bas*, **84**, 1169 (1965).

TABLE III

IONIZATION CONSTANTS AND σ VALUES FOR NINE THENOIC ACIDS

Compd	Registry no.	pK_a[a,b]	σ_θ	σ[c]
2-Thenoic acid	527-72-0	3.617 ± 0.016	0.000[d]	
5-Methyl-2-thenoic acid	1918-79-2	3.784 ± 0.019	−0.167 ± 0.035	−0.170 ± 0.02
5-Chloro-2-thenoic acid	24065-33-6	3.341 ± 0.014	0.276 ± 0.030	0.227 ± 0.02
5-Nitro-2-thenoic acid	6317-37-9	2.620 ± 0.018	0.997 ± 0.034	0.778 ± 0.02
5-Fluoro-2-thenoic acid	4377-58-6	3.430 ± 0.014	0.187 ± 0.030	0.062 ± 0.02
5-Methoxy-2-thenoic acid	29212-22-4	3.842 ± 0.014	−0.225 ± 0.030	−0.268 ± 0.02
3-Thenoic acid	88-13-1	4.157 ± 0.014		
3-Benzo[*b*]thenoic acid	5381-25-9	4.032 ± 0.036	0.125 ± 0.050[e]	0.042 ± 0.02
2-Benzo[*b*]thenoic acid	6314-28-9	3.336 ± 0.012	0.251 ± 0.028	0.042 ± 0.02

[a] At 49.5°; ranges are the average of the standard deviations of three runs of nine determinations each. [b] Corrections to thermodynamic pK values may be made from the extended Debye–Hückel equation with the ion size parameter = 9 Å, and the ionic strength ~0.001. This will raise the pK values given by 0.015, but this value cancels in calculating σ_θ. [c] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [d] By definition. [e] Based on the pK_a of 3-thenoic acid.

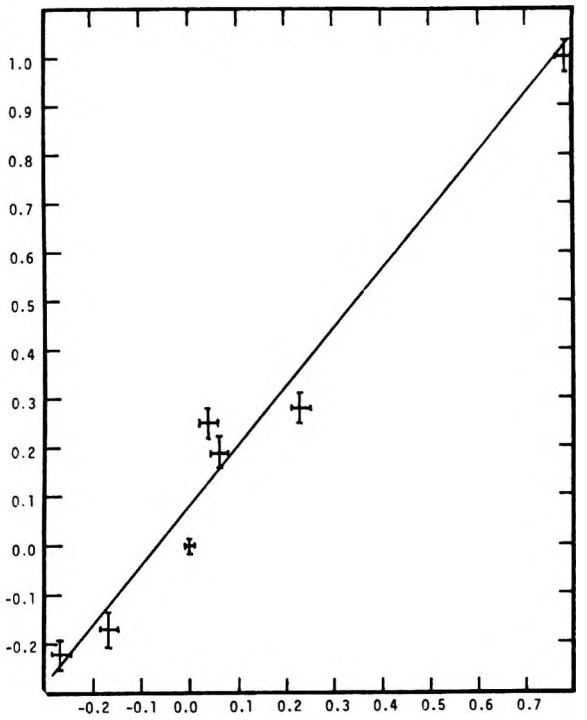


Figure 1.—Plot of σ *vs.* σ_θ based on the data in Table III.

equilibrium reaction between the thenil and hydroxide or the rearrangement of that intermediate to the thenilate anion, depending on the relative free energies of activation for each step.

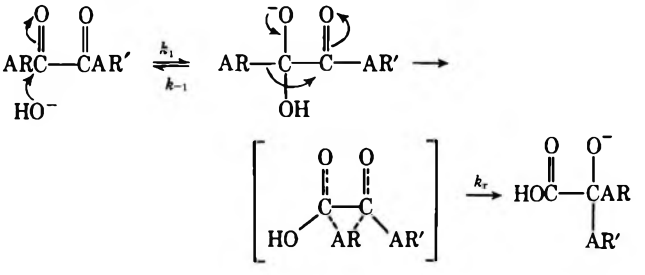
Other factors, such as differences in solvation between the ground state and the transition state, will also affect the entropy of activation, but such effects should be small relative to steric effects.

The rearrangement of 2,2′-thenil is faster [k = 1.22 × 10^{-3} l./(mol sec)] than benzil [k = 1.00 × 10^4 l./(mol sec[13])] at 50° in 2:1 dioxane–water. This is a rather clear manifestation of the electron-withdrawing nature of the 2-thienyl group which parallels the acidity of benzoic acid (pK_a = 4.229 at 49.5°) *vs.* 2-thenoic acid (pK_a = 3.617 at 49.5°). One is tempted to postulate stabilization of the incipient negative charge at the migration origin *via* d-orbital interaction, although at this point there is nothing to substantiate this. It can be noted, though, that 3,3′-thenil in which the sulfur is one more carbon removed from the active site of the diketone rearranges at a rate much closer to that of benzil.

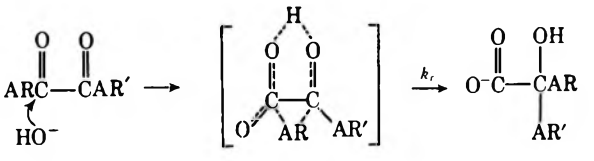
From Table III, it is evident that while electron-donating substituents have roughly the same magnitude electron-withdrawing substituent effects are enhanced in thiophene compounds compared to the corresponding benzene compounds. Thus, it appears that there cannot be an accurate, simple relationship between substituent effects in benzene *vis-à-vis* substituent effects in 5-substituted 2-thiophenes, especially those with electron-withdrawing groups. This is further exemplified by a plot of σ *vs.* σ_θ from Table III. This plot (Figure 1), shows only a "fair"[14] correlation, r = 0.943. Considerable improvement in correlating reactivities in thiophenes might be expected by using σ_θ instead of σ.

Returning to the benzilic acid rearrangement, in either the concerted (Smith–Clark) or the two-step (Ingold) mechanism, the rate of rearrangement should be dependent on the electrophilicity of the carbonyl carbons (plural) and to some extent on the stabilization of the developing negative character at the migration origin.

Ingold mechanism



Smith–Clark mechanism



Evidence of this is shown in the Hammett plot (Figure 2) for which a linear relationship is given when using the sum of the substituent constants for 2,2′-thenil, 5-methyl-2,2′-thenil, and 5,5′-dimethyl-2,2′-

(13) J. Hine and H. W. Haworth, *J. Amer. Chem. Soc.*, **80**, 2274 (1958).

(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

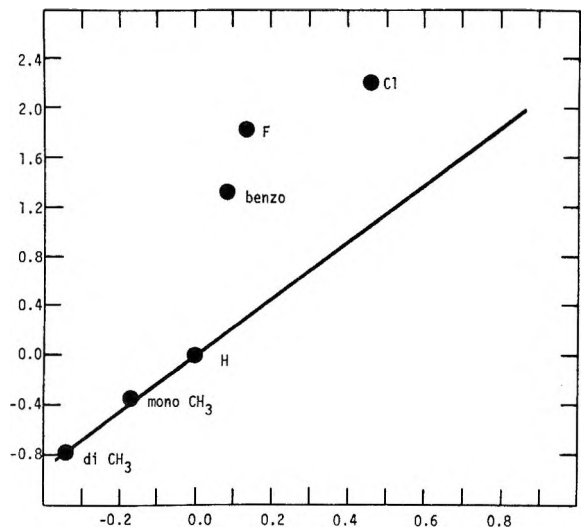


Figure 2.—Hammett plot at 50° based on σ for the first six compounds in Table II (r = 0.923). The line through the first three points has been extended to show the deviation from linearity as a result of the electron-withdrawing substituents.

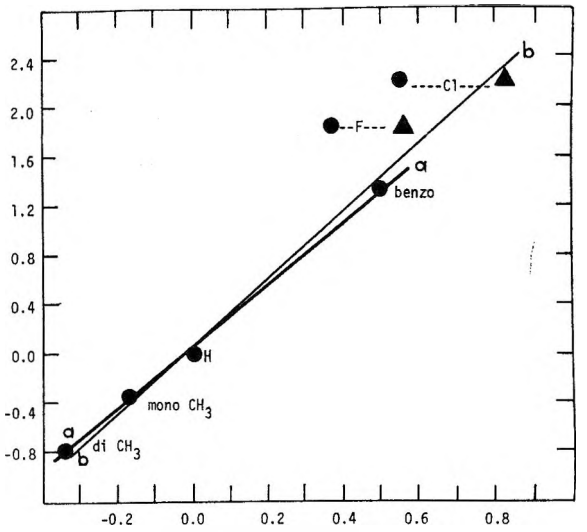


Figure 3.—Hammett plot at 50° based on σ_θ for the first six compounds in Table II: a, plotted by $2\sigma_\theta$ (r = 0.964); b, same as a but with the chloro and fluoro σ_θ values multiplied by 3 rather than 2 (r = 0.994).

thenil.[15] Thus, in all of the Hammett plots the substituent constants were summed.

The correlation coefficient for the plot in Figure 2 is only fair, r = 0.923. The main deviation is caused by the electron-withdrawing groups. If the plot is made using σ_θ (Figure 3) instead of σ, the correlation is much improved, r = 0.964, although still less than desirable. It can be noted that the benzo group now falls in line, but the halo substituents are still considerably displaced from linearity.[16] If the sum of the σ_θ's for chloro and fluoro are multiplied by 1.5, the fit to the Hammett plot in Figure 3 becomes excellent, r = 0.994.

It is tempting to conclude that this rate enhancement due to the halo substituents, above that predicted on the basis of their σ_θ values, would be evidence for the equilibrium step in accord with the Ingold mechanism. However, the observed kinetic data can give information concerning only the overall energy of activation encountered in going from reactants to products.

If the $\Delta F^{\pm}$ for the formation of the complex is much less than the $\Delta F^{\pm}$ for the rearrangement of the complex, we would observe kinetically only substituent effects on the latter. Such results would be indistinguishable from the case with no prior equilibrium, *i.e.*, the Smith–Clark mechanism. A break in the Hammett plot could be ascribed to other mechanistic perturbations. However, it may be noted that the effect of the substituents may be disproportionate in regard to the magnitude of the free energies of activation for each step especially in going from electron-donating to electron-withdrawing groups. This would also cause a break in the Hammett plot.[17]

The slope of the regression line (ρ) for the plot in Figure 3 was virtually temperature independent, 2.624–2.667 in the range of 15–80°. The magnitude of ρ again emphasizes the enhancement of the reaction rate by electron-withdrawing groups.

Evidence has shown[18] that the 2-thienyl group can function as a resonant electron donor or an inductive electron-withdrawing group. While 5-(2′-thienyl)-2-thenoic acid was too insoluble to permit potentiometric pK_a determinations, a secondary value for σ_θ could be determined. Using a value of 2.66 for ρ, the Hammett plot yields a value of +0.04 for σ_θ of 2-thienyl. While this figure is agreeably comparable to the σ value for phenyl (−0.01 ± 0.05), it is probably more evident that the substituent constant for 2-thienyl will be reaction dependent and no one value can be properly assigned.

Experimental Section

The thenoic acids, whose pK_a's were determined, were prepared by silver oxide oxidation of the corresponding aldehydes.[19] They were purified by three crystallizations from water followed by drying in a pistol at 56° (1 Torr) and then stored over phosphorus pentoxide for 1 week. The ionization constants were determined in water according to the method of Albert and Serjeant,[20] using a Beckman Model 1019 research pH meter equipped with Corning No. 476002 reference electrode and a Beckman No. 40498 glass electrode. The cell in which the pK_a determinations were made was thermostated at 49.5°. Care was taken to ensure temperature equilibrium of the entire system including the electrodes before measurements were made. The titrant, CO_2-free potassium hydroxide, was prepared from 0.1 *N* "Acculutes" (Anachemia Chemical Co., Champlain, N. Y.). Only distilled freshly boiled water was used in all dilutions. Reagent grade dioxane was further purified by stirring over lithium aluminum hydride for 24 hr, followed by a 6-hr reflux and then distillation. It was stored over 5A molecular sieves. After 3 days, any unused dioxane was repurified. Temperatures were determined using a Will Scientific No. 26846, −5 to +101° thermometer stated to comply with NBS Circular No. 8. The temperatures were further checked by a calibrated

(15) The rate constants for the rearrangement are also related by $k = (k_0k')^{1/2}$ where k is for the hybrid compound and k_0 and k, are the rate constants for the symmetrical thenils. The same relationship holds (within experimental error) for 2,2′-thenil, 2-thienylphenyl diketone (the "hybrid"), and benzil.

(16) A plot of $\Delta F^{\pm}$ for the rearrangement of these thenils *vs.* σ_θ also exhibits a break for the halo substituente.

(17) J. O. Schreck, *J. Chem. Educ.*, **48**, 103 (1971).

(18) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 89 (1963); E. A. Hill, M. L. Gross, M. Stasiewics, and M. Manion, *J. Amer. Chem. Soc.*, **91**, 7381 (1969); D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *J. Org. Chem.*, **35**, 1718 (1970).

(19) See part I of this series and ref 9 for the preparation of the aldehydes. The oxidation procedure was essentially that of E. Campaigne and W. M. LeSuer, *Org. Syn.*, **33**, 94 (1953).

(20) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, Chapter 2.

Hewlett-Packard No. 2801A quartz digital thermometer. Temperatures are believed accurate to +0.04°.

Kinetic measurements for all of the thenils, with the exception of 3,3′-benzo[b]thenil, 2,2′-benzo[b]thenil, and 5,5′-di(2″-thienyl)-2,2′-thenil, were carried out in the same manner. A sample of the thenil, in the range of 2.5–3.0 mmol, was weighed to 0.1 mg and placed in a 250-ml Teflon screw cap bottle, along with a magnetic stirring bar. The thenil was dissolved in 100.0 ml of equilibrated dioxane with stirring. The solution was continuously stirred during the kinetic run by means of a submersible magnetic stirrer mounted directly beneath the reaction vessel. A 50.00-ml quantity of 0.1 *N* temperature equilibrated potassium hydroxide solution was pipetted into the thenil solution with vigorous stirring. The vessel was sealed with a screw cap arrangement that permitted the insertion and withdrawal of a pipette. A 10.00-ml aliquot of the thenil solution was immediately withdrawn. The aliquot was quenched in a 10-ml sample of ice cold acetone and the clock was started.

The sample was titrated to either a phenolphthalein (pH 8.3) or thymol blue (pH 8.0) end point with 0.01 *N* hydrochloric acid. At various intervals, depending on the rate of potassium hydroxide disappearance, 10-ml aliquots were withdrawn and titrated in the same manner. Simultaneously with the kinetic runs, a blank sample was determined under the same conditions described above, except that the thenil was omitted. In this manner it was possible to correct for any acidic impurity present in the thenil and also for any reaction of the base with the solvent. During the 80° runs and to a lesser extent at 70°, a small correction (by never more than 3%) was found to be necessary. At other temperature, the correction was too small to be measured.

Samples of 3,3′-benzo[b]thenil, 2,2′-benzo[b]thenil, and 5,5′-di(2″-thienyl)-2,2′-thenil were too insoluble to be determined at the concentrations used above for the other thenils. Accordingly, samples in the range 0.3–0.8 mmol, but never less than 0.1000 g, were used in the kinetic determinations. The amount of dioxane used was 100 ml, but the 50 ml of potassium hydroxide was replaced by 15 ml of potassium hydroxide and 35 ml of water. All other conditions were the same.

Since a mixture of dioxane and water does not constitute an ideal solution in the thermodynamic sense, the following equation was used to calculate the actual volume of the reaction mixture at the start of a given kinetic run

$$V_{mix} = \frac{v_1(\rho_1) + v_2(\rho_2)}{\rho_{mix}}$$

where v_1 and v_2 are the volumes of dioxane and water measured out, ρ_1 and ρ_2 are the densities of dioxane and water at a given temperature,[21] and ρ_{mix} is the density of the mixture at the same temperature.[22] In these calculations, the thenils and potassium hydroxide are assumed to behave ideally. All linear plots were refined by least-squares analysis. All calculations were preformed on a Wang 320 electronic calculator.

Acknowledgments.—The authors wish to extend their gratitude to Professor Matt Zabik, Department of Entomology, Michigan State University, for the loan of the Beckman 1019 pH meter.

(21) F. Horvaka, R. A. Schaefer, and D. Dreisbach, *J. Amer. Chem. Soc.*, **58**, 2264 (1936).

(22) H. Hartmann, *Z. Phys. Chem. (Leipzig)*, **191**, 197 (1942).

Metal-Catalyzed Hydroperoxide Reactions. II.[1] Molybdenum-Catalyzed Epoxidations of Styrene and Some Substituted Styrenes

G. R. HOWE AND R. R. HIATT*

Department of Chemistry, Brock University, St. Catharines, Ontario, Canada

Received January 11, 1971

A kinetic study has been carried out on the epoxidation of styrene and some substituted styrenes by *tert*-butyl hydroperoxide in the presence of molybdenum naphthenate. In benzene solution the reaction is first order in peroxide (in the range 0.1–0.3 *M*), in alkene (0.2–0.4 *M*), and in catalyst (0.0–4.58 × 10^{-4} g-atom of Mo kg^{-1}). The rates for the substituted styrenes show considerable scatter for attempted correlations with various free-energy relationships; however, a $\rho\sigma$ plot gives $\rho = -1.4 \pm 0.6$ (95% confidence levels). Thus, the rate-determining step presumably involves electrophilic attack upon the alkene. With styrene as solvent the reaction is first order in hydroperoxide but displays no simple dependence on molybdenum concentration. The apparent order in catalyst decreases as its concentration is increased in a manner which, though not fully understood, suggests either some form of special complexing or lack of true solubility in the medium.

Alkenes are readily epoxidized by organic hydroperoxides in the presence of catalytic amounts of molybdenum and vanadium compounds.[2–7] The kinetics of the epoxidation have been reported for 1- and 2-octene in the presence of molybdenum hexacarbonyl[4,5] and for cyclohexene with vanadium acetylacetonate.[7] The former reaction is first order in catalyst and alkene,[4] and apparently first order in peroxide, but the first-order rate constants obtained vary with initial peroxide concentration.[5] The vanadium-catalyzed cyclohexene epoxidation is also first order in catalyst and alkene, but the rate dependence on peroxide has been shown to be analogous to the Michaelis–Menten equation for enzyme catalysis.[7] Two noticeable features of this latter reaction are the marked inhibition by small quantities of *tert*-butyl alcohol, a reaction product, and rapid catalyst deactivation, effects apparently absent in the molybdenum-catalyzed octene epoxidation.[4,5] The proposed mechanism[4–7] involves rapid reversible complex formation between peroxide and catalyst preceding a rate-determining heterolysis of the complex O–O bond.

This paper describes a kinetic investigation of the molybdenum catalyzed epoxidation of styrene and some substituted styrenes, in order to clarify the position with regard to the kinetics and mechanism of the molybdenum-catalyzed epoxidation and also as part of a general study of substituent effects in aromatic systems.

Results and Discussion

Epoxidations were carried out using *tert*-butyl hydroperoxide (subsequently referred to simply as "peroxide") and followed by iodometric titrations of re-

(1) (a) The research described in this paper has been carried out under support by the National Research Council of Canada, Grant No. 34-02-01. (b) Part I: G. R. Howe and R. R. Hiatt, *J. Org. Chem.*, **35**, 4007 (1970).

(2) J. Kollar, Belgium Patent 641,452 (1964).

(3) N. Indictor and W. F. Brill, *J. Org. Chem.*, **30**, 2074 (1965).

(4) M. N. Sheng and J. G. Zajacek, *Advan. Chem. Ser.*, **76**, 418 (1968).

(5) M. N. Sheng, J. G. Zajacek, and T. N. Baker III, Symposium on New Olefin Chemistry, Houston, Texas, Feb. 1970.

(6) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970).

(7) E. S. Gould, R. R. Hiatt, and K. C. Irwin, *J. Amer. Chem. Soc.*, **90**, 4573 (1968).

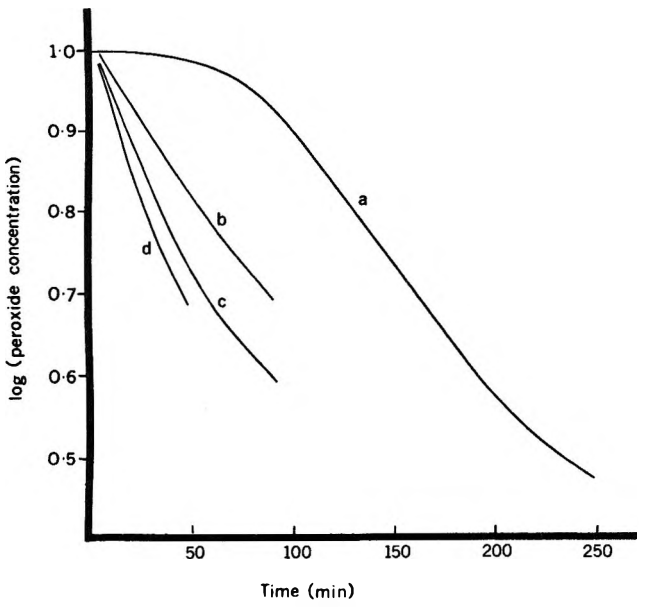


Figure 1.—Semilog plot of peroxide concentration *vs.* time at various catalyst concentrations.

sidual peroxide. To inhibit any concurrent homolytic processes (styrene polymerization, etc.), a small quantity of di-*tert*-butyl-*p*-cresol was added to each run. Thus the reaction could be considered to obey the stoichiometry of the equation

$$\textit{tert}\text{-BuO}_2\text{H} + \text{PhCH}{=}\text{CH}_2 \xrightarrow{\text{Mo}} \textit{tert}\text{-BuOH} + \text{PhCH}\overset{\text{O}}{\diagup\diagdown}\text{CH}_2$$

The quantitative yield of epoxide, based on peroxide reduced, was demonstrated (Experimental Section) as it has been in many previous reports.[2-7]

Epoxidations in Styrene.—Under the kinetic conditions subsequently described no reaction occurred in the absence of either catalyst or styrene. Molybdenum hexacarbonyl when used as a catalyst had an induction period (when very little reaction took place) of 5–30 min (Figure 1, a); this has been attributed to a need to lose one CO ligand prior to reaction.[4] In view of the necessity of determining initial rates, molybdenum naphthenate was used in all subsequent kinetic runs to avoid this induction period. Kinetic runs in styrene at 60° showed the following features. (1) Catalyst degradation occurred readily, deviations in the rates being measurable when the reaction had proceeded between 10 and 30%. The higher the catalyst concentration, the lower the percentage of reaction at which such deviations become apparent (Figure 1, b–d). (2) The reaction is first order in peroxide in the range 0.1–0.4 *M* as shown by the linearity of the plot of log (peroxide) *vs.* time over the initial part of the reaction (Figure 1, b–d). The pseudo-first-order rate constant so determined was independent both of initial peroxide concentration and of added initial *tert*-butyl alcohol (0.25 *M*) (Table I). (3) Yields of styrene oxide, determined for run a, Table I at 25 and 50% reduction, were quantitative within the limits of the vpc analysis (±4%). This included both linear and nonlinear sections of the plot (Figure 1, b). (4) The rate dependence on catalyst concentration was complex. Table II lists pseudo-first-order rate constants for peroxide disappearance as a function of molybdenum concentration, and Figure 2 shows a plot of this function. The plot is linear in the range 0.2–5.5 × 10^{-4} g-atom of Mo kg^{-1}, with a slope less than unity. Below 0.2 the slope is greater than unity, the line passing through the origin. A log–log plot indicates an apparent order of $^3/_2$ at the lower concentrations and of $^1/_2$ at higher. Either order can be rationalized on the basis of catalyst dimers and/or special complexing, but it is difficult to encompass both in a single mechanism. We are forced to note that odd changing orders are more common than otherwise for metal ion catalyzed hydroperoxide reactions and that there is disagreement over whether the phenomenon is due to complexation or to lack of true solubility of the catalyst in the medium.[8] The medium effect is emphasized by the fact that the reactions using dilute solu-

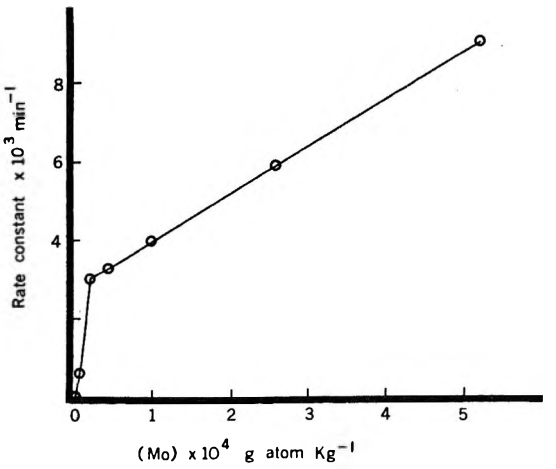


Figure 2.—First-order rate constants *vs.* catalyst concentration.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS AND 95% CONFIDENCE LEVELS FOR MOLYBDENUM-CATALYZED EPOXIDATION OF STYRENE[a]

	[*tert*-BuOOH]$_0$,[b] *M*	[*tert*-BuOH]$_0$,[c] *M*	Rate constant × 10^3 min^{-1}	Confidence level
a	0.25	0.0	4.0	0.3
b	0.40	0.0	3.9	0.2
c	0.25	0.25	4.1	0.3

[a] Reactions conditions: molybdenum naphthenate (1.01 × 10^{-4} g-atom kg^{-1}) and peroxide in styrene at 60.0°. [b] Initial peroxide concentration. [c] Initial *tert*-butyl alcohol concentration.

TABLE II

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE EPOXIDATION OF STYRENE[a] AT 60°

Mo[b] concentration × 10^4 g-atom kg^{-1}	Rate constant × 10^3 min^{-1}	95% confidence level
0.000	0.00	
0.070	0.57	0.07
0.213	3.02	0.50
0.441	3.14	0.07
1.011	4.00	0.3
2.627	5.95	0.37
5.535	8.89	0.48

[a] Reaction conditions: *tert*-butyl hydroperoxide (0.25 *M*) in styrene. [b] As molybdenum naphthenate.

(8) R. Hiatt, K. C. Irwin, and C. W. Gould, *J. Org. Chem.*, **33**, 1430 (1968).

tions of styrene in benzene showed good first-order dependence on catalyst concentrations, as shown below.

Styrene Epoxidations in Benzene.—Kinetic studies were carried out using approximately equal concentrations of styrene and peroxide in benzene at 60°. Second-order rate plots (first order in styrene and peroxide) were linear over some 20% of the reaction. Table III

TABLE III
SECOND-ORDER RATE CONSTANTS FOR STYRENE[a] EPOXIDATION IN BENZENE AT 60°

	[*tert*-BuOOH]$_0$,[b] *M*	[*tert*-BuOH]$_0$,[c] *M*	[Mo][d]	Rate constant × 10^4 M^{-1} min^{-1}	95% confidence level
a	0.245	0.0	3.10	26.7	2.1
b	0.243	0.25	3.10	26.9	3.0
c	0.237	0.0	2.00	18.4	1.7
d	0.549	0.0	3.22	27.6	2.2
e	0.582	0.0	4.58	42.0	3.1

[a] Initial styrene concentration = 0.4 *M*. [b] Initial peroxide concentration. [c] Initial *tert*-butyl alcohol concentration. [d] Molybdenum naphthenate concentration (× 10^4 g-atom kg^{-1}).

lists initial second-order rate constants measured under various conditions. These show that the rate constant is (1) independent of initial peroxide concentration (Table III, runs a and d) and (2) independent of initial, added *tert*-butyl alcohol (a and b), and the rate is first order in molybdenum (a, c–e, Figure 3).

Epoxidation of Substituted Styrenes in Benzene.—Substituent effects upon rates of metal-catalyzed hydroperoxide epoxidations have been studied only for the case of hydrocarbon substituents in alkyl systems.[4-6] The effect of some heteroatom substituents in aniline upon rates of metal-catalyzed hydroperoxide oxidations have been reported,[1b] and the results obtained have been useful both for interpreting the mechanism of these reactions and for studies upon the nature of substituent effects in general. Consequently, second-order rate constants for the epoxidation in benzene of a series of ring-substituted styrenes were determined using the identical catalyst concentration in every case[9] (3.10 × 10^{-4} g-atom of Mo kg^{-1}). The results (Table IV) show that the meta nitro group de-

TABLE IV
SECOND-ORDER RATE CONSTANTS FOR THE EPOXIDATION[a] OF SOME SUBSTITUTED STYRENES IN BENZENE AT 60°

Substituent	Registry no.	Rate constant × 10^4 M^{-1} min^{-1}	95% confidence level
None	100-42-5	26.7	2.1
m-Cl	2039-85-2	21.8	3.0
p-Cl	1073-67-2	30.5	0.25
m-Br	2039-86-3	26.1	2.7
p-Br	2039-82-9	31.0	3.7
m-NO_2	586-39-0	3.10	0.5
p-Me	622-97-9	39.6	9.5

[a] Reaction conditions: peroxide (0.25 *M*), substituted styrene (0.4–0.5 *M*), and molybdenum naphthenate (3.10 × 10^{-4} g-atom kg^{-1}).

creases the reaction rate and the para methyl increases it, as is to be expected for a reaction including an elec-

(9) The competitive method of part I[1b] could not be used in the present case due to difficulties in the vpc analysis of these compounds.

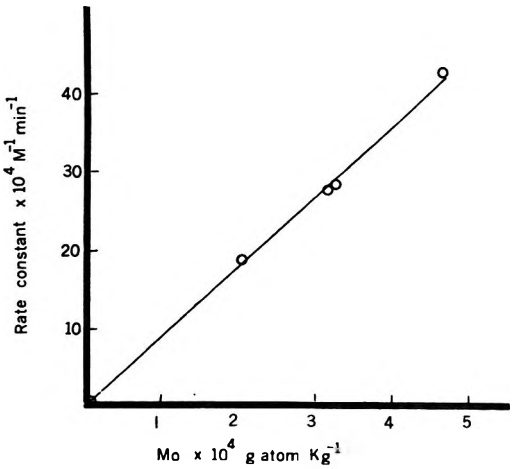


Figure 3.—Second-order rate constants *vs.* catalyst concentration.

tron-deficient transition state. The effect of halogen substituents is small and for the para position appears to be in contradiction to the expected order. However, consideration of the 95% confidence levels indicates that the present technique of initial rate determinations is not accurate enough to place too much significance on this apparent reversal of the customary effect.

Correlation of Substituent Effects by Linear Free-Energy Relationships.—Linear multiple regression analyses were carried out using the relationships discussed in part I,[1b] *viz.*, with Hammett σ constants,[10] with Brown–Okomoto σ^+ constants,[11] with the Yukawa–Tsuno equation,[12] and with the three variable, dual-effect equation discussed in part I.[13] Parameters used in the latter eq 1 are as follows. *F* and *M* were

$$\lg \frac{k}{k_0} = A + BFX_{SR} + CMY_{SR} \quad (1)$$

from the *F* and *R* values of Swain and Lupton.[14] Y_{SR} is the Hückel molecular orbital atom–atom polarizability[15] (π_{RS}) between the carbon atom (S) to which the substituent is attached and the carbon atom (R) which is the reaction center; separate calculations were made using both of the ethylenic carbon atoms (α and β) as reaction centers. All four functional forms of *X* described in part I[1b] were used, in combination with the appropriate polarizabilities. The normalized standard errors[1b] and variable *t* statistics for these analyses are given in Table V. In considering these results, the reservation concerning the relative accuracy of the present technique previously discussed should be borne in mind. Nevertheless, the correlations appear to be uniformly poor, especially for the dual effect equations, and there appears to be no linear free-energy relationship between the present reaction and more conven-

(10) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970.

(11) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(12) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 971 (1959), and preceeding papers.

(13) (a) G. R. Howe, Ph.D. Thesis, University of Leicester, 1969; (b) K. C. C. Bancroft and G. R. Howe, *J. Chem. Soc. B*, in press.

(14) C. G. Swain and E. C. Lupton Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(15) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3539, 3541, 3546, 3548 (1962), and references therein.

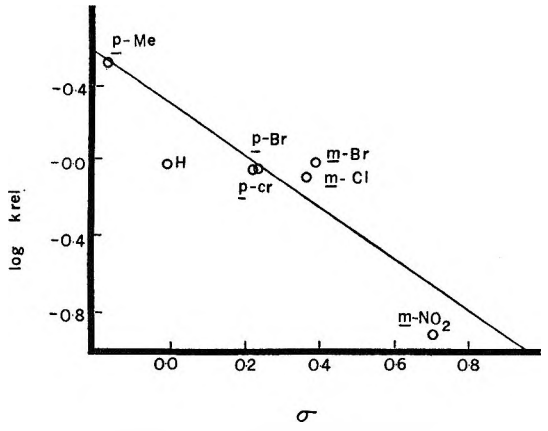


Figure 4.—Log K/K_0 for substituted styrenes *vs.* σ constants.

tional aromatic substitution reactions, in contrast to the vanadium-catalyzed oxidation of substituted anilines.[1b] Presumably interaction between the π MO's of the styrene system and the AO's of the molybdenum ion is sufficient to lead to differences in the differential change of activation enthalpy with respect to substrate structure. With the number of degrees of freedom of the various analyses used, the t values are not statistically significant enough to use the correlational results to interpret mechanism; *e.g.*, one cannot distinguish with any certainty between a greater positive charge on the α carbon atom rather than the β carbon atom in the transition state of the reaction. An illustrative plot of log (k/k_0) *vs* σ constants (which give the best correlation) is shown in Figure 4. The ρ value (-1.37) compares with a value of -1.63 for the hydroperoxide–molybdenum aniline oxidation.[1b]

TABLE V

NORMALIZED STANDARD ERRORS[a] AND VARIABLE t STATISTICS[b] FOR REGRESSION ANALYSES[c]

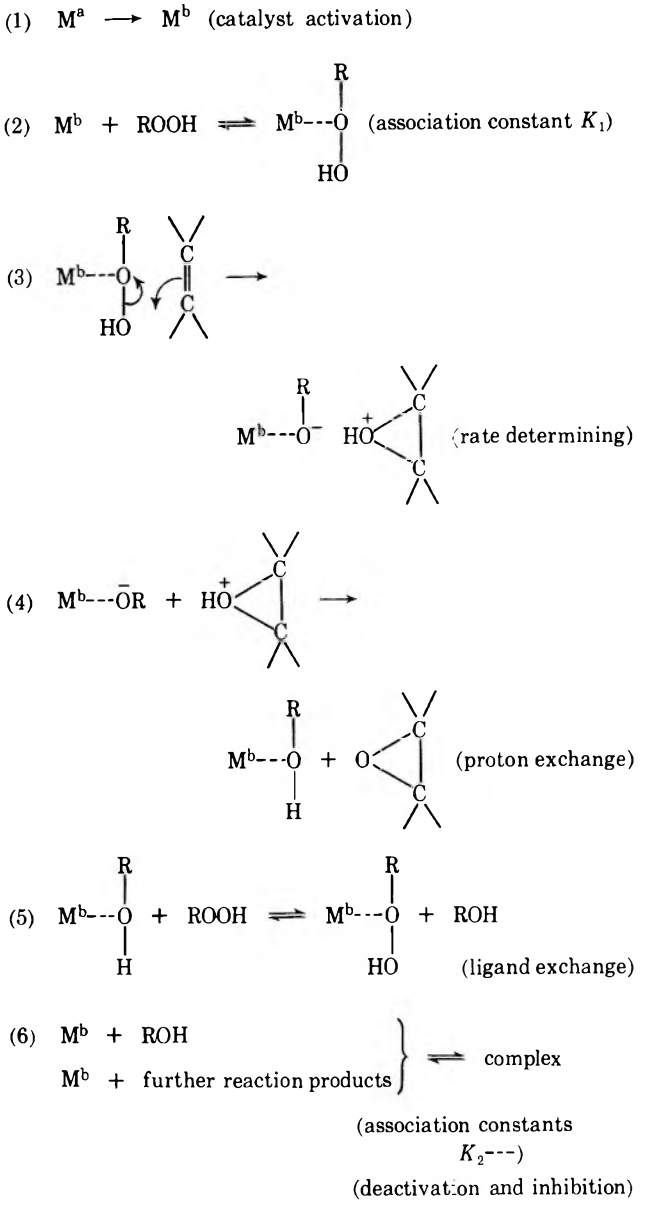
Correlation with		NSE	t_b	t_c
σ		0.53	4.37	
σ^+		0.56	4.09	
Yukawa-Tsuno		0.60	3.43	0.05
Eq 1				
Y	X			
$\pi(\alpha)$	$1/d$	0.69	2.59	1.32
	$1/d^2$	0.69	2.59	1.08
	$\cos^-/d$	0.72	2.42	2.13
	$\cos^-/d^2$	0.70	2.50	1.94
$\pi(\beta)$	$1/d$	0.74	2.50	0.96
	$1/d^2$	0.73	2.56	0.75
	$\cos^-/d$	0.81	2.12	1.61
	$\cos^-/d^2$	0.79	2.25	1.46

[a] Defined in part I.[1b] [b] t_B = ratio of variable B to standard deviation of B. [c] Using functions log $(k/k_0) = A + BX_1$ or $A + BX_1 + CX_2$ as appropriate.

Mechanism of the Epoxidation.—The metal-catalyzed epoxidation is well established to involve a heterolytic mechanism.[3-7] The difference in kinetic behavior shown by the three kinetic studies so far made, namely the vanadium acetylacetonate catalyzed cyclohexene reaction,[7] the molybdenum hexacarbonyl catalyzed octene epoxidation,[4] and the present study, is however consistent with the previously proposed common mechanism[4,7] shown in generalized format as Scheme I.[16] The first-order dependence in alkene and catalyst shown by all three reactions, the first-order

SCHEME I

EPOXIDATION MECHANISM



dependence in peroxide shown by the molybdenum catalyzed reactions, and the Michaelis–Menten equation dependence on peroxide shown by the vanadium-catalyzed reaction imply that a single molecule of each reactant is involved in the transition state. This further implies that two of the components have interacted at some prior stage, and a peroxide-catalyst complex seems the logical explanation. The difference in kinetic behavior between vanadium and molybdenum is

(16) It should be noted, however, that complete consistency is shown only for dilute reactants in an inert solvent. Kinetic anomalies observed for reactions in neat olefin which are not as yet understood include the variation in pseudo-first-order rate constants with $(RO_2H)_0$ shown by the molybdenum hexacarbonyl–octene reaction[3] and the here reported complexity of rate dependence on molybdenum concentration for the reaction in styrene. Equally inexplicable is the fact that the reaction is not a good route for laboratory synthesis of epoxides if efficient utilization of olefin is required. (R. Hiatt and C. McColeman, unpublished work.) Beyond a certain point no further epoxidation takes place even with hydroperoxide in substantial excess and with fresh catalyst added.

then explained by a much smaller value of K (the complex association constant) in the latter case, when the Michaelis–Menten equation reduces to effective first order in peroxide. The electrophilic nature of the reaction, as indicated by the substituent effects in styrene, implies a strong polarization of the peroxide O–O bond by the catalyst, which suggests that the metal ion is in a comparatively high oxidation state. Correspondingly, one would expect an initial activation of the catalyst from its lower oxidation state, which explains the induction period observed in the case of molybdenum hexacarbonyl. Inhibition by *tert*-butyl alcohol, observed for the vanadium reaction, but not for the molybdenum, has been postulated as being due to competition for the catalyst by the alcohol.[7] In the molybdenum case presumably K_2 (the alcohol–catalyst association constant) is much smaller than K_1. Catalyst deactivation could be caused by catalyst complexing with further reaction products of the epoxidation. This deactivation has been observed in all cases except the molybdenum hexacarbonyl–octene system; in the latter case one suspects the octene further reaction products do not complex; this is borne out by the deactivation shown by molybdenum hexacarbonyl in the present work.

The mechanism shown (Scheme I) fits the experimental facts;[16] inevitably postulates have to be made regarding the relative values of the association constants of the various catalysts with the various reaction components; in the absence of direct experimental evidence concerning such complexes, however, the present scheme does satisfactorily explain the epoxidation observations.

Experimental Section

Materials.—*tert*-Butyl hydroperoxide (*i.e.*, Lucidol) was generally used as received, as a 90% aqueous solution; for some of the kinetic experiments samples were purified to greater than 99.5% peroxide by vacuum distillation, though this made no detectable difference to the kinetics. All other chemicals were purified and dried by standard means. In particular, vpc analysis of styrene and substituted styrenes failed to detect any impurities, using a variety of columns. Molybdenum naphthenate, 3% molybdenum by weight, was used as obtained from K & K Laboratories.

Analyses.—Peroxide concentrations were determined by refluxing an aliquot for 5 min with potassium iodide in 2-propanol–glacial acetic acid (2:1 v/v) followed by thiosulfate titration of the released iodine. Styrene oxide concentrations for the determination of stoichiometry were determined by vpc analysis on a 6 ft × 0.25 in. SE-54 column at 130°, using an F & M Model 700 gas chromatograph equipped with a Disc integrator. For example, in a given instance (Table I, run a), a sample in which 0.055 mmol of peroxide/g had reacted showed the presence of 0.053 mmol/g of styrene oxide.

Kinetic Experiments.—Typically, a solution of styrene (0.4 M), *tert*-butyl hydroperoxide (0.25 M), and di-*tert*-butyl-*p*-cresol (0.0002 g) (to inhibit homolytic reaction) in benzene (10.00 ml) was allowed to equilibrate at reaction temperature. The reaction was initiated by adding a solution of molybdenum naphthenate in benzene (freshly made up for each run), prewarmed to reaction temperature. Periodically, samples of about 1 g were withdrawn, weighed, and analyzed for peroxide as above.

Registry No.—*tert*-Butyl hydroperoxide, 75-91-2.

Transition Metal Complexes as Selective Isomerization Catalysts. Preparation of Compounds Having an Exocyclic Double Bond

JAMES E. LYONS

Sun Oil Company, Research and Development, Marcus Hook, Pennsylvania 19061

Received January 11, 1970

The selective isomerization of vinylcycloalkenes and vinylcycloalkanes to compounds having an exocyclic double bond has been studied using three metal complexes: $RuCl_2(Ph_3P)_3$ in the presence of air or hydroperoxides, $PtCl_2(Ph_3P)_2$ and $SnCl_2$ under hydrogen pressure, and $IrCl(CO)(Ph_3P)_2$. The reactions are highly selective for retaining the double bond in the exocyclic position in contrast to conventional acid- or base-catalyzed isomerizations and consequently have synthetic utility as a catalytic method for formation of the exocyclic double bond. The ruthenium(II) complex exhibits catalytic activity in the presence of small amounts of air or hydroperoxides but is quite inactive in their absence. A carbonyl complex having high catalytic activity is formed when air or hydroperoxides react with olefin solutions of $RuCl_2(Ph_3P)_3$. The cis/trans ratio of isomers formed varies with the catalyst used showing that in certain instances cis/trans isomerization is not rapid in comparison with double bond migration. A steric argument is offered to explain observed selectivity.

Advances in homogeneous transition metal catalysis during the past decade have provided many useful examples of the selective hydrogenation of unsaturated organic compounds.[1] It is also known that many of the same complexes used in olefin hydrogenation are effective catalysts for olefin isomerization.[2] This paper describes the selective migration of a double bond on a vinyl side chain of a cyclic hydrocarbon into a position exocyclic to the ring by three group VIII metal complexes well known for their ability to catalyze olefin hydrogenation: $RuCl_2(Ph_3P)_3$, shown by Wilkinson[3] and his coworkers to be a selective hydrogenation catalyst; the $PtCl_2(Ph_3P)_2$–$SnCl_2$–H_2 system studied extensively by Bailar;[4] and Vaska's complex,[5] $IrCl(CO)(Ph_3P)_2$. It appears that, as in the case of homogeneous hydrogenation, steric factors govern the course of the reaction and are the cause of the observed selectivity in retaining the exocyclic double bond.

The interconversions between semicyclic, exocyclic, and endocyclic olefins have been extensively studied

(1) For a recent review of selective hydrogenation, see J. E. Lyons, L. E. Rennick, and J. L. Burmesiter, *Ind. Eng. Chem., Prod. Res. Develop.*, **9**, 2 (1970).

(2) For reviews of olefin isomerization catalyzed by metal complexes, see C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Academic Press, New York, N. Y., 1967, Chapter 3; M. Orchin, *Advan. Catal.*, **16**, 1 (1966).

(3) P. S. Hallman, B. R. McGarvey, and G. Wilkinson, *J. Chem. Soc. A*, 3143 (1968), and references cited therein.

(4) (a) R. W. Adams, G. E. Batley, and J. C. Bailar, Jr., *J. Amer. Chem. Soc.*, **90**, 6051 (1968). (b) J. C. Bailar, Jr., and H. Itatani, *ibid.*, **89**, 1592 (1967); H. A. Tayim and J. C. Bailar, Jr., *ibid.*, **89**, 4300 (1967).

(5) (a) L. Vaska and J. DiLuzio, *ibid.*, **84**, 679 (1962); L. Vaska and R. E. Rhodes, *ibid.*, **87**, 4970 (1965), and references cited therein.

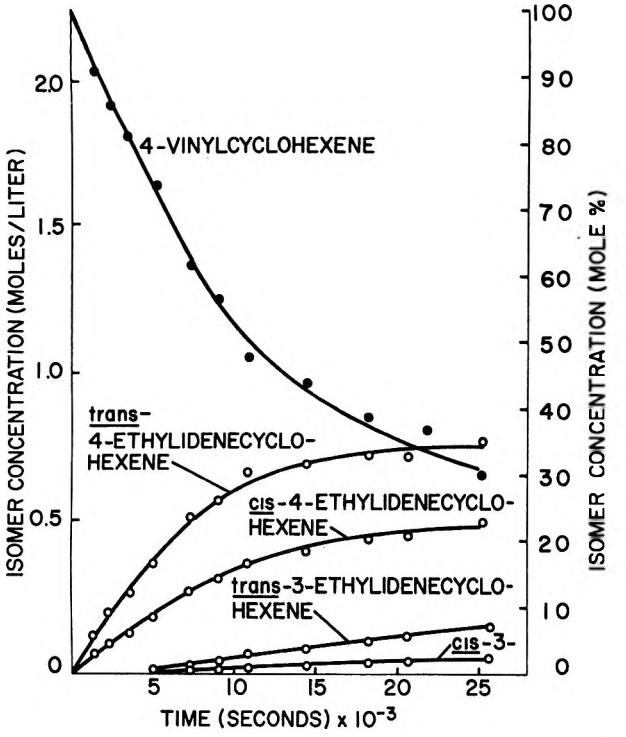


Figure 1.—Isomerization of 4-vinylcyclohexene using $PtCl_2(Ph_3P)_2$–$SnCl_2$ under hydrogen pressure. Reaction run in a methanol solution which was 2.2 M in 4-vinylcyclohexene, 8.3×10^{-3} M in $PtCl_2(Ph_3P)_2$, and 8.8×10^{-2} M in $SnCl_2$ at 65° under 100 psi of hydrogen.

using both acids[6-8] and bases[9-11] as catalysts. Acid catalysts rapidly isomerize an exocyclic double bond into a more thermodynamically stable position inside the hydrocarbon ring.[6] Equilibration of methylenecyclohexane ($t_{1/2}$ <5 hr) and methylenecyclopentane ($t_{1/2}$ = 10 min) was accomplished by Cope[6] and coworkers using catalytic amounts of *p*-toluenesulfonic acid in acetic acid at 25°. The authors report endo/exo ratios of 99.9 and 99.6 for the six- and five-membered rings, respectively, at equilibrium. Benkeser[7] and Turner[8] have studied the acid-catalyzed isomerizations of vinylcyclohexane and ethylidenecyclohexane using the same catalyst system at higher temperatures and have found a preponderance (96%)[7] of the endocyclic isomer at equilibrium. Although examples of kinetic control in base-catalyzed isomerizations of cyclic monoolefins have been observed,[10] systems containing more than one double bond are more difficult to isomerize in a completely selective manner. For example, Bank, Rowe, Schriescheim, and Naslund[9] found that the isomerization of 4-vinylcyclohexene, catalyzed by potassium *tert*-butoxide in dimethyl sulfoxide (DMSO), gives the *cis*- and *trans*-3-ethylidenecyclohexenes (51%) and the isomeric ethylcyclohexadienes (9%) after reaction is 60% complete. Although this catalyst system is far more selective than conventional acidic or heterogeneous catalysts,[9] the *cis*- and *trans*-4-ethylidenecyclohexenes which would result from migration of *only* the vinyl double bond are not reported. The transition metal complexes which we have studied, on the other hand, catalyze the stepwise migration of a double bond in similar systems in a manner which is highly selective and in some cases exhibits a certain degree of stereospecificity.

(6) (a) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and J. Jacura, *J. Amer. Chem. Soc.*, **82**, 1150 (1960); (b) R. B. Bates E. S. Caldwell, and H. P. Klein, *J. Org. Chem.*, **34**, 2615 (1969).

(7) R. A. Benkeser and J. J. Hazdra, *J. Amer. Chem. Soc.*, **81**, 228 (1959).

(8) R. B. Turner and R. H. Garner, *ibid.*, **80**, 1424 (1958).

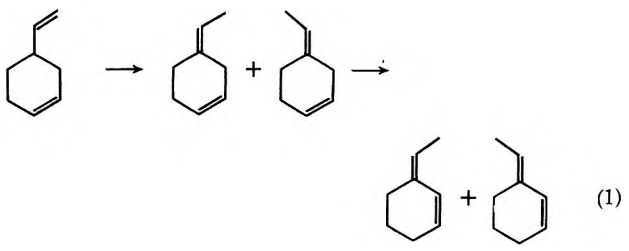
(9) S. Bank, C. A. Rowe, Jr., A. Schriescheim, and L. A. Naslund, *J. Org. Chem.*, **33**, 221 (1968).

(10) Reviewed in D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

(11) (a) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **77**, 347 (1955); (b) H. Pines and H. E. Eschinayia, *ibid.*, **78**, 5950 (1956); (c) A. Schriescheim, R. J. Muller, and C. A. Rowe, Jr., *ibid.*, **84**, 3164 (1962).

Results

Isomerization of 4-Vinylcyclohexene. A. Reactions Catalyzed by $PtCl_2(Ph_3P)_2$–$SnCl_2$ under Hydrogen Pressure. —A mixture of $SnCl_2$ and $PtCl_2(Ph_3P)_2$ in a 10:1 molar ratio in methanolic solution under 100 psi of hydrogen is a very selective isomerization catalyst. The active catalytic species in this system is most probably $PtH(SnCl_3)(Ph_3P)_2$ which forms an olefin complex in solution.[4] Products of hydrogenation are not observed under the mild conditions of the isomerization. The isomerization of 4-vinylcyclohexene, readily available from butadiene by Diels–Alder dimerization, proceeds smoothly in this medium at 60–70°. The double bond migration occurs in a stepwise manner giving the four isomeric ethylidenecyclohexenes (eq 1) from which the *cis*- and *trans*-4-ethylidenecyclohexenes are obtained in over 65% yield and may be separated from the conjugated isomers by fractional distillation. Thus, high yields of the thermodynamically less stable unconjugated exocyclic olefins may be readily obtained by this method.



(1)

This catalyst system combines the desirable characteristic of rapid rate with a high degree of selectivity and consequently has considerable preparative utility in catalytic isomerization reactions. It can be seen (Figure 1) that the rates of isomerization of the 4-ethylidenecyclohexenes to the conjugated isomers are appreciably slower than the rate of isomerization of the starting material. Although *cis*- and *trans*-3-ethylidenecyclohexene[12] could be separated and isolated in the pure state using preparative gas chromatography, *cis*- and *trans*-4-ethylidenecyclohexene could not be isolated in a similar way. The unconjugated isomers could be separated adequately on a 150-ft capillary column, however, and tentative stereochemical assignments were made by inspection of the kinetic curve obtained for the isomerization (Figure 1). It was assumed that the isomer formed in higher yield was the precursor to *trans*-3-ethylidenecyclohexene and the isomer formed in lower yield was the precursor to *cis*-3-ethylidenecyclohexene. This assumption was consistent with an experiment which showed that geometrical isomerization of the *cis*- and *trans*-4-ethylidenecyclohexenes was very slow relative to double bond isomerization in the exocyclic dienes. The cis/trans

(12) C. Cardenas, *Tetrahedron Lett.*, 4013 (1969).

ratio of the 4-ethylidenecyclohexenes remains fairly constant (0.5) during the initial stages of the reaction and the cis/trans ratio in the forming conjugated exocyclic dienes is somewhat lower than this.

Polar solvents are necessary for isomerizations using the platinum–tin system due to the insolubility of the inorganic species in the olefin. Both protic (alcohols) or aprotic (methylene chloride, *o*-dichlorobenzene) media are suitable for the reaction. Results are summarized in Table I.

B. Reactions Catalyzed by $RuCl_2(Ph_3P)_3$.—The selective isomerization of 4-vinylcyclohexene can be accomplished using 10^{-2}–10^{-3} *M* solutions of $RuCl_2(Ph_3P)_3$, I, in the neat diene (99% purity) at 90–100°. Again the double bond migration occurs in a stepwise manner but gives 90–95% yields of *cis*- and *trans*-3-ethylidenecyclohexene (eq 1). The remainder of the reaction product consists mainly of small amounts of unreacted starting material, *cis*- and *trans*-4-ethylidenecyclohexene, ethylbenzene, and the ethylcyclohexenes. Unlike the acid-[6] or base-catalyzed[9] isomerizations, the soluble transition metal complex exhibits little tendency to catalyze migration of the double bond into the ring under mild conditions. This method, therefore, affords a convenient way to obtain high yields of the *cis*- and *trans*-3-ethylidenecyclohexenes.

It is interesting that, although the reaction is carried out in the neat diene, the ruthenium(II) complex is converted to a complex II having a CO ligand unless air or hydroperoxides have been scrupulously removed from the starting material. After reaction is complete, the new complex may be precipitated from solution in approximately 60% yield by the addition of excess pentane to the reaction mixture. This material is a tan solid having intense infrared absorptions at 1994 and 1092 cm^{-1} characteristic of ruthenium–carbonyl[13] and coordinated triphenylphosphine, respectively. Compound II has catalytic activity similar to the starting complex and is most probably an intermediate in the isomerization reaction. The elemental analysis and molecular weight is consistent with the formula, $RuCl_2(CO)(Ph_3P)_2(C_8H_{12})$. Although it was initially thought that the isolable intermediate II could have been a hydrido complex,[14] the elemental analysis, together with the absence of a detectable Ru–H signal in the nmr spectrum[15] and the failure of the material to undergo exchange reactions[15] with deuterium gas, all showed that the initial assumption was incorrect. A carbonyl complex II has been formed, perhaps by Ru(II)-catalyzed decarbonylation of hydroperoxide impurities in the olefin. Thus, when 4-vinylcyclohexene was freed of oxygen-containing impurities by percolation through activated silica gel, much of the $RuCl_2(Ph_3P)_3$, I, did not dissolve in the diene, the rate of isomerization was greatly diminished, and a yellow solid III (40% of the weight of complex used) having no infrared absorptions in the 2000-cm^{-1} region was recovered from the

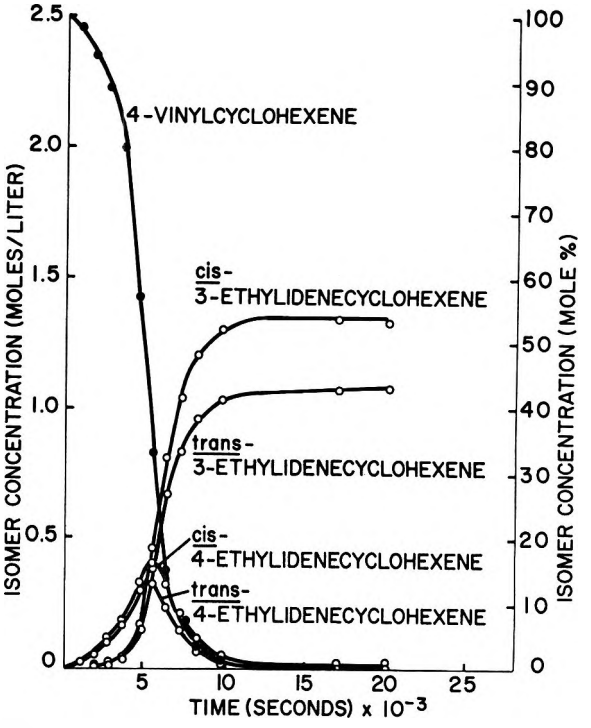


Figure 2.—Isomerization of 4-vinylcyclohexene using $RuCl_2(Ph_3P)_3$ as the catalyst. Reaction run in a 1:1 benzene–ethanol solution which was 2.5 *M* in 4-vinylcyclohexene and 6.5×10^{-3} *M* in $RuCl_2(Ph_3P)_3$ under nitrogen at 80°.

reaction mixture. The total yield of isomerization products using the purified olefin was less than 2% after 24 hr at 95°. On introduction of small amounts of air or *tert*-butyl hydroperoxide into the purified olefin, rapid rates of Ru(II)-catalyzed isomerization were again observed.

We have demonstrated, therefore, that, when the *pure* olefin is contacted with $RuCl_2(Ph_3P)_3$, *little or no isomerization occurs unless small amounts of air or hydroperoxides are added.* Furthermore, the carbonyl complex II is an isomerization catalyst in the neat diene even in the absence of air or hydroperoxides, indicating that *the introduction of air or hydroperoxides into the isomerization reaction results in formation of a catalytically active carbonyl complex.*[16]

Isomerization reactions catalyzed by I occur much more rapidly in 1:1 benzene–ethanol solution than in the neat diene and give a 97% yield of *cis*- and *trans*-3-ethylidenecyclohexene at completion. The reaction may be stopped at an intermediate stage, giving up to 29% yield of the unconjugated 4-ethylidenecyclohexenes. The overall stereochemistry is the reverse of what was observed using the platinum–tin catalyst system. The cis/trans ratio of the 3-ethylidenecyclohexenes was 1.3 at complete conversion and the cis/trans ratio of the 4-ethylidenecyclohexenes at their maximum value (29%) was 1.2.

The relatively slow initial rate of isomerization of 4-vinylcyclohexene (Figure 2) suggests an autocatalytic reaction wherein I is slowly converted to the active species. During this initial period the reaction mixtures change from dark red to orange or amber colored solutions. The reactions then became pseudo zero order in 4-vinylcyclohexene over the approximate range of 20–80% of reaction. Several reactions were run in

(13) S. D. Robinson and G. Wilkinson, *J. Chem. Soc. A*, 300 (1966).

(14) Recently it has been reported that toluene reacts with $RuCl_2(Ph_3P)_3$ at 22° to give a solution which exhibits infrared bands at 1950–1985 cm^{-1}: J. Blum, *et al.*, *J. Chem. Soc. B*, 1000 (1969). This observation was cited as evidence for the insertion of Ru(II) into the benzyl–hydrogen bond. Our data show that infrared absorptions in the neighborhood of 2000 cm^{-1} are not sufficient to establish the existence of metal hydrides as reaction intermediates.

(15) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 945 (1966).

(16) J. E. Lyons, *Chem. Commun.*, 562 (1971).

TABLE I

FORMATION OF OLEFINS HAVING AN EXOCYCLIC DOUBLE BOND BY SELECTIVE HOMOGENEOUS ISOMERIZATION OF UNSATURATED CYCLIC HYDROCARBONS

Complex used	Catalyst concn, $M \times 10^{-3}$	Substrate[a]	Solvent	Initial substrate concn, vol %	Temp, °C	Reaction time, hr	Isomerization of substrate, %	Exocyclic isomer yield, %	Exocyclic isomer(s) (product %)
$RuCl_2(Ph_3P)_3$	7.1		None	100	95	66	98	93	*cis*-3-Ethylidenecyclohexene (51.5) *trans*-3-Ethylidenecyclohexene (41.5)
	3.2		DMA	33	95	24	100	98.6	*cis*-3-Ethylidenecyclohexene (54.1) *trans*-3-Ethylidenecyclohexene (44.5)
	1.5		Benzene–ethanol[b]	33	80	6.5	99	97	*cis*-3-Ethylidenecyclohexene (54) *trans*-3-Ethylidenecyclohexene (43)
	5.2		*o*-Dichlorobenzene	33	100	1	39	31	*cis*-4-Ethylidenecyclohexene (12) *trans*-4-Ethylidenecyclohexene (10) *cis*-3-Ethylidenecyclohexene (5) *trans*-3-Ethylidenecyclohexene (4)
	2.6		Benzene–ethanol	33	80	21	7.3	3.6	*cis*- + *trans*-5-ethylidenebicyclo-[2.2.1]-2-heptene (3.6)
	8.6		None	100	95	46	70	70	Ethylidenecyclohexane (70)
	2.7		DMA	33	101	45	79	78	Ethylidenecyclohexane (78)
	1.6		Benzene–ethanol	33	80	4.2	99	99	Ethylidenecyclohexane (99)
	8.3		None	100	90	165	99	92	Ethylidenecyclopentane (92)
	5.8		None	100	95	45	74	0.5	Propylidenecyclopentane (0.5)
	8.3		Benzene–ethanol	33	70	20	>99	79	Propylidenecyclopentane (79)
$PtCl_2(Ph_3P)_2$–$SnCl_2$[c]	9.1		Methanol	9	65	5	86	81	*cis*-4-Ethylidenecyclohexene (28.5) *trans*-4-Ethylidenecyclohexene (36.5) *cis*-3-Ethylidenecyclohexene (4.5) *trans*-3-Ethylidenecyclohexene (11.5)
	8.3		Methanol	33	65	6	65	61	*cis*-4-Ethylidenecyclohexene (20) *trans*-4-Ethylidenecyclohexene (34) *cis*-3-Ethylidenecyclohexene (1.7) *trans*-3-Ethylidenecyclohexene (5.3)

$PtCl_2(Ph_3P)_2$–$SnCl_2$[c]	8.3		Methylene chloride	33	65	5	81	72	*cis*-4-Ethylidenecyclohexene (23.1) *trans*-4-Ethylidenecyclohexene (41.5) *cis*-3-Ethylidenecyclohexene (1.6) *trans*-3-Ethylidenecyclohexene (6.0)
	8.3		*o*-Dichlorobenzene	33	65	5	84	80	*cis*-4-Ethylidenecyclohexene (23.6) *trans*-4-Ethylidenecyclohexene (45.5) *cis*-3-Ethylidenecyclohexene (1.8) *trans*-3-Ethylidenecyclohexene (9.4)
	8.3		*o*-Dichlorobenzene	33	95	1	61	40	*cis*- + *trans*-5-ethylidenebicyclo-[2.2.1]-2-heptene (40)
$IrCl(CO)(Ph_3P)_2$	7.7		None	100	105	170	72	60	*cis*-4-Ethylidenecyclohexene (28) *trans*-4-Ethylidenecyclohexene (20) *cis*-3-Ethylidenecyclohexene (8) *trans*-3-Ethylidenecyclohexene (12)
	6.2		None	100	100	41	9.5	9	Ethylidenecyclohexane (9)

[a] Purified by distillation under nitrogen. No attempt was made to remove peroxides with silica gel. [b] A 1:1 mixture of benzene and ethanol. [c] A 1:10 mole ratio of $PtCl_2(Ph_3P)_2$ and $SnCl_2$ were used. Reactions were run under 100 psi of hydrogen.

which the concentration of I was varied from 10^{-3} to 10^{-4} M which demonstrated that from 20 to 80% of reaction the isomerization is first order in ruthenium complex and has a pseudo-first-order rate constant of 4.6×10^{-2} sec^{-1}.

During the course of the isomerization in benzene–ethanol the original complex I was converted to an orange carbonyl complex IV which was precipitated by addition of excess pentane to the solution after reaction was complete. Although the infrared spectrum, elemental analysis, and catalytic activity of IV suggest that it is similar to II, the molecular weight and melting point are considerably higher.

The ruthenium(II)-catalyzed isomerization of 4-vinylcyclohexene may also be carried out in polar aprotic solvents such as *o*-dichlorobenzene or *N*,*N*-dimethylacetamide (DMA). In all cases high yields (92–99%) of the 3-ethylidenecyclohexenes can be achieved after long reaction times, and substantial quantities (22–28%) of the 4-ethylidenecyclohexenes may be obtained by interrupting the reaction at an intermediate stage. The results of these reactions are summarized in Table I.

C. Reactions Catalyzed by $IrCl(CO)(Ph_3P)_2$.—As in the previous case, Vaska's complex catalyzes the isomerization of 4-vinylcyclohexene in a selective and stepwise manner. The maximum attainable yield of the unconjugated 4-ethylidenecyclohexenes is 48% when the neat diene is isomerized at 105°. The cis/trans ratio of the 4-ethylidenecyclohexenes at their maximum value is 1.9, whereas the cis/trans ratio of the 3-ethylidenecyclohexenes is 0.81. The reaction may be run either in the neat diene or in solution (Table I). Rates are generally much slower than with the ruthenium or platinum catalysts. An induction period is observed during which the active species may form; however, when the reaction mixture is treated with excess pentane at the conclusion of the reaction, the starting complex, $IrCl(CO)(Ph_3P)_2$, is recovered in 80–90% yield. Ethylbenzene and the ethylcyclohexenes are minor products resulting from a slow disproportionation reaction[17] as in the ruthenium(II) system. Results of these reactions are summarized in Table I.

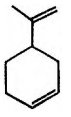
Isomerization of 5-Vinylnorbornene.—The isomerization of 5-vinylbicyclo[2.2.1]-2-heptene, a compound which is easily obtained from Diels–Alder dimerization of butadiene and cyclopentadiene, occurs in the presence of catalytic amounts of either $RuCl_2(Ph_3P)_3$ or the platinum–tin system under conditions similar to those used for 4-vinylcyclohexene (eq 2). When a

(2)

10:1 mixture of $SnCl_2$ and $PtCl_2(Ph_3P)_2$ in methanol was used under hydrogen pressure, a 40% yield of ethylidenenorbornene was obtained after 1 hr. This reaction was not so selective as the isomerization of 4-vinylcyclohexene since isomers other than ethylidenenorbornene were formed in 20% yield. The ruthenium(II) catalyst gave far slower rates in 1:1 benzene–ethanol than with 4-vinylcyclohexene. The

(17) J. E. Lyons, *Chem. Commun.*, 564 (1969).

yield of ethylidenenorbornene obtained after 21 hr at 80° was only 3.6%. The color change during reaction and the nature of the complex formed showed that when no effort was made to remove hydroperoxides a carbonyl complex was again formed. Presumably the steric requirements are such that the rate of isomerization of 5-vinylbicyclo[2.2.1]-2-heptene was slow even in the presence of the ruthenium–carbonyl complex. The carbonyl complex formed in 60% yield was an orange solid having an infrared spectrum similar to those of II and IV (ν_{Ru-Co} ~1980 cm^{-1}; ν_{PPh_3} ~1090 cm^{-1}). Attempts to selectively isomerize *d*-limonene V with both the ruthenium(II) catalyst and the platinum–tin system met with little success. The presence of a



V

methyl substituent on the vinyl double bond apparently caused the reaction rate to be slow. This resulted in competitive double bond migrations both within the ring and of the exocyclic double bond which was being formed. In the case of the $RuCl_2(Ph_3P)_3$-catalyzed reaction, the carbonyl complex which was recovered was a bright orange solid having infrared absorption bands at 2030 (m), 1920 (s), and 1090 cm^{-1} (s).

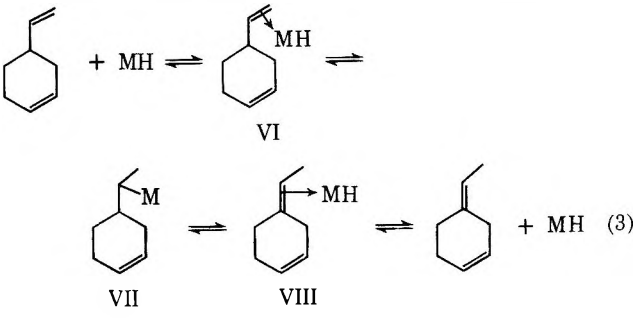
Isomerization of Vinyl- and Allylcycloalkanes. — Vinylcyclohexane and vinylcyclopentane were isomerized to give high yields of ethylidenecyclohexane[18] and ethylidenecyclopentane, respectively, in the presence of catalytic quantities of $RuCl_2(Ph_3P)_3$ (I). A 10^{-3} *M* solution of the ruthenium(II) complex in neat vinylcyclohexane was warmed at 100° for 112 hr. After this time, the reaction mixture contained vinylcyclohexane (5%), ethylidenecyclohexane (94%), and an unidentified product (1%). A similar experiment using vinylcyclopentane gave ethylidenecyclopentane (92%), three unidentified products (7%), and starting material (1%). These reactions occur at a somewhat faster rate in *N*,*N*-dimethylacetamide than in the neat olefin. Vinylcyclohexane reacts to form ethylidenecyclohexane in 99% yield after 4 hr in benzene–ethanol at 80° in the presence of I. An induction period is observed followed by an interval, from 20 to 60% of reaction, where the reaction appears to be pseudo zero order in olefin. Vaska's complex is a catalyst for the reaction as well; however, rates are much slower than with the ruthenium complex. In cases where I was used, traces of oxygen or oxygen-containing impurities promoted reaction, and whenever high catalytic activity was observed, ruthenium carbonyls were isolated after reaction. The results of these experiments appear in Table I. Allylcyclopentane was isomerized in benzene–ethanol solutions containing I over a 22-hr period to a mixture of propylidenecyclopentane (79%) and propylcyclopentene (21%). Allylcyclohexane, however, yielded the *cis*- and *trans*-propenylcyclohexanes (92%), and isomer which might be propylidenecyclohexane (3%) and unreacted starting material (5%) under similar conditions.

(18) Iron carbonyl has been found to catalyze this reaction in an unselective manner: T. A. Manuel, *J. Org. Chem.*, **27**, 3941 (1962).

Discussion

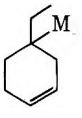
The selective formation of an exocyclic double bond in isomerization reactions of vinyl-substituted ring compounds using transition metal complexes is an example of a rather high degree of kinetic control. The type of selectivity which we have observed, in contrast to what is found in acid- and base-catalyzed isomerizations, may be largely the result of steric interactions in the organometallic intermediates which are formed during the course of the reaction.

The first step in the transition metal catalyzed isomerization is presumed to be abstraction of hydrogen from the medium to produce a metal hydride[4,19] which may form a π bond[20] with the olefin. It has been argued that, although the presence of alkyl substituents on a double bond need not have a large effect on the rate of π-complex formation with a hydrido complex, the alkyl groups can have a profound effect on the rate of the subsequent hydrogen transfer step to form a square planar alkyl complex due to interactions with the bulky phosphine ligands.[3,21] For this reason it is possible to selectively hydrogenate the vinyl group of 4-vinylcyclohexene using either $RuCl_2(Ph_3P)_3$[3] (I) or the $PtCl_2(Ph_3P)_2$–$SnCl_2$ catalyst system.[4] The probable mechanism of the selective isomerization of 4-vinylcyclohexene by transition metal complexes is schematically represented in eq 3. It is felt that the essential feature that determines the selectivity which



(3)

we have observed in this system is the reluctance of intermediate VIII to rearrange to the metal alkyl IX, a transformation which is expected to be sterically un-



IX

favorable.[3,21] In addition, the π complex VIII should be somewhat more hindered and perhaps less stable than VI. Electronic effects apparently operate in the same direction as steric effects since it is known that electron-releasing alkyl substituents on an olefinic double bond tend to decrease the stability of platinum–olefin complexes.[22] In support of this reasoning, it is known that the equilibrium constants for formation of silver nitrate–olefin complexes with vinylcyclohexane, ethylidenecyclohexane, and 1-ethylcyclohexene

(19) J. Halpern, *Discuss. Faraday Soc.*, 13 (1968).

(20) B. Hudson, P. C. Taylor, D. E. Webster, and P. B. Wells, *ibid.*, 37 (1968), and references cited therein.

(21) C. O'Connor and G. Wilkinson, *J. Chem. Soc. A*, 2265 (1968).

(22) M. L. H. Green, "Organometallic Compounds," Vol. 2, Methuen & Co., London 1968, p 21.

are 5.9, 1.6, and 0.5 l./mol, respectively.[23] Thus, it is evident that coordination of an olefin to a metal center is quite sensitive to the degree of alkyl substitution even when the metal is not surrounded by bulky phosphine ligands. Nonetheless, it seems that bulky ligands substantially enhance the selectivity of the catalytic isomerization of vinylcycloalkanes. This is apparent from a comparison of $Fe(CO)_5$ and the catalysts reported in Table I. Iron carbonyl isomerizes vinylcyclohexane to a mixture of ethylcyclohexene and ethylidenecyclohexane,[16] whereas complex I is highly selective for formation of ethylidenecyclohexane in 99% yield.[24]

It should be emphasized that eq 3 is only a schematic representation and not a precise mechanism. Although it is known that in reactions of 4-vinylcyclohexene with rhodium(I)[25] and platinum(II)[26,27] chlorides the diene behaves as a bidentate ligand, it is not certain whether platinum(II) and ruthenium(II) *phosphine* complexes would incorporate 4-vinylcyclohexene as a monodentate or a bidentate ligand. Since reaction initially occurs at the vinyl group, a second coordinate π bond is omitted in eq 3.

Finally, our observation that air and hydroperoxides enhance the rate of olefin isomerization in the presence of $RuCl_2(Ph_3P)_3$, I, and that a carbonyl complex, II, $RuCl_2(Ph_3P)_2(CO)(C_8H_{12})$, is formed in 40–60% yield, requires additional comment. The addition of small amounts of oxygen has been found to promote extensive double bond isomerization during the hydrogenation of olefins catalyzed by $RhCl(Ph_3P)_3$ in benzene–ethanol.[28] An oxidized rhodium complex having an infrared band at 850 cm^{-1} characteristic of metal peroxide has been implicated in the double bond isomerization reaction.[28] We have observed small amounts of solids formed in the $RuCl_2(Ph_3P)_3$-catalyzed reactions whose infrared spectra indicate the presence of metal peroxide; however, the carbonyl complexes which we isolate are usually free of infrared bands in the region from 800 to 900 cm^{-1}. In the case of the $RuCl_2(Ph_3P)_3$-catalyzed isomerizations in neat olefin which we have examined, the reaction rate when air was added was rapid compared with reactions run in the absence of air. The recovery of a carbonyl complex II when air was added but only an olefin complex III when air was absent strongly suggest that the CO arises from an interaction between oxygen and the olefin. It is known that rhodium(I) complexes catalyze (a) oxidation of olefins in the allylic position,[29] (b) decomposition of hydroperoxides to form alcohols,[30] (c) rearrangement of allyl alcohol to give propionaldehyde,[31] and (d) decarbonylation of aldehydes to form CO and hydrocarbons.[32] A series of similar reactions occurring at the ruthenium center could be offered as a tentative explanation for the formation of CO complexes on addition of air or hydroperoxides to olefin solutions of $RuCl_2(Ph_3P)_3$. A complex in which CO has replaced a phosphine ligand would be expected to be more reactive toward olefin on steric grounds. Not only would the metal center be more accessible to entering olefin but the trans-directing influence of a CO is somewhat greater than that of a phosphine ligand[33] and reactions of hydride or alkyl ligands (eq 3) trans to CO would occur at an accelerated rate. It is reasonable, therefore, that complex II is capable of forming the active species, possibly a metal hydride (eq 3), more readily than complex I. Speculation regarding the origin of II as well as the rationale for its greater catalytic activity must be regarded as highly tentative at this point.

(23) M. A. Muhs and F. T. Weiss, *J. Amer. Chem. Soc.*, **84**, 4697 (1962).

(24) In further support of this reasoning, it has recently been shown that, in the absence of phosphine ligands, $RhCl_3$ in refluxing ethanol catalyzes the *unselective* isomerization of 4-vinylcyclohexene to give a mixture of products including the ethylcyclohexadienes and products of disproportionation: C. J. Attridge and P. J. Wilkinson, *Chem. Commun.*, 620 (1971).

(25) (a) G. Winkaus and G. Singer, *Chem. Ber.*, **99**, 3602 (1966); (b) J. F. Young, R. D. Gillard, and G. Wilkinson, *J. Chem. Soc.*, 5177 (1964).

(26) R. Palumbo, A. Penzi, A. Panunzi, and G. Paiaro, *J. Amer. Chem. Soc.*, **91**, 3874 (1969).

(27) E. Kuljian and H. Frye, *Z. Naturforsch., B*, **20**, 204 (1965).

(28) R. L. Augustine and J. F. VanReppen, *Chem. Commun.*, 495 (1970); *ibid.*, 497 (1970).

(29) J. E. Baldwin and J. C. Swallow, *Angew. Chem., Int. Ed. Engl.*, **8**, 601 (1969).

(30) B. Bierling, K. Kirschke, H. Oberender, and M. Schuly, *Z. Chem.*, **9**, 105 (1969).

(31) J. E. Lyons, unpublished results.

(32) J. Tsuji and K. Ohno, *Syn.*, 157 (1969)

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared spectra were determined on Perkin-Elmer infrared spectrophotometers Models 137-B and 21. Nmr spectra were run using Varian T-60 and A-60 spectrometers. Gas chromatographic analyses were carried out on a Perkin-Elmer Model 226 instrument equipped with a 150-ft capillary column coated with UCON 550-X. Fractional distillations were performed on a Nester-Faust 18-in. semimicro spinning-band column equipped with a stainless steel band. Elemental analyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Molecular weights were determined by vapor pressure osmometry using a Hewlett-Packard Mechrolab Model 302 osmometer.

Materials.—Vinylcyclopentane, vinylcyclohexane, allylcyclopentane, allylcyclohexane, and 4-vinylcyclohexene all in 99% purity or greater were obtained from Aldrich Chemical Co. Vinylnorbornene was obtained from Union Carbide Corp. Dichlorobis(triphenylphosphine)platinum(II) and chlorocarbonylbis(triphenylphosphine)iridium(I) were purchased from Strem Chemical Co. and dichlorotris(triphenylphosphine)ruthenium(II) was prepared according to the method of Wilkinson.[3]

Isomerizations Using $RuCl_2(Ph_3P)_3$ as Catalyst. Isomerization of 4-Vinylcyclohexene in Benzene–Ethanol.—A solution of benzene (16.0 ml), ethanol (16.0 ml), and 4-vinylcyclohexene (16.0 ml) was stirred magnetically at 80 ± 1° under nitrogen. Each of the components of the solution had been deaerated by bubbling a rapid stream of nitrogen through them for 30 min prior to mixing and all transfers were made in a nitrogen atmosphere. $RuCl_2(Ph_3P)_3$, 0.3004 g, was added and dissolved within 3 min to give a dark red solution. Aliquots were syringed from the stirred solution at 15-min intervals and analyzed by gas chromatography.[34] Isomerization was complete within 6 hr giving *cis*-3-ethylidenecyclohexene, 54%, and *trans*-ethylidenecyclohexene, 43%, as the major products (Table I, Figure 1). From the linear portion of the kinetic curve (Figure 1), a pseudo-first-order rate constant of 4.15×10^{-2} sec^{-1} was calculated.

The reaction mixture, a clear orange solution, was allowed to cool to room temperature and then poured into 300 ml of deaerated *n*-pentane which had been percolated through activated silica gel under nitrogen. The pentane solution was vigorously stirred under nitrogen and within several seconds an orange solid began to precipitate. The solid was allowed to settle over a 2-hr period, and then the mixture was filtered through sintered glass using nitrogen pressure. An orange solid, IV, 0.16 g, mp ~190° dec, was collected, washed with 5 ml of deaerated pentane,

(33) F. Basolo and R. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., p 355.

(34) It was established using pure standards that no isomerization of products or starting material occurred during glpc analysis of product mixtures. Standardization was performed with the chromatograph used for analysis of reaction mixtures containing dissolved complexes, as well as with an instrument which had not been used for analysis of solutions containing metal complexes. Results were identical. Thus, the possibility of appreciable isomerization in the injection port due to decomposed complexes was eliminated.

and dried under vacuum. An ir of IV (25% solution in deaerated methylene chloride) exhibited sharp, strong bands at 1994 (ν_{Ru-CO}) and 1092 cm^{-1} (ν_{Ph_3P}). The nmr spectrum (Varian T-60) of a 25% solution of IV in deuteriomethylene chloride showed an intense signal at δ 7.3 due to aromatic protons and several broad multiplets from δ 3.0 to 0.8 attributed to allylic and other aliphatic protons. No signal was observed which could be assigned to vinyl protons; however, the area around δ 5.3 was obscured by the residual protons of deuteriomethylene chloride. The ratio of aromatic to aliphatic protons was approximately 3.5:1. No signal was observed in the region τ 10–30, whereas a 25% solution of $RuHCl(Ph_3P)_3$ in deuteriomethylene chloride showed a well-defined quartet at τ 28. It is concluded that the complex IV is not a ruthenium hydride but a carbonyl complex.

Anal. Calcd for $C_{45}H_{42}Cl_2OP_2Ru$: C, 64.90; H, 5.08; Cl, 8.51; P, 7.44; Ru, 12.14; mol wt, 833. Found: C, 64.79; H, 5.14; Cl, 9.02; P, 7.90; Ru, 12.18; mol wt. 1022.

The pentane solution was flash evaporated away from a small amount of dissolved solid at room temperature under vacuum and the clear volatile material distilled on a semimicro spinning band column giving 12.0 g [bp 147° (lit.[9] 146–148°), >99% glpc purity] of a mixture of *cis*- and *trans*-3-ethylidenecyclohexene. The pure isomers were isolated by gas chromatography (30 ft × 0.25 in. column packed with 10% cyanopropylphenylsilicone on 60–80 mesh Chromosorb P). The configurations were assigned by a comparison of infrared, uv, and nmr spectra with literature[9,12] values. For the cis isomer we observed a uv absorption maximum at 234 mμ (ϵ 17,200) [lit.[9] 237 mμ (ϵ 17,400)] and an nmr signal at δ 3.6 (doublet) (lit.[12] δ 3.63, d) characteristic of the internal vinyl proton of the cis structure.[12] The rest of the nmr and the infrared spectrum are identical with those reported in the literature.[9] The trans isomer exhibited uv maxima at 228 mμ (ϵ 15,000) and 234 (15,500) [lit.[9] 229 mμ (ϵ 15,600), 235 (15,100)]. The nmr spectrum showed a signal at δ 4.0 (lit.[12] δ 4.00) attributed to the internal vinyl proton of *trans*-3-ethylidenecyclohexene and the rest of the spectrum was consistent with this assignment. Similar experiments were run using 0.0381, 0.0500, and 0.2968 g of $RuCl_2(Ph_3P)_3$. From plots of the linear portions of the kinetic curves (*i.e.*, Figure 2), pseudo-first-order rate constants of 4.55 × 10^{-2}, 4.81 × 10^{-2}, and 4.64 × 10^{-2} sec^{-1}, respectively, were calculated. The average rate constant for the four runs was 4.6 × 10^{-2} sec^{-1}.

Isomerization of 4-Vinylcyclohexene in Aprotic Solvents.—Using a procedure and quantities of 4-vinylcyclohexene and $RuCl_2(Ph_3P)_3$ similar to those in the above example, isomerizations were carried out in 32.0 ml of DMA at 95° and in 32.0 ml of *o*-dichlorobenzene at 100°. The results of the glpc analyses are listed in Table I.

Isomerization of 4-Vinylcyclohexene in the Absence of Solvent.—A solution of 0.700 g of $RuCl_2(Ph_3P)_3$ in 100 ml of 4-vinylcyclohexene was stirred under nitrogen for 20 hr at 100°. Gas chromatographic analysis of the reaction mixture showed the formation of *cis*-3-ethylidenecyclohexene (52%) and *trans*-3-ethylidenecyclohexene (42%). Addition of the cooled orange solution to 300 ml of deaerated *n*-pentane with stirring caused a tan solid to precipitate. The mixture was filtered after standing under nitrogen 2 hr giving a tan solid II which was washed with *n*-pentane and dried in a stream of nitrogen, 0.405 g, mp 115–116°. The ir spectrum (ν_{Ru-CO} ~1990, ν_{Ph_3P} ~1090 cm^{-1}, Nujol) and nmr spectrum in CD_2Cl_2 are similar to those of IV. The elemental analysis and molecular weight are consistent with the structure $RuCl_2(CO)(Ph_3P)_2(C_8H_{12})$.

Anal. Calcd for $C_{45}H_{42}Cl_2OP_2Ru$: C, 64.90; H, 5.08; Cl, 8.51; P, 7.44; Ru, 12.14; mol wt, 833. Found: C, 64.74; H, 5.13; Cl, 8.94; P, 7.45; Ru, 12.69; mol wt, 833.

Effect of Air and *tert*-Butyl Hydroperoxide on the $RuCl_2(Ph_3P)_3$-Catalyzed Isomerization of 4-Vinylcyclohexene. Isomerization of Peroxide-Free Olefin.—4-Vinylcyclohexene was distilled under nitrogen and then passed through a column of freshly activated (190° at 1 mm for 18 hr) silica gel under nitrogen. The olefin, 40 ml, was transferred through a syringe into a clean dry reaction flask under nitrogen containing 0.251 g of $RuCl_2(Ph_3P)_3$ and the mixture heated at 100° for 18 hr. After this time a large amount of a dark brown complex had still not dissolved and the olefin solution was yellow. Analysis by gas chromatography showed that nearly 99% of the starting 4-vinylcyclohexene had remained unchanged. The reaction mixture was filtered giving 0.06 g of dark brown complex having an infrared spectrum similar to that of the starting complex. The yellow solution was allowed to stand at room temperature for 2 hr during which time a gold solid (III) crystallized. It was filtered, washed, and dried under vacuum for 3 hr. III, 0.12 g, mp 110–113°, exhibited bands in the ir at 6.4 (ν_{olefin} ?) and 9.1 μ (ν_{Ph_3P}) but no bands attributable to Ru–CO. The elemental analysis was consistent with a ruthenium–phosphine complex having a ratio of Cl/P of >1.

Anal. Found: C, 65.90; H, 5.74; Cl, 10.33; P, 7.01; Ru, 11.73.

Isomerization Using Peroxide-Free Olefin with Added Air.—A reaction was carried out in a manner identical with that described in the above example except that air was bubbled through the olefin for 2 min just prior to contact with the catalyst. The complex fully dissolved to give a deep orange solution and after 18 hr at 100°, isomerization was at least 98% (glpc analysis) complete. The products were mainly *cis*- and *trans*-3-ethylidenecyclohexene. Addition of excess pentane to the cool orange solution precipitated 0.10 g of a tan solid, mp 115–117°, exhibiting bands in the infrared at ~1990 and ~1090 cm^{-1} (Nujol mull).

Isomerization Using Peroxide-Free Olefin with Added *tert*-Butyl Hydroperoxide.—A reaction was run similar to those cited above using distilled, chromatographed 4-vinylcyclohexene to which 0.20 ml of *tert*-butyl hydroperoxide had been added. The complex dissolved slowly over several hours to give an orange solution. After 22 hr reaction was 90% complete and a tan complex, 0.09 g, mp 115–119°, ν_{Ru-CO} 1990 cm^{-1} (Nujol), was recovered as before.

Isomerization of Peroxide-Free Olefin by Complex II.—Distilled, silica gel treated 4-vinylcyclohexene, 10 ml, and complex II, 0.070 g, were heated under nitrogen at 100° for 18 hr. The complex dissolved to give a deep orange solution from which II, mp 115–120°, ν_{Ru-CO} 1990 cm^{-1}, could be precipitated with excess pentane. Analysis of the reaction mixture showed at least 99% of the olefin had isomerized. The major products were *cis*- and *trans*-3-vinylcyclohexene (94%). In similar experiments, complex IV was shown to be catalytically active both in benzene–ethanol and in the neat diene.

Isomerization of Other Vinyl Compounds.—Vinylcyclohexene, vinylcyclopentane, and 5-vinylnorbornene were isomerized either neat or in DMA or benzene–ethanol solutions. Reactions were carried out in the same way as with 4-vinylcyclohexene. Conditions and results are summarized in Table I.

Isomerization of Allylcyclopentane.—The catalyst, $RuCl_2(Ph_3P)_3$, 0.062 g, was added to a solution of allylcyclopentane, 3.0 ml, benzene, 3.0 ml, and ethanol, 3.0 ml, all components of which had been deaerated by bubbling nitrogen through them for 30 sec. The solution was stirred for 22 hr under nitrogen at 70°. Flash evaporation of volatiles left 0.1 g of a gummy solid exhibiting a deep ir band at ~1980 cm^{-1} (Nujol). Gas chromatographic analysis of the volatiles showed two reaction products, propylidenecyclopentane (79%) and an unidentified product, possibly 1-propylcyclopentene (21%). Microdistillation gave 1.0 ml of an olefinic material whose nmr spectrum confirmed that it was propylidenecyclopentane.

Isomerizations Using $IrCl(CO)(Ph_3P)_2$ as Catalyst.—Reactions were carried out in the neat olefins in a manner analogous to reactions described above. Conditions and results are given in Table I. Addition of excess pentane to reaction mixtures resulted in recovery of only $IrCl(CO)(Ph_3P)_2$ in 80–90% yield.

Isomerizations Catalyzed by $PtCl_2(Ph_3P)_2$–$SnCl_2$ under Hydrogen Pressure.—A mixture of $PtCl_2(Ph_3P)_2$, 0.0656 g, $SnCl_2$, 0.167 g, deaerated methanol, 7.0 ml, and deaerated 4-vinylcyclohexene, 3.0 ml, was stirred magnetically in a Fisher-Porter aerosol tube connected to a hydrogen pressure line. Fitted to the Fisher-Porter tube was a capillary sampling device permitting periodic removal of liquid samples under pressure. Solution occurred when the stirred reaction mixture was heated at 65° under 100 psi of hydrogen. Samples were removed periodically and analyzed by gas chromatography (Figure 1). After 6 hr the reaction mixture contained *cis*-4-ethylidenecyclohexene (22%), *trans*-4-ethylidenecyclohexene (33%), *cis*-3-ethylidenecyclohexene (3%), *trans*-3-ethylidenecyclohexene (7%), and 4-vinylcyclohexene (35%).

A similar reaction was run on a scale 10 times the size of the above experiment. Results were nearly identical and are reported in Table I. The reaction mixture was distilled on a semimicro spinning-band column under nitrogen. A constant-boiling fraction (4.5 ml, bp 141°, $n^{20}D$ 1.4812, >99% glpc purity) was shown by nmr to be *cis*- and *trans*-4-ethylidenecyclohexene: δ 5.63 (singlet, 2 protons, H>C=C<H), 5.23 (quartet, 1 proton >C=C<H), 2.70 (singlet, 2 protons =CCH$_2$C=), 2.17 (broad,

4 protons, $=CCH_2$), 1.58 (doublet, 3 protons, CH_3); all signals showed some fine structure. Although it was possible to separate the *cis*- and *trans*-4-ethylidenecyclohexanes using a 150-ft capillary column coated with UCON 550-X, the packed column used for collecting pure *cis*- and *trans*-3-ethylidenecyclohexene was not efficient enough for collection of the pure isomers of 4-ethylidenecyclohexene. Stereochemical assignment was made by inspection of the kinetic curve of the $PtCl_2(Ph_3P)_2$–$SnCl_2$-catalyzed isomerization. It was assumed that the isomer formed in higher yield was the precursor to *trans*-3-ethylidenecyclohexene and the isomer formed in lower yield was the precursor to *cis*-3-ethylidenecyclohexene. This assumption was consistent with an experiment which showed that geometrical isomerization of the *cis*- and *trans*-4-ethylidenecyclohexenes obtained from the Ru(II)-catalyzed isomerizations was very slow relative to double bond isomerization to the 3-ethylidenecyclohexenes.

Registry No.—$RuCl_2(Ph_3P)_3$, 15529-49-4; 4-vinylcyclohexene, 100-40-3; $RuCl_2(CO)(Ph_3P)_2(C_4H_{12})$, 12521-89-0; allylcyclopentane, 3524-75-2; $IrCl(CO)(Ph_3P)_2$, 14871-41-1; $PtCl_2(Ph_3P)_2$, 10199-34-5; *cis*-4-ethylidenecyclohexene, 30318-84-4; *trans*-4-ethylidenecyclohexene, 30319-25-6; 5-vinylnorbornene, 3048-64-4; vinylcyclohexane, 695-12-5; vinylcyclopentane, 3742-34-5.

Acknowledgment.—The author gratefully acknowledges the assistance of Miss Caroline Link who carried out much of the experimental work, and Mrs. Ruth Jenkins and Mr. Arthur Raymond for gas chromatographic analyses.

The Condensation of α Olefins with Paraformaldehyde, Acetylating Agents, and Hydrogen Chloride[1]

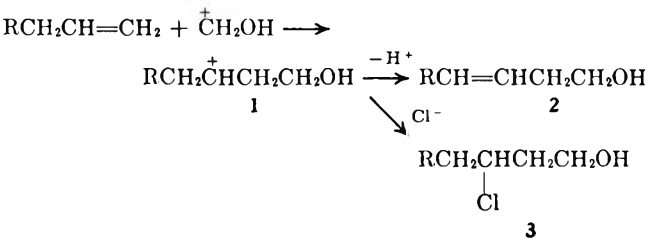
PAUL R. STAPP

Phillips Petroleum Company Research and Development Department, Bartlesville, Oklahoma 74003

Received November 30, 1970

Reaction of 1-hexene, paraformaldehyde, and either acetonitrile, acetic anhydride, or acetyl chloride, with hydrogen chloride at −60 to −70° gave principally acyclic materials. The major component (30–50% yield) was identified as a *cis*- and *trans*-3-heptenyl acetate (**8**) mixture, and smaller quantities of *cis*- and *trans*-4-chloro-3-propyltetrahydropyran (**9**) and 3-chloro-1-heptyl acetate (**11**) were found. In addition, 20–40% yields of 2-chlorohexane (**4**) were obtained and minor amounts of 2-methyl-3-hexen-1-yl acetate (**7**) and 3-chloro-2-methyl-1-hexyl acetate (**10**) were separated and identified. Similar product mixtures were obtained from propylene. This procedure provides a convenient one-step synthesis of homoallylic acetates from readily available 1 olefins.

Recent articles[2-5] have described a modification of the Prins reaction in which various types of olefins were condensed with paraformaldehyde and hydrogen halides at low temperatures. The nature of the product was dependent on the structure of the starting olefin, but in each case it appeared that it was derived from initial electrophilic attack of protonated formaldehyde upon the double bond. Cyclic deprotonation[2] of the



adduct **1** led to the homoallylic alcohol **2**, a precursor to other observed products, while chloride ion capture gave the corresponding 3-chloro-1-alkanol (**3**).

During the study of extensions of the modified Prins reaction it has been observed that, if the reaction is carried out in the presence of acetylating agents, predominantly linear materials are produced. In the initial experiment it was found that 1-hexene, paraformaldehyde, and acetonitrile reacted smoothly with hydrogen chloride in methylene chloride at −60 to −70°. Glpc analysis of the reaction mixture after an aqueous work-up showed that, in addition to low yields of a mixture of *cis*- and *trans*-4-chloro-3-propyltetrahydropyran (**9**), 3-chloro-1-heptyl acetate (**11**), and 40% of 2-chlorohexane (**4**), a rather substantial quantity of still another compound was formed (40% yield). This was purified by fractionation and identified as 3-heptenyl acetate (**8**) by elemental analysis and infrared, nmr, and mass spectra. Analogous experiments substituting acetyl chloride or acetic anhydride for the acetonitrile gave similar reaction mixtures. Treatment of a solution of acetonitrile in methylene chloride with hydrogen chloride, followed by addition of the other reactants and again introducing hydrogen chloride, gave a product mixture indistinguishable from that obtained using free acetonitrile. Similar experiments with propylene gave mixtures containing 3-butenyl acetate, 4-chlorotetrahydropyran, and 3-chloro-1-butyl acetate in somewhat lower yields, presumably due to losses because of greater water solubility during the aqueous work-up. Although the yields of unsaturated esters are moderate by this procedure, it does represent a simple one-step synthesis of homoallylic acetates from readily available starting materials.

In the condensations with 1-hexene, several minor components were consistently present in varying amounts depending on the reaction conditions. These were separated by preparative glpc and identified by nmr, infrared, and mass spectra. Scheme I summarizes the compounds observed in a typical experiment and Table I shows typical product distributions under identical conditions with the different acetylating agents.

A single sharp peak (on both UCON and Carbowax glpc columns) appeared to be a mixture of chloromethyl acetate (**5**) and 2-hexyl acetate (**6**), in approximately

(1) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 29–April 2, 1971.
(2) P. R. Stapp, *J. Org. Chem.*, **34**, 479 (1969).
(3) P. R. Stapp, *ibid.*, **34**, 1143 (1969).
(4) P. R. Stapp and D. S. Weinberg, *ibid.*, **34**, 3592 (1969).
(5) P. R. Stapp and J. C. Randall, *ibid.*, **35**, 2943 (1970).

SCHEME I

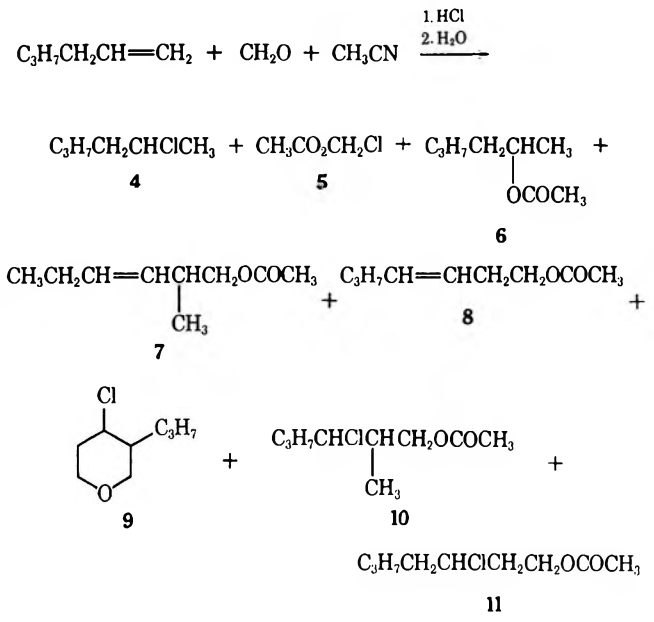


TABLE I

REACTION OF 1-HEXENE, PARAFORMALDEHYDE, ACETYLATING AGENTS, AND HYDROGEN CHLORIDE AT −65°

$$C_3H_7CH_2CH{=}CH_2 + CH_2O + CH_3Z \xrightarrow{HCl^a} \text{product}$$

	—Z = -COCl—		—Z = -CO2CO—		—Z = -CN—	
	Yield,[b]	Yield,[c]	Yield,[b]	Yield,[c]	Yield,[b]	Yield,[c]
Product	%	%	%	%	%	%
4	41		41		24	
5 + 6	Trace	Trace	Trace	Trace	Trace	Trace
7	5	7	4	6	3	4
8	21[d]	32	31[e]	47	34[f]	51
9	10	30	8	23	6	18
10	2	3	1	2	2	3
11	6	9	7	10	10	15
	85	81	92	88	79	91

[a] Reactions were run using 3.0 mol of 1-hexene, 2.0 mol of 97% paraformaldehyde, and 2.0 mol of acetylating agent. [b] Based on olefin. [c] Based on paraformaldehyde. [d] Contained 66% trans and 34% cis. [e] 61% trans. [f] 60% trans.

equal proportions, by a combination of infrared and nmr spectra. 2-Methyl-3-hexen-1-yl acetate (**7**) and 3-chloro-2-methyl-1-hexyl acetate (**10**) were separated and the structures assigned by spectroscopic methods (see Experimental Section) and their mode of formation. In this system, as in the earlier modification,[2] low temperatures favored the reaction; very little reaction was observed upon treatment of a mixture of acetic anhydride, 1-hexene, and paraformaldehyde with hydrogen chloride at 0–10°.

In this set of runs very little heavier material was produced and material balances are reasonably good. Neither methylene diacetate[6] nor 4-butyl-1,3-dioxane[7] were present in detectable amounts by glpc (each was resolved on spiking the reaction mixtures with authentic samples). It is of particular interest that the yield of 4-chloro-3-propyltetrahydropyran (**9**) is relatively low under these conditions. In the earlier work[2] yields of 80–90% were found in the absence of acetylating agent. In Table II, however, which shows

(6) M. Descudé, *Bull. Soc. Chim. Fr.*, **27**, 867 (1902).
(7) P. R. Stapp, *J. Org. Chem.*, **35**, 2419 (1970).

TABLE II

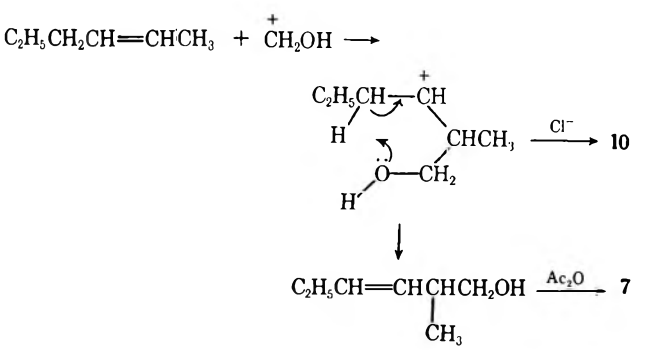
VARIATION OF OLEFIN/ACETIC ANHYDRIDE RATIO[a]

	3.0 mol of 1-hexene, 2.0 mol of acetic anhydride		2.08 mol of 1-hexene, 2.0 mol of acetic anhydride		2.0 mol of 1-hexene, 3.0 mol of acetic anhydride	
	Yield,[b]	Yield,[c]	Yield,[b]	Yield,[c]	Yield,[b]	Yield,[c]
Product	%	%	%	%	%	%
4	41		39		39	
7	4	6	4	4	3	3
8	31	47	29	30	22	22
9	8	23	14	30	20	40
10	1	2	2	2		
11	7	10	8	9	13	13

[a] Reactions were run using 2.0 mol of 97% paraformaldehyde. [b] Based on olefin. [c] Based on paraformaldehyde.

the effect of variation in olefin/acetylating agent ratio, higher concentrations of acetylating agent appear to increase the rate of formation of tetrahydropyran relative to acyclic product. The rather high proportion of **4** in the system using an excess of acetylating agent is also rather surprising.

Mechanism.—We have previously proposed[2] a mechanism to account for the production of **9** and 3-chloro-1-heptanol in the low temperature modification of the Prins reaction and have established that 3-chloro-1-alkanol formation from *cis*- and *trans*-2-butene is about 80% stereoselective.[4] Superficially, it appears tempting to extrapolate the same line of reasoning to the present system. Thus, formation of 4-chlorotetrahydropyrans occurs *via* cyclization of an unstable chloromethyl ether of the intermediate homoallylic alcohol **2**.[2,8] In the present case, the homoallylic alcohol is acetylated by either acetyl chloride, acetic anhydride, or an acetonitrile/hydrogen chloride complex,[9] giving **8** in competition with chloromethyl ether formation. Similarly, chloride ion capture before deprotonation would give 3-chloro-1-heptanol, which is acetylated to give **11**. Formation of the methyl-branched compounds **7** and **10** is more difficult to explain. It may be that 1-hexene is slowly isomerized to 2-hexene in the reaction medium and a similar process occurs as in the production of the open chain materials.



No evidence was found for the production of branched chain materials in the earlier work[2] nor was 3-chlorohexane (from competitive HCl addition to 2-hexene) detected in this study. It is possible that the present system, presumably of higher dielectric constant, would tend to increase the rate of isomerization

(8) J. Colonge and P. Boisde, *Bull. Soc. Chim. Fr.*, **23**, 824 (1956).
(9) The structure of the reaction product of acetonitrile with 2 mol of hydrogen chloride has been formulated as either acetimidoyl chloride hydrochloride, $CH_3CCl{=}NH_2^+Cl^-$, or a nitrillium salt, $CH_3C{\equiv}NH^+HCl_2^-$. A literature survey as well as evidence favoring the latter structure is discussed by G. J. Janz and S. S. Danyluk, *J. Amer. Chem. Soc.*, **81**, 3850 (1959).

of the starting 1-hexene but that the concentration of 3-chlorohexane produced, if any, might still be so low as to escape detection. Alternatively, the rate of attack of protonated formaldehyde upon the internal olefin may be sufficiently fast that competitive HCl addition is not observed. The observation that the ratio of trans to cis olefin in **8** is approximately constant (and near the thermodynamic ratio) is not unexpected since the cyclic deprotonation would not be stereospecific. This supports the earlier assumption[4] that stereoselective chloride ion capture must involve either an associated charged intermediate or a concerted reaction.

Although all of the observed products can be rationalized from the above scheme, two puzzling aspects remain. Very little HCl addition to the starting olefin was observed in the earlier work and the relatively high yield of **4** is surprising. In addition, the effect of higher concentrations of acetic anhydride in producing more 4-chloro-3-propyltetrahydropyran (**9**) (Table II) is not easy to explain. If the acetylation reaction is relatively slow at these temperatures, it may be that the increase in rate of formation of **9** in more polar solvents[2] might become a dominant factor and override the expected increase in rate of acetylation.

Although a small amount of chloromethyl acetate (**5**) was observed in each of these runs, no methylene diacetate could ever be detected. It appeared possible that hydrogen chloride might promote ionization of methylene diacetate to the acetoxymethyl cation which would give electrophilic attack upon the starting olefin and give rise to the observed products. Treatment of 1-hexene and methylene diacetate with hydrogen chloride at −65° gave no detectable condensation products and confirmed that the initial step in the process is formaldehyde protonation.

$$CH_2(OCOCH_3)_2 \xrightarrow{HCl} CH_3CO_2H + \overset{+}{C}H_2OCOCH_3 + Cl^-$$

Experimental Section[10]

Reaction of 1-Hexene, Paraformaldehyde, Acetonitrile, and Hydrogen Chloride.—Only a typical procedure is given. Hydrogen chloride was passed into a mixture of 62 g (2.0 mol) of 97% paraformaldehyde, 252 g (3.0 mol) of 1-hexene, 82 g (2.0 mol) of dry acetonitrile, and 300 ml of methylene chloride at −60 to −70° (Dry Ice–acetone bath) for 2.5 hr, and the mixture was stirred an additional 1 hr and allowed to warm to room temperature overnight. The mixture was treated with 500 ml of water and stirred for 1 hr at room temperature. The layers were separated, the organic layer was washed with sodium carbonate solution and dried ($MgSO_4$), the solvent was removed, and the residue was distilled through a short column under reduced pressure to give 363.2 g of colorless oil, bp 35–130° (12 mm), and 7.3 g of residue. Fractionation through a 4-ft helices packed column gave 120 g (38.5%) of 3-heptenyl acetate, bp 90–93° (30 mm), containing 60% of the trans isomer.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.4; H, 10.3. Found: C, 69.2; H, 10.4.

Glpc analysis of a duplicate run gave the distribution shown in Table I with the following order of elution from the 5-ft UCON column at 200°: **4**, **5** + **6**, **7**, **8**, **9**, **10**, and **11**. Preparative glpc on a 20 ft × 0.75 in. Carbowax 20M column gave the same elution order and furnished **5** + **6** as a mixture and the rest of the compounds as pure materials. Compounds **4**, **8**, **9**, and **11** were identified by comparison of infrared and nmr spectra with authentic samples in addition to their retention times. The nmr spectrum of **7** was in agreement with the assigned structure with 2 vinyl protons centered at −325 Hz, 2 protons at −234 Hz as the AB portion of an ABX system [$C(=O)OCH_2$—$CH<$], a 3-proton singlet at −120 Hz (CH_3CO_2) overlapping a complex 3-proton allylic resonance from −90 to −160 Hz, and 6 methyl protons consisting of a doublet overlapping a triplet centered at −60 Hz (CH_3CH_2 and CH_3CH). The infrared spectrum showed a strong trans adsorption at 970 cm^{-1} and the mass spectrum was in full agreement with the assigned structure. The nmr spectrum of **10** was in general agreement with the indicated structure with a 3-proton signal from −210 to −260 Hz consisting of an AB portion of an ABX system [$C(O)OCH_2CH$] overlapping a complex resonance of the methine proton α to the chlorine atom, a 3-proton singlet at −222 Hz (CH_3CO_2), a 5-proton complex resonance centered at −93 Hz representing the methylene protons, and 6 methyl protons (doublet overlapping a triplet) at −60 Hz. Mass and infrared spectra were in agreement with the assigned structure.

Registry No.—**4**, 638-28-8; **7**, 1708-86-7; *cis*-**8**, 1576-78-9; *trans*-**8**, 1576-77-8; *cis*-**9**, 18755-78-7; *trans*-**9**, 18755-79-8; **10**, 30275-71-9; **11**, 30316-05-3.

Acknowledgment.—The author wishes to thank Dr. J. C. Randall, Mrs. Joy Buell, and Mr. C. Stafford for assistance in determination and interpretation of nmr and mass spectra, Mr. C. G. Long for carrying out the preparative glpc separations, and Mr. W. F. Bowen for technical assistance.

(10) All melting and boiling points are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer in chloroform-*d* with tetramethylsilane as internal standard. Glpc analyses were carried out on a Perkin-Elmer Model 720 gas chromatograph using a 5 ft × 0.25 in. column of 20% UCON LB-550-X on Chromosorb P for the complete analysis and a 5 ft × 0.25 in. 20% tris(cyanoethoxy)propane on Chromosorb P column to separate *cis*- and *trans*-3-heptenyl acetate. Olefins used were Phillips Petroleum Co. pure grade materials. Pure *trans*-3-hepten-1-ol was obtained from Chemical Samples Co., and a cis/trans mixture was obtained from K & K Laboratories. 3-Chloro-1-heptanol was obtained as previously described[2] and all were converted to the acetates by standard techniques.

Fragmentation of Some Trityl Compounds by Means of Hydride Transfer. A Reinvestigation of an Unusual Reaction Reported by Gomberg[1]

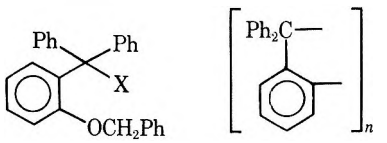
W. H. STARNES, JR.

Esso Research and Engineering Company, Baytown Research and Development Division, Baytown, Texas 77520

Received January 20, 1971

The thermal decomposition of trityl chloride **1a**, previously studied by Gomberg and Nishida, has now been reinterpreted with the aid of new experimental data. This reaction does not yield 1,1-diphenylbenzocyclopropene (**3a**) or products derived therefrom. At 70° in dry benzene-d_6, **1a** rearranges into an isomer **9** *via* a mechanism involving hydride transfer. The rearrangement is catalyzed by HCl, and it can be prevented by the addition of 2,6-lutidine. By-products of the rearrangement are benzaldehyde, phenol **7**, and acetal **10**; their formation involves adventitious moisture. In dry benzene-d_6 at room temperature, alcohol **1b** can be quantitatively converted into benzaldehyde and **7** by treatment with trifluoroacetic acid. The decompositions of **1a** and **1b** are shown to be similar mechanistically.

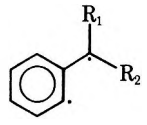
In 1923 Gomberg and Nishida[2] reported a remarkable reaction of the trityl chloride **1a**. Thermal decomposition of this substance was said to give benzaldehyde, HCl, and a "very interesting hydrocarbon..., unsaturated to the extent of two hydrogen atoms," which was capable of forming **2** by "instant polymerization."[2] The monomeric hydrocarbon was not actually isolated, and its structure received no further discussion. However, from these data[2] and more recent facts as well, it seemed to us that the monomer might have been either 1,1-diphenylbenzocyclopropene[3] (**3a**) or an isomeric diradical species **4a**. In agreement with this hypothesis, benzocyclopropenes containing radical-stabilizing substituents at C-1 (*e.g.*, **3b**) were known to experience facile thermal homolysis,[4] and the resulting diradicals (*e.g.*, **4b**) evidently could polymerize when other reaction paths were not favored.[4] Moreover, the formation of **3a** in a concerted manner (**5**, arrows) was recognizable as a [2 + 2 + 2] "cycloaddition" process, allowed by orbital symmetry.[5] Nevertheless, the proposed reaction[2] obviously lacked analogy, and an approximate thermochemical calculation suggested that it would require an activation energy, irrespective of mechanism, amounting to at least 46 kcal/mol (if **3a** were indeed a product).[6] Thus, it seemed that the process could not have occurred at the rates required by the existing data.[9]



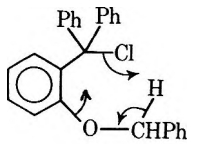
1a, X = Cl
b, X = OH

2

3a, $R_1 = R_2$ = Ph
b, R_1 = CN; R_2 = Me



4a, $R_1 = R_2$ = Ph
b, R_1 = CN; R_2 = Me



5

The present paper reinterprets the unusual decomposition behavior of **1a** from the standpoint of new experimental information. An auxiliary investigation of a related reaction (the acid-catalyzed decomposition of alcohol **1b**) is also described herein.

Results and Discussion

Decomposition of Chloride 1a.—The chloride was prepared from diol **6** by a simple two-step sequence

(6) The overall process can be regarded as the sum of the following steps.

$$\mathbf{1a} \xrightarrow{\Delta H_1} (C_6H_4)Ph_2CCl + PhCH_2O\cdot$$

$$PhCH_2O\cdot \xrightarrow{\Delta H_2} PhCHO + H\cdot$$

$$(C_6H_4)Ph_2CCl \xrightarrow{\Delta H_3} \mathbf{4a} + Cl\cdot$$

$$H\cdot + Cl\cdot \xrightarrow{\Delta H_4} HCl$$

$$\mathbf{4a} \xrightarrow{\Delta H_5} \mathbf{3a}$$

A value of 102 kcal/mol is assigned to ΔH_1, since ΔH_1 should be closely approximated by D (Ph–OR) (where R = alkyl), and recent ΔH_{f° data[7] indicate that D (Ph–OMe) ≅ D (Ph–OEt) = 102 ± 1 kcal/mol. Literature values for ΔH_2 and ΔH_4 are 20 [estimated by P. Gray, P. Rathbone, and A. Williams, *J. Chem. Soc.*, 3932 (1960)] and −103 kcal/mol [S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965)], respectively. For ΔH_3, we use 48 kcal/mol, the reported value for D (Ph_3C–Cl).[8] To estimate ΔH_5, we first make the reasonable assumption that D (Ph_3C–Me) − D (Ph_3C–Cl) = D (*tert*-Bu–Me) − D (*tert*-Bu–Cl). From ΔH_{f° data,[7a] D (*tert*-Bu–Me) = 82 and D (*tert*-Bu–Cl) = 80 kcal/mol; hence, D (Ph_3C–Me) − 48 = 82 − 80, and D (Ph_3C–Me) = 50 kcal/mol. We next introduce ΔH_6 (**3b** → **4b**) and assume that $-\Delta H_5 - \Delta H_6 = D$ (Ph_3C–Me) − D [Ph(CN)(Me)C–Me]. From work reported by Closs,[4a] ΔH_6 is "slightly lower" than 25 kcal/mol, and D [Ph(CN)(Me)C–Me] has been assigned a value (perhaps rather questionable) of 54 kcal/mol [M. Hunt, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 5074 (1965)]. Therefore, $-\Delta H_5 - 25 = 50 - 54$; $\Delta H_5 = -21$ kcal/mol. Summing, we obtain ΔH (**1a** → HCl + PhCHO + **3a**) = $\Sigma\Delta H_{1-5}$ = 102 + 20 + 48 − 103 − 21 = 46 kcal/mol.

(7) (a) S. W. Benson and R. Shaw, *Advan. Chem. Ser.*, **75**, 288 (1968); D. M. Golden and S. W. Benson, *Chem. Rev.*, **69**, 125 (1969); S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *ibid.*, **69**, 279 (1969); (b) D. H. Fine and J. B. Westmore, *Chem. Commun.*, 273 (1969).

(8) A. H. Sehon and M. Szwarc, *Annu. Rev. Phys. Chem.*, **8**, 439 (1957).

(9) From yield data reported by Gomberg and Nishida,[2] half-lives can be calculated for their proposed decomposition of **1a**. Typical values obtained in this way (assuming first-order kinetics) are 39 hr (25°, xylene solution), 14 hr (100–120°, xylene solution), and 1.6 hr (140–150°, no solvent). In contrast, half-lives of *ca.* 10^{17}–10^{7} hr are expected at 25–150° for a first-order reaction having an activation energy of 46 kcal/mol and a "normal" frequency factor of 10^{13} sec^{-1}. Ridiculously high frequency factors would have to be assumed to obtain agreement with experiment, and the experimental activation energy should certainly be higher than the overall ΔH for the reaction under discussion.

(1) Presented in part at the Combined Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2, 1970.

(2) M. Gomberg and D. Nishida, *J. Amer. Chem. Soc.*, **45**, 190 (1923).

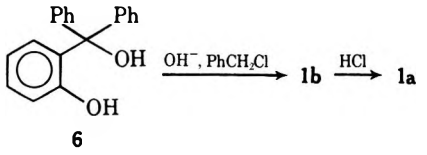
(3) The first benzocyclopropene to be generally regarded as authentic was reported by R. Anet and F. A. L. Anet, *ibid.*, **86**, 525 (1964).

(4) (a) G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 69 (1966); (b) G. L. Closs, L. R. Kaplan, and V. I. Bendall, *J. Amer. Chem. Soc.*, **89**, 3376 (1967).

(5) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, pp 101–107.

(Scheme I), using procedures similar to those already described.[2] Despite careful attempts at purification,

SCHEME I

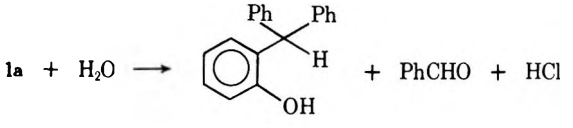


6

our samples of **1a** contained 3–6 mol % of alcohol **1b**. However, a comparison of melting points and analytical data indicated that these samples were at least as pure as the product obtained by the earlier workers.[2]

Gomberg and Nishida[2] studied the decomposition of neat **1a** at temperatures ranging from 60 to 130°. They also carried out decompositions of **1a** in xylene at 25–120°. Yields of HCl were determined in these experiments, but no organic products were isolated or identified. However, Gomberg and Nishida noted that the chloride acquired the odor of benzaldehyde on standing, and from a decomposition of the neat material at 140–150° they were able to isolate a considerable amount (73%) of benzaldehyde and a material thought to be **2** ($n = 4$), as well. With the expectation that decompositions in dilute solution would be much cleaner than those performed otherwise, we elected to begin our investigation of **1a** by observing its stability in benzene-d_6. This solvent was used rather than xylene[2] in order to permit direct monitoring of reactions by nmr spectrometry.

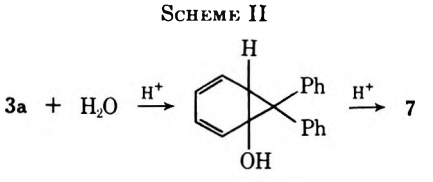
In the initial experiment, a solution of **1a** in dry benzene-d_6 was allowed to stand at room temperature under nitrogen. Slow formation of **1b** occurred despite the precautions taken to exclude moisture. After a few days, the solution also contained small amounts of benzaldehyde and a material later shown to be **7**. When the reaction was brought to completion by heating at 70°, quantitative yields of benzaldehyde and **7** were obtained. The adventitious incursion of 1 mol of water is required by this result, and the overall reaction therefore has the following stoichiometry.



7

A mechanism involving acid-catalyzed hydration of benzocyclopropene **3a**, followed by an acid-catalyzed reorganization of the hydrate (Scheme II), was con-

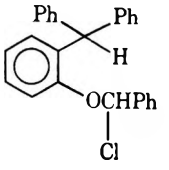
SCHEME II



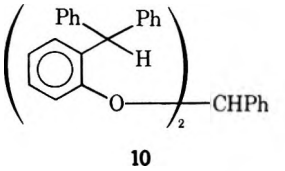
8

sidered as a possible route to **7**. The hydration step did not seem entirely unreasonable, since iodine (an electrophilic reagent) had been reported to add to benzocyclopropene (unsubstituted) in a similar manner.[10] However, other mechanistic considerations suggested that the hydration of **3a** might well have given tritanol, a product which was not observed. Moreover, the absence of a cycloheptadienone also appeared to be significant, since such a product could have easily been formed from **8** *via* an alternative mode of cleavage.[10]

Further decomposition experiments provided definitive information about the detailed course and mechanism of the reaction. These runs were carried out in benzene-d_6 at 70° with no preliminary period of standing at room temperature. The extent of involvement of moisture was greatly reduced by this procedure, and in a typical case the products obtained (mol/mol of starting material) were the rearranged chloride **9** (0.85), acetal **10** (0.04), phenol **7** (0.08), and benzaldehyde (0.12). Compounds **9** and **10** were not actually iso-



9



10

lated, but their presence was revealed by a variety of observations. Resonances due to the aliphatic protons of **9** and **10** were easily detected in the nmr spectra of the product mixtures, and the addition of pure **7** caused spectral changes which were consistent with the occurrence of an anticipated reaction:[11] **7** + **9** → **10** + HCl. Since the reaction involving moisture had already been shown to give equivalent amounts of benzaldehyde and **7**, the observed stoichiometry (**10** + **7** = benzaldehyde) was in accord with expectations. Slow hydrolysis of a product mixture with water-saturated benzene-d_6 indicated the presence of two species hydrolyzing at different rates, and treatment of other product mixtures with an excess of water containing 20% ^{18}O caused rapid and quantitative conversion of **9** and **10** into benzaldehyde and **7**. Mass spectral analysis showed that the **7** contained no ^{18}O (within the limits of experimental error), whereas the benzaldehyde contained 100 ± 5% of the theoretical maximum amount of the label. These results conclusively establish the presence of **9** and **10**, and they also rule out the mechanism of Scheme II, since that mechanism requires incorporation of ^{18}O into **7**.

The rearrangement of **1a** into **9** seemed to be the crucial decomposition step, and its mechanism was of obvious interest. Considering first the possibility of a rearrangement mechanism involving radicals, we note that D (C–Cl) in trityl chloride has been reported to be only 48 kcal/mol.[8] In the case of compound **1a**, D (C–Cl) should be lower by 1–3 kcal/mol.[12] Even so, the rate of the C–Cl homolysis of **1a** is undoubtedly very slow at 70°, and for this reason a *nonchain* radical

(10) E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Lett.*, 3625 (1965).

(11) H. Meerwein in "Methoden der Organischen Chemie (Houben-Weyl)," E. Müller Ed., Vol. VI, part 3, Georg Thieme Verlag, Stuttgart, 1965, pp 237–239, and references cited therein.

(12) This range of values was estimated from equilibrium data for the homolytic dissociation of *o*-alkoxytrityl dimers and *o*-alkoxytrityl iodides. For the data used see (a) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience, New York, N. Y., 1956, p 12; (b) S. T. Bowden, *J. Chem. Soc.*, 4235 (1957); (c) S. T. Bowden and D. T. Zalichi, *ibid.*, 4240 (1957).

rearrangement process seems extremely unlikely.[13] However, radical chain mechanisms initiated by C–Cl homolysis would appear to merit further consideration. Scheme III shows the propagation steps for two possible mechanisms of this type.

SCHEME III

Mechanism A

$$Ph_2\dot{C}(C_6H_4)OCH_2Ph \longrightarrow Ph_2CH(C_6H_4)\dot{O}CHPh$$

$$\underset{\mathbf{11}}{Ph_2CH(C_6H_4)\dot{O}CHPh} + \mathbf{1a} \longrightarrow \mathbf{9} + Ph_2\dot{C}(C_6H_4)OCH_2Ph$$

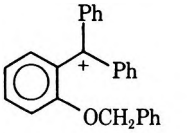
Mechanism B

$$Ph_2CCl(C_6H_4)\dot{O}CHPh \longrightarrow Ph_2\dot{C}(C_6H_4)OCHClPh$$

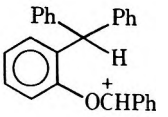
$$Ph_2\dot{C}(C_6H_4)OCHClPh + \mathbf{1a} \longrightarrow \mathbf{9} + Ph_2CCl(C_6H_4)\dot{O}CHPh$$

The resonance-stabilized radicals of Scheme III should resemble the polystyryl radical in their relative reactivity toward various substrates. Reactivity data for polystyryl radical are available in the form of chain transfer constants, which indicate that *p*-benzoquinone should be an extremely effective inhibitor for both mechanisms of Scheme III.[14] Experimental tests showed that *p*-benzoquinone did not significantly retard the rate of rearrangement of **1a**; thus we conclude that the rearrangement is not a homolytic process.

An alternative mechanistic possibility is an ionic path which, in its simplest variation, would involve hydride transfer to a carbonium ion intermediate. This hypothesis appears much more reasonable. In benzene solution, trityl chloride ionizes to a limited extent,[15] and the process is strongly catalyzed by potential proton donors.[15,16] Compound **1a** should behave similarly and, indeed, further experiments showed that its rearrangement was significantly accelerated by dry HCl and completely inhibited by 2,6-lutidine. These observations constitute very strong evidence for a heterolytic path, and they are considered further below. The carbonium ion[17] **12** derived from **1a** could be converted into **13** by an intramolecular 1,5-



12



13

hydride shift.[18] Capture of **13** by chloride ion would give the rearranged chloride **9**, while reaction of **13** with moisture would give a protonated hemiacetal which should undergo rapid conversion into benzaldehyde and **7**. Reaction of **13** with **7** would give acetal **10**. Nucleophilic displacements on **9** could also give benzaldehyde, **7**, and **10**; such reactions were, in fact, demonstrated experimentally (see above).

Mechanisms involving intermolecular hydride transfer can also be written for the decomposition of **1a**, but an intramolecular shift appears more likely. In the absence of overriding steric constraints, the intramolecular path seems highly favored for 1,5-hydride transfers to carbonium ions, in general, since this route is followed exclusively even in completely flexible acyclic systems.[19] Decomposition of **1a** *via* an intermolecular mechanism could have led to the buildup of metastable intermediates, but such products were never detected. It is true, of course, that the possible transition states for intermolecular hydride transfer should be stabilized by electron donation from two oxygen-containing substituents, whereas intramolecular transfer would be assisted by conjugative interaction involving only a single atom of oxygen. However, oxygen conjugation might be particularly helpful in the intramolecular case, since it would tend to impart quasi-aromatic character to the six-atom cyclic transition state required for intramolecular rearrangement of **12**. The apparent stability of the para isomer[20] of **1a** also argues against a mechanism involving intermolecular hydride transfer. Finally, it should be noted that intramolecular 1,5-hydride abstraction by a triaryl carbonium ion has been reported previously in at least one instance,[21] although the system studied was, admittedly, very favorably disposed toward an intramolecular path because of its spatial arrangement. These arguments are highly suggestive, but they cannot be regarded as conclusive. They do not rigorously exclude, for example, a mechanism for decomposition of **1a** involving anchimeric assistance by neighboring chlorine in an intermolecular hydride-transfer step.

The hindered base, 2,6-lutidine, undoubtedly inhibits the decomposition by scavenging adventitious HCl. As was mentioned previously, all of our samples of **1a** contained small amounts of alcohol **1b**. In the absence of 2,6-lutidine, the nmr spectra of these

(13) A half-life of 9×10^{11} hr is expected at 70° for a first-order reaction having a frequency factor of 10^{13} sec^{-1} and an activation energy of 45 kcal/mol. Our experimental half-life for decomposition of **1a** at 70° was never greater than 50 hr (see later discussion).

(14) At 70° *p*-benzoquinone is *ca.* 200 times as reactive as CBr_4 toward polystyryl radical. *D* (C–Br) in CBr_4 is *ca.* 49 ± 3 kcal/mol [A. H. Sehon and M. Szwarc, *Proc. Roy. Soc., Ser. A*, **209**, 110 (1951); T. L. Cottrell, "The Strengths of Chemical Bonds," Butterworths, London, England, 1958, p 205, and references cited therein], a value comparable to *D* (C–Cl) in compound **1a** (see above). However, polar effects might tend to cause radical **11** of mechanism A to be less reactive toward the C–Cl bond of **1a** than toward a C–Br bond of CBr_4 (*cf.* C. Walling, 'Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 379–380), since **11** should be even more nucleophilic than the polystyryl radical, whose nucleophilicity is well established [Y. L. Spirin, *Russ. Chem. Rev.*, **38**, 529 (1969), and references cited therein]. In addition, the reactivity of **1a** toward halogen abstraction should be reduced, relative to that of CBr_4, by steric factors and by a statistical factor of 4. Furthermore, a consideration of polar and steric effects suggests that **11** is likely to be more reactive than polystyryl radical toward *p*-benzoquinone, due to a predominating influence of polar factors. We therefore conclude that p-benzoquinone should be more than 800 times as reactive as the C–Cl bond of **1a**, toward radical **11** at 70°. Toward polystyryl radical at 68°, the relative reactivities of *p*-benzoquinone and benzyl methyl ether are *ca.* 4×10^2 and 6×10^{-4}, respectively, and toward this radical at 60°, *p*-benzoquinone is *ca.* 2×10^5 times as reactive as *p*-benzyloxyphenol-*O*-*d*. The quinone should therefore compete very effectively with **1a** in the intermolecular propagation step of mechanism B, and this competition should also be aided by polar and (probably) steric factors as well. These conclusions are based on chain-transfer constants tabulated by L. J. Young, G. Brandrup, and J. Brandrup in "Polymer Handbook," J. Brandrup and E. H. Immergut, Ed., Interscience, New York, N. Y., 1967, pp II 108–110 and II 113.

(15) C. G. Swain and M. M. Kreevoy, *J. Amer. Chem. Soc.*, **77**, 1122 (1955); E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1265 (1957), and accompanying papers.

(16) (a) C. G. Swain and E. E. Pegues, *J. Amer. Chem. Soc.*, **80**, 812 (1958); (b) A. G. Evans, I. H. McEwan, and J. H. Thomas, *J. Chem. Soc.*, 4644 (1957).

(17) Throughout most of the discussion, the term "ion" is used for simplicity, although it is recognized that ions exist primarily as ion pairs or higher aggregates in benzene solution.

(18) For a recent review of intramolecular hydride transfers, see J. L. Fry and G. J. Karabatsos in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley–Interscience, New York, N. Y., 1970, Chapter 14.

(19) R. K. Hill and R. M. Carlson, *J. Amer. Chem. Soc.*, **87**, 2772 (1965).

(20) M. Gomberg and C. C. Buchler, *ibid.*, **45**, 207 (1923).

(21) R. L. Letsinger and P. T. Lansbury, *ibid.*, **81**, 935 (1959).

samples failed to show the alcoholic proton peak. However, this peak appeared in its expected position when the lutidine was present. These results are consistent with the occurrence of a rapid exchange which is catalyzed by acid and suppressed by the hindered base. The presence of varying amounts of HCl thus accounts for the variability of the decomposition rates obtained with different samples of **1a** in the absence of any additives (see Experimental Section).

Ion **12** is presumably formed from **1a** in benzene-d_6, even in the absence of catalysts,[15] and the equilibrium constant for its quaternization reaction with 2,6-lutidine might prove to be rather large.[22] However, quaternization could not have caused a significant reduction in the decomposition rate, since it did not significantly reduce the concentration of **12**. This conclusion follows from the realization that **12** also equilibrates with un-ionized **1a**, whose concentration was not noticeably decreased by the base.[22]

Although **1a** failed to rearrange in the presence of 2,6-lutidine, it did undergo slow conversion to **1b**. This result was not expected. By analogy with conclusions reached by previous workers[15,13a] concerning nucleophilic displacements on trityl chloride, hydrolysis of **1a** should occur *via* ion **12** in benzene containing very small amounts of water. Furthermore the work of Swain, *et al.*,[16a,22] on trityl chloride methanolysis suggests that 2,6-lutidine would not increase the hydrolysis rate of **1a** under our experimental conditions. If hydride transfer can indeed occur *via* **12**, it is therefore difficult to understand why **1a** did not rearrange to some extent when 2,6-lutidine was present. A possible explanation is that the spontaneous ionization of **1a** gives an intimate ion pair which is too stable to undergo hydride transfer, whereas HCl-catalyzed ionization produces (to some small degree) a more open ion pair (or, indeed, free **12**) whose reactivity is greater. However, several other rationalizations are also tenable at present, and no firm conclusions can be drawn in the absence of detailed kinetic studies.

Summarizing the results presented thus far, we conclude that the decomposition of **1a** in benzene-d_6 does not give **3a** and does not involve free radicals. It proceeds instead *via* an ionic path which involves hydride transfer and is extremely susceptible to acid catalysis. The exact nature of the hydride-transfer process remains an open question, and no evidence is available now with regard to the possible merger of discrete reaction steps into one or more concerted interactions.

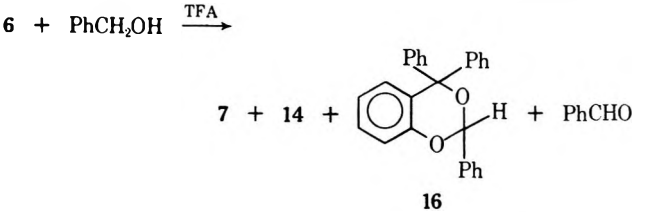
Several attempts were made to reproduce the results obtained by Gomberg and Nishida[2] in their decomposition of neat **1a** at 140–150° (see above). These experiments afforded complex product mixtures containing none of the starting chloride. Diphenylmethane and **7** were shown to be present, but the yields of benzaldehyde were very low (<4%), and no evidence could be obtained for the formation of **3a** or polymers derived therefrom. A similar reaction run at 180° gave 5–10% of benzaldehyde, as well as a number of impure solid fractions with molecular weights ranging from 869 to 2050. One of these fractions had properties (color, melting point, and molecular weight) which were similar to those reported[2] for **2** (n = 4). However, all of the fractions exhibited strong infrared absorption in the OH stretching region, and they were shown to contain 7–9% oxygen by elemental analysis. The reason for the discrepancy between these results and those reported by Gomberg and Nishida[2] is not apparent at present, but, in any event, it is clear that **1a** does not undergo high-temperature decomposition in the manner previously proposed.[2]

Decomposition of Alcohol 1b.—On the basis of the observations reported above, alcohol **1b** was expected to undergo facile acid-catalyzed fragmentation. Such behavior was indeed observed. At room temperature in benzene-d_6, the fragmentation was strongly catalyzed by trifluoroacetic acid (referred to hereafter as TFA), and it gave quantitative yields of benzaldehyde and **7** when it was carried out under these conditions. In a parallel experiment, TFA-*d* was used to catalyze the fragmentation of **1b**-*O*-*d*, and the resulting **7** was found to contain no methine deuterium. This observation supports the occurrence of hydride transfer[23] and rules out any route to **7** involving a benzocyclopropene intermediate (*cf.* Scheme II).

Under certain conditions, TFA had been reported to cleave aryl benzyl ethers into phenols and (presumably) benzyl trifluoroacetates.[24] This result suggested that the TFA-catalyzed fragmentation of **1b** might have occurred, at least in part, *via* a route involving ether cleavage followed by intermolecular hydride transfer. All steps after cleavage were required to be fast, since there was no evidence for the accumulation of stable intermediates (see Experimental Section). Mechanisms of this type are summarized in Scheme IV.

Scheme IV was tested in several ways, but no evidence was obtained for its operation. When excess TFA (10 mol equiv) was added to a benzene-d_6 solution of **14** (1.2 mol equiv) and **6** (1.0 mol equiv), phenol **7** was formed in a slow reaction. However, none of the starting ester was consumed, and neither benzaldehyde nor **16** (see below) could be detected among the products. No attempts were made to elucidate the detailed course of this reaction, although the TFA-induced formation of **7** from **6** alone was verified by a separate experiment.

A benzene-d_6 solution of **6** (1.0 mol equiv) and benzyl alcohol (1.3 mol equiv) was treated with TFA (15 mol equiv). The ensuing reaction was rapid initially, but its rate decreased markedly before **6** was consumed. At a conversion level of 83%, the products (mol/mol of starting **6**) were **7** (0.50), **14** (0.78), **16** (0.33), and benzaldehyde (0.17). Benzaldehyde and **7** must have resulted from the reduction of ion **15** with benzyl alcohol, while formation of **14** by direct esterification of



16

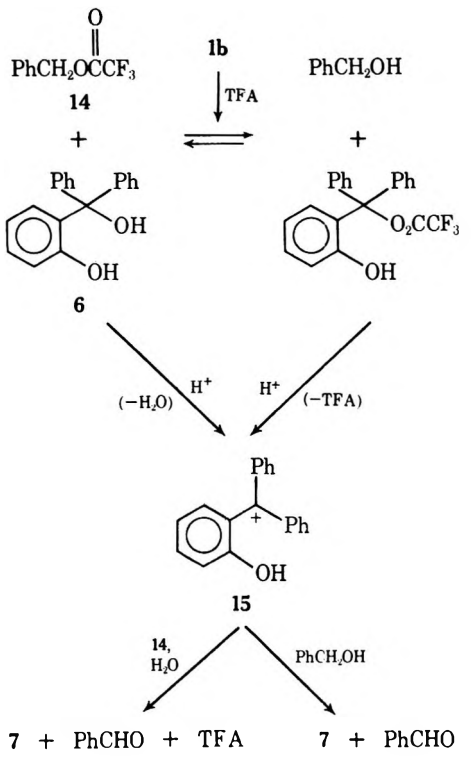
TFA was independently shown to be feasible. The structure of **16** and its mode of formation were estab-

(22) *Cf.* C. G. Swain and Y. Okamoto, *J. Amer. Chem. Soc.*, **92**, 3409 (1970), and references cited therein.

(23) *Cf.* P. D. Bartlett and J. D. McCollum, *ibid.*, **78**, 1441 (1956).

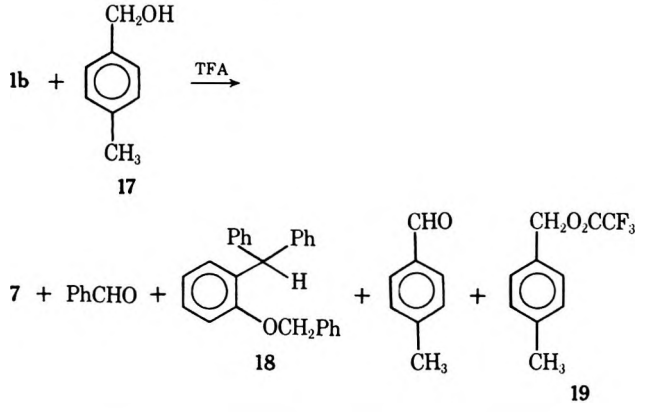
(24) J. P. Marsh, Jr., and L. Goodman, *J. Org. Chem.*, **30**, 2491 (1965).

SCHEME IV



lished by a separate synthesis of the substance from benzaldehyde and **6**, using TFA as the catalyst. Since **14** and **16** were not produced in the TFA-catalyzed decomposition of **1b**, their formation from benzyl alcohol and **6** was regarded as further evidence against the mechanisms of Scheme IV. However, Scheme IV was already known to require very rapid formation of benzaldehyde and **7** following the initial cleavage, and this could have accounted for the different product distributions observed in the two different systems.

A reaction of **1b** (1.0 mol equiv) with alcohol **17** (2.9 mol equiv) and TFA (6.0 mol equiv) was carried out under the usual conditions. When all of **1b** had reacted, 0.11 mol equiv of **17** remained, and the products (mol/mol of **1b**) were **7** (0.84), benzaldehyde (0.84), **18** (0.16, identified by comparison with a reference sample prepared by benzylation of **7**), *p*-tolualdehyde (0.16), and



19 (2.60). The aldehydes, phenol **7**, and ether **18** were undoubtedly formed *via* hydride transfers, while **19** evidently resulted from a direct esterification. Alcohol **17** was present in relatively high concentration (greater than the concentration of **1b**) throughout the course of the reaction, and its intrinsic hydride-donating ability was predicted to be greater than that of benzyl alcohol or ester **14** under these experimental conditions.[25] Therefore, if the mechanism(s) of Scheme IV had been operative, fragmentation of **1b** in the presence of **17** should have given considerable amounts of **14** and/or benzyl alcohol, which would have been largely converted to **14** *in situ*. Moreover, the following stoichiometric relationships should then have been observed for the products: benzaldehyde < **7**, *p*-tolualdehyde > **18**. Since these inequalities did not obtain and no **14** was detected, we conclude that *none* of the fragmentation occurred *via* Scheme IV. It should also be noted that this experiment gave the "normal" cleavage products (benzaldehyde and **7**) in relatively high yields, a result constituting permissive evidence for hydride transfer by a rapid intramolecular route.

The behavior of **1b** toward formic acid was also a matter of interest. Formic acid is ordinarily an excellent reagent for the reduction of tritanols to triarylmethanes.[12c,26] However, its reaction with **1b** gave no **18**, and the major products were shown to be benzaldehyde and **7**. By analogy with behavior reported for similar molecules,[27] **1b** would be expected to undergo very rapid and extensive (perhaps essentially quantitative) ionization (to form **12**) upon dissolution in formic acid. Intermolecular hydride transfer between two positively charged species is not a favored process; thus the fragmentation of **1b** observed in formic acid would seem to be best rationalized in terms of an intramolecular transfer path.

From the foregoing observations we conclude that the acid-catalyzed decomposition of **1b** proceeds by a mechanism which closely resembles, in all probability, the one proposed for **1a**.

Related Reactions.—Although *o*-alkoxytrityl cations have been generated previously in many chemical and physicochemical studies,[28] their self-induced decomposition due to hydride transfer has apparently not been noticed before. Unlike **1a**, *o*-methoxy-[2,28a,29] and *o*-ethoxytrityl chloride[12c] seem to have no tendency to undergo spontaneous fragmentation. (*o*-Methoxyphenyl)diphenylmethanol does not decompose in hot acid solution under nonreducing conditions,[28a] and both it[26a,c,d] and the corresponding *o*-ethoxy alcohol[12c] give triarylmethanes when they are treated with formic acid. Solutions of the *o*-methoxytrityl cation have

(25) Extensive protonation of the potential hydride-donating species might have altered their relative reactivities,[23] but this effect should have been insignificant under the conditions employed here.

(26) For representative examples, see (a) H. Kauffmann and P. Pannwitz, *Ber.*, **45**, 766 (1912); (b) A. Kovache, *Ann. Chim. (Paris)*, **10**, 184 (1918) [*Chem. Abstr.*, **13**, 441 (1919)]; (c) D. I. Roberts and S. T. Bowden, *Recl. Trav. Chim. Pays-Bas*, **49**, 665 (1930); (d) S. T. Bowden, D. L. Clarke, and W. E. Harris, *J. Chem. Soc.*, 874 (1940); (e) S. T. Bowden and K. I. Beynon, *ibid.*, 4244, 4253 (1957); (f) R. Grinter and S. F. Mason, *Trans. Faraday Soc.*, **60**, 889 (1964).

(27) W. R. B. Arthur, A. G. Evans, and E. Whittle, *J. Chem. Soc.*, 1940 (1959); R. Stewart and T. Mathews, *Can. J. Chem.*, **38**, 602 (1960).

(28) See *inter alia*, ref 2, 12c, 26a,c,d and (a) A. Baeyer, *Justus Liebigs Ann. Chem.*, **354**, 152 (1907); (b) K. Ziegler and H. Wollschitt, *ibid.*, **479**, 90 (1930); (c) K. Brand, *J. Prakt. Chem.*, [2], **109**, 1 (1925); (d) H. Lund, *J. Amer. Chem. Soc.*, **49**, 1346 (1927); (e) J. C. Martin and R. G. Smith, *ibid.*, **86**, 2252 (1964); (f) M. J. Sabacky, C. S. Johnson, Jr., R. G. Smith, H. S. Gutowsky, and J. C. Martin, *ibid.*, **89**, 2054 (1967); (g) I. Lifschitz, *Recl. Trav. Chim. Pays-Bas*, **53**, 191 (1934); (h) H. Kauffmann and I. Fritz, *Ber.*, **41**, 4423 (1908); (i) H. Kauffmann and F. Kieser, *ibid.*, **45**, 2333 (1912); (j) H. Kauffmann and F. Kieser, *ibid.*, **46**, 3788 (1913); (k) G. Wittig and G. Fuhrmann, *ibid.*, **73**, 1197 (1940); (l) G. Wittig and G. Harborth, *ibid.*, **77**, 306 (1944).

(29) C. S. Marvel, J. Whitson, and H. W. Johnston, *J. Amer. Chem. Soc.*, **66**, 415 (1944).

been studied spectrally[28c] and by conductometry[2,28b] with apparently no evidence of decomposition. Facile rearrangement of mono-*o*-alkoxytrityl cations thus seems to require a substituent which is more reactive than methoxy or ethoxy, although it is possible that trityl cations containing these and other simple *o*-alkoxy substituents might be found to rearrange if the reaction were looked for carefully under favorable conditions.

Hydride transfer from the benzyloxy group gives a very stable carbonium ion and is obviously a favored process, but clear-cut evidence for the rearrangement of an *o*-benzyloxytrityl cation has not been forthcoming until now. However, Gomberg and McGill[30] found that (3-benzyloxy-2-naphthyl)diphenylchloromethane acquired the odor of benzaldehyde on standing, and this observation presumably signifies the occurrence of another reaction which is analogous to those described herein.

Experimental Section[31]

Materials.—Reagent grade benzene and benzene-d_6 were dried over sodium. The redried ether used for operations with **1a** (see below) was prepared by treating commercial anhydrous ether with calcium chloride and sodium, in succession (sodium reacted vigorously when the predrying step was omitted). Petroleum ether was the fraction boiling at 30–60°. Oxygen-18-enriched water (Diaprep Inc.) had a nominal ^{18}O content of 20 atom % and was stated by the supplier to contain less than 10 atom % of deuterium. A mass spectral analysis of this material indicated an ^{18}O content of 20.7 atom %. Trifluoroacetic acid-*d* (Diaprep Inc.) was shown to contain 99.1 ± 0.1 atom % deuterium by nmr analysis *vs.* an internal standard (anhydrous toluene). Gaseous HCl was dried by passage through sulfuric acid. *p*-Benzoquinone was purified by sublimation; 2,6-lutidine (Aldrich) was dried over potassium hydroxide. The other chemicals used were either commercial materials of high quality or substances prepared by standard literature procedures. Purities were established by spectrometric methods, vpc analysis, and the determination of appropriate physical constants.

Instrumental Analysis.—Infrared, 100-MHz nmr, and high-resolution mass spectra were obtained with Perkin-Elmer Model 21, Varian Model HA-100, and AEI MS-9 spectrometers, respectively. Unless noted otherwise, nmr measurements were made at ambient temperature on dilute solutions containing TMS. Quantitative nmr analyses of benzene-d_6 solutions were corrected for slight solvent absorptions. Nmr peak multiplicities are designated as s (singlet) or m (complex multiplet). Exact measurements of m/e are referred to $C = 12$ amu. Oxygen-18 analyses were performed directly on total product mixtures, using high-resolution mass spectrometry. The analytical peaks were parent m/e's; their elemental compositions were established by exact mass measurements. Sensitivity factors for peaks differing only in isotopic composition were assumed to be identical. Benzaldehyde peak intensities were corrected for contributions due to fragments derived from **7**; these contributions were determined from the mass spectrum of pure **7** and found to be quite small. Programmed temperature vpc analyses were performed with an F & M instrument (Model 500) equipped with a 15 ft. × 0.25 in. (o.d.) stainless steel column containing SE-30 (2%) on acid-washed, DMCS-treated Chromosorb W (40–60 mesh). The carrier gas was helium; column temperature was increased from 100 to 350° at the rate of 8°/min.

(*o*-Benzyloxyphenyl)diphenylmethanol (1b).—Gomberg and Nishida's description[2] of the preparation of **1b** omits several useful details. The following method may be regarded as an amplification of their procedure.

A nitrogen-blanketed suspension of (*o*-hydroxyphenyl)diphenylmethanol[2,28a] (6, 14.00 g, 0.0507 mol) in 1 *N* aqueous sodium hydroxide (60 ml) was stirred rapidly at 85° until complete dissolution of the diol occurred. Benzyl chloride (9.0 g, 0.071 mol) was then added, and after an additional 30 min of warming (85 ± 1°) and stirring under nitrogen, the hot mixture was filtered with suction. The recovered solid was washed several times with water and then with cold (−78°) methanol; it weighed 15.19 g (82% yield; larger scale runs occasionally gave crude yields as high as 96%) and melted at 176.5–178°. A single recrystallization of the product from benzene, followed by thorough washing of the recovered crystals with dry ether, gave 14.37 g of pure **1b** as white clusters: mp 177–177.5° (lit.[2] mp 172°); ir (CS_2) 3505 cm^{-1} (medium, sharp, hindered OH), no C=O; nmr (CCl_4, 60°) δ 6.4–7.3 (m, 19, aromatic H), 4.83 (s, 2, CH_2), and 4.72 ppm (s, 1, OH).

Samples of **1b** containing no impurities detectable by nmr occasionally melted over very wide ranges of temperature (beginning as low as 70°) and acquired the odor of benzaldehyde on melting. These samples usually exhibited the correct melting point for pure **1b** after rigorous drying *in vacuo* at 60°, or after thorough washing with anhydrous ether.

Benzyl α-Chloro-α,α-diphenyl-*o*-tolyl Ether (1a).—In our hands, attempts to obtain **1a** by the published method[2] invariably gave impure products that failed to melt sharply and usually gave evidence of decomposition (benzaldehyde odor, brown melt) on melting. High sensitivity of **1a** toward moisture and/or incomplete conversion of **1b** were apparently the principal sources of difficulty, since the impure chloride was always found to contain a considerable amount of the starting alcohol. Repeated trials eventually led to development of the following modified procedure, which consistently afforded **1a** in a satisfactory state of purity.

A well-stirred mixture of alcohol **1b** (10.00 g, 27.3 mmol), anhydrous calcium chloride (10 g), and benzene (110 ml) was bubbled with a rapid stream of dry HCl for 20 min. No undissolved **1b** could be detected visually at the end of this time. An additional 20 g of the drying agent was added, and the mixture was stoppered tightly under an atmosphere of dry HCl and allowed to stand for 6 hr in the dark with occasional shaking. The drying agent was then removed by suction filtration and washed with several fresh portions of dry benzene. Concentration *in vacuo* of the combined filtrate and washings to a volume of *ca.* 35 ml, followed by refrigeration under argon, suction filtration, and rapid washing of the recovered solid with cold (5°) redried ether (see "Materials," above), gave 7.20 g of the crude chloride, mp 148–156° with slight decomposition. Dissolution of the product in hot redried ether (*ca.* 35 ml/g), followed by chilling to 5°, afforded 4.17 g (40%) of purified **1a** as small snow-white needles: mp 150–153° (lit.[2] mp 146°); ir (CS_2) 3520 cm^{-1} (very weak, OH of residual **1b**); nmr (CCl_4) δ 6.7–7.4 (m, 19, aromatic H) and 4.84 ppm (s, 2, CH_2). In C_6D_6 the CH_2 protons of **1a** and **1b** appear at δ 4.56 and 4.36 ppm, respectively. Quantitative nmr analyses of C_6D_6 solutions showed that our best samples of **1a** contained *ca.* 3 mol % of the alcohol.

Anal.[32] Calcd for $C_{26}H_{21}ClO$: Cl, 9.21. Found: Cl, 9.39.

In agreement with earlier observations,[2] **1a** was found to decompose slowly on storage. However, purified samples were reasonably stable when stored with proper precautions. One sample of the purified material was kept for 8 weeks over Drierite in a darkened, continuously evacuated vessel (pressure ≦ 10 mm). The sample had then acquired a pink color and was found to contain 6 mol % of **1b**; no other impurities were detected.

A small portion of **1a** (0.20 g, 0.52 mmol) was stirred overnight with 1 *N* aqueous sodium hydroxide (20 ml) and dioxane (10 ml). The suspended solid was then removed by suction filtration and washed well with water; from its melting point (172.5–176.5°) it was judged to be mostly **1b** (0.19 g, 100% crude yield). Recrystallization of the solid from benzene–petroleum ether gave 0.09 g of white microcrystals which were shown to be pure **1b** by melting point, mixture melting point, and ir spectral comparisons.

Decompositions of Chloride 1a. A. In Benzene-d_6 Solution.—These reactions were carried out in nmr tubes under nitrogen, using chloride samples that contained 3–6 mol % of **1b**. Product compositions are reported as (moles of compound)/(moles of starting **1a** + moles of starting **1b**); they were calculated from

(30) M. Gomberg and W. J. McGill, *J. Amer. Chem. Soc.*, **47**, 2392 (1925).

(31) Boiling points and melting points are uncorrected. The melting points were determined with a Fisher-Johns apparatus. Unless noted otherwise, elemental analyses and molecular weight determinations were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The drying agent was usually Drierite; all exceptions are noted appropriately. Evaporations were carried out on rotary evaporators at room temperature under *ca.* 10 mm of pressure.

(32) Analysis by neutron activation was performed in this laboratory under the direction of Mr. J. O. Beauxis.

nmr spectra with an accuracy estimated to be within ±5% of the values given.

A solution of the chloride (18 mg, 0.044 mmol of **1a**, 0.003 mmol of **1b**) in dry benzene-d_6 (0.45 ml) was allowed to stand at room temperature. Slow formation of additional **1b** was the only reaction detected initially. Small amounts of benzaldehyde and **7** were present after a few days, and after 1 week of standing the mixture had the following composition: **1a**, 0.67; **1b**, 0.17; benzaldehyde, 0.16; **7**, 0.16 mol/mol. The solution was then heated at 70 ± 1° for 3 days, allowed to stand at room temperature for an additional 5 days, and reanalyzed. The only detectable constituents were benzaldehyde and **7**; their identifications were confirmed by comparisons of chemical shifts and vpc retention times, using authentic materials as references.

Several decompositions of **1a** were carried out in dry benzene-d_6 at 70 ± 1° without a preliminary period of standing at room temperature. In a typical experiment, the starting material (35 mg, 0.086 mmol of **1a**, 0.005 mmol of **1b**) was dissolved in 0.39 ml of solvent. Complete decomposition had occurred after 42 hr of heating, and the product composition was then shown to be: **7**, 0.08; **9**, 0.85; **10**, 0.04; benzaldehyde, 0.12 mol/mol. Compound **9** gave sharp singlets at δ 6.73 [(ArO)CHClPh] and 6.06 ppm (Ph_2ArCH). These peaks appeared to be equal in intensity, although accurate integration of the downfield peak was prevented by aromatic end absorption. Compound **10** produced singlets at δ 6.54 [1, $(ArO)_2CHPh$] and 6.09 ppm (2, Ph_2ArCH). Addition of one drop of water caused the very rapid destruction of both **9** and **10**, and after a few minutes the spectrum indicated the formation of benzaldehyde and **7** in essentially quantitative yields. These substances were identified by the usual comparisons, and the absence of other products was confirmed by vpc analysis. In a separate experiment, the product mixture was hydrolyzed more slowly by adding water-saturated benzene-d_6 instead of pure water. In this case the singlets assigned to **10** disappeared faster than those assigned to **9**, a result verifying the presence of two hydrolyzable constituents. A further experiment involved the addition of a large amount of **7** to an unhydrolyzed product mixture (in benzene-d_6). This addition caused immediate formation of more **10** and decreased the **9**:**10** ratio. Several product mixtures were hydrolyzed with $H_2{}^{18}O$ and then quickly subjected to mass spectral analysis following rapid concentration under nitrogen. Maximum theoretical ^{18}O contents were calculated on the assumption that the benzaldehyde and **7** already formed by adventitious hydrolysis would not undergo isotopic exchange with the labeled water. The experimentally determined ^{18}O contents follow: for benzaldehyde, 95–105; for **7**, 0–3% (of the theoretical maximum values).

Product analyses at intermediate conversion levels provided data which were used to calculate half-lives for the rearrangement of **1a** in benzene-d_6 at 70 ± 1°, assuming first-order kinetics. These one-point kinetic runs gave half-lives ranging from *ca.* 6 to 50 hr for different samples of the chloride. However, aliquots taken from the same batch of chloride over a period of 1–3 days showed half-lives that were reproducible to within ±25%. Table I presents typical data for a series of runs made with some aliquots of this type. No new products were formed in the runs with *p*-benzoquinone and HCl, and the quinone caused no significant changes in product distribution. Compound **10** could not be detected in runs using HCl, but the product distributions obtained in these runs were not significantly altered otherwise. The half-life given for the lutidine experiment was calculated by assuming 1% rearrangement at 89.1 hr. No rearrangement was actually detected, although the **1b** content had risen to 16 mol % at the end of this time.

TABLE I

HALF-LIVES FOR THE REARRANGEMENT OF **1a** (0.2 *M*) IN BENZENE-d_6 AT 70°

Additive (mol equiv)[a]	Half-life, hr
	8.1 ± 2.0[b]
p-Benzoquinone (1.2)	11.4
HCl (g)[c]	4.2 ± 0.1[b]
2,6-Lutidine (1.1)	>6 × 10³ [d]

[a] Mol/mol of (**1a** + **1b**). All **1a** samples contained *ca.* 5 mol % of **1b**. [b] Average of two runs. [c] Saturated solution. [d] See text.

B. Without Solvent.—These decompositions were carried out in a small thermostated distilling flask equipped with a gas inlet tube (wide-bore capillary) extending nearly to the surface of the vessel's contents. The side arm of the flask led to a chilled U-tube receiver. Before application of heat, the assembled apparatus (containing **1a**) was purged with inert gas, which was dry CO_2 unless noted otherwise. A rapid inert gas sweep was maintained throughout the heating period.

In an attempt to repeat the experiment described by Gomberg and Nishida,[2] 3.00 g of purified **1a** was heated for 3.0 hr at 145–146° while the temperature of the cold trap was kept at *ca.* −15°. Slow evolution of benzaldehyde (detected by odor) and HCl (detected with pH paper) occurred throughout the reaction period, but no condensate was collected in the cold trap, and the pot residue (a reddish brown glass when cool) had decreased in weight by only 0.14 g. [In the experiment of Gomberg and Nishida,[2] 0.6 g (73%) of benzaldehyde was said to have been collected in the distillation receiver.] Analysis of the residue by vpc, nmr, and mass spectrometry indicated that it was a complex mixture containing appreciable amounts of **7** and diphenylmethane (identified by appropriate comparisons with authentic specimens), as well as several unidentified substances. Benzaldehyde and **1a** were shown to be absent, and no evidence could be obtained for the presence of polymers derived from **3a**. In accordance with the reported work-up procedure,[2] one-half of the residue was crystallized from ethanol–ether. Chilling to −10° was necessary to induce precipitation. The recovered material (0.10 g) was a pale yellow powder that melted at 85–95° and was shown by nmr and mass spectral analysis to be a mixture of **7** and other materials. The nmr spectrum showed several unidentified peaks in the aliphatic region, and the mass spectrum again provided no evidence for the presence of polymerized **3a**. Further concentration and chilling of the ethanol–ether solution yielded a yellow gum that could not be induced to crystallize.

In a second experiment, 1.93 g of **1a** was heated under argon for 3.2 hr while the pressure of the system was kept at 240–250 mm by means of a vacuum line equipped with a manostat. The pot residue weighed 1.82 g, and the cold trap contained only 0.02 g of impure benzaldehyde (yield, *ca.* 4%).

The first experiment was repeated using a cold trap temperature of −40°. Only 0.02 g of material (mostly water by nmr analysis) was collected in the trap, and the pot residue weighed 2.93 g. Crystallization of the residue from ethanol–ether gave 0.24 g of cream-colored powder: mp 85–95° (*cf.* above); ir (CS_2) 3505 (medium, OH) and 3320 cm^{-1} (medium, OH), no C=O.

Anal. Found: C, 83.64; H, 5.59; Cl, 0.28; mol wt (benzene), 702.

In another experiment, 2.90 g of **1a** was heated at 180° for 3.0 hr while the cold trap was cooled to −40°. The distillate weighed 0.08 g, and its major constituent was shown to be benzaldehyde (yield, 5–10%) by nmr analysis. Programmed temperature vpc analysis showed that the residue contained only traces of volatile constituents. No evidence for **3a** (either monomeric or polymerized) was forthcoming from the residue's mass spectrum, and the nmr spectrum showed that benzaldehyde and **1a** were absent. Crystallization of the residue from ethanol–ether gave the following fractions (fraction number, weight, melting point, molecular weight in benzene): 1, 0.48 g, 155–165°, 2050;[33] 2, 0.50 g, 149–160°, 1120; 3, 0.36 g, 139–147°, 1370;[33] 4, 0.58 g, 125–133°, 990; 5, 0.20 g, 107–117°, 869. All fractions were pale orange powders. Fraction 4 was of particular interest because of its apparent similarity to the supposed tetrameric **3a** (lit.[2] mp 126–129°, lit.[2] mol wt 860–869) of Gomberg and Nishida. However, fraction 4 was conclusively shown not to have this type of structure by a variety of observations: ir (CS_2) 3540 cm^{-1} (strong, OH), no C=O; nmr (CCl_4) δ 6.1–7.4 (poorly resolved m, relative area *ca.* 17, aromatic H), 5.4–5.7 (poorly resolved m, relative area 1.0, Ar_3CH? and Ar_2CHO?), and 4.2–5.3 ppm (several broad, weak, and poorly resolved peaks, some of which disappeared on acidification).

Anal. Found: C, 86.53; H, 5.71; Cl, 0.12.

The other fractions had similar elemental compositions (ranges of found values: C, 85.7–87.0; H, 5.4–5.8; Cl, 0.1–0.4), and their nmr and ir spectra were similar to those of fraction 4.

(33) Osmometric molecular weight determination was performed in this laboratory under the direction of Dr. L. Westerman.

α,α-Diphenyl-o-cresol (7).—The following method of synthesis was employed by Baeyer,[28a] who did not include procedural details in his published account of the experiment.

A mixture of diol **6** (5.00 g, 18.1 mmol), zinc dust (7.5 g), and glacial acetic acid (25 ml) was stirred vigorously and heated under reflux for 2 hr. The hot mixture was filtered with suction, and the filter cake was washed with several portions of fresh solvent. Water was added in increments, with stirring, to the combined filtrate and washings until precipitation appeared complete. The crude product was then recovered by suction filtration and washed well with water; it weighed 4.65 g (yield, 99%) and was actually quite pure [mp 126–126.5° (lit.[28a] mp 124°)]. Recrystallization from benzene–petroleum ether gave **7** as white clumps: mp 127–127.5°; ir (CS_2) 3560 cm^{-1} (medium and rather broad, phenolic OH); nmr (CCl_4) δ 6.5–7.4 (m, 14, aromatic H), 5.62 (s, 1, aliphatic H), and 4.39 ppm (s, 1, disappears on acidification, OH); mass spectrum (70 eV) *m/e* 260.1199 (strong; calcd for $C_{19}H_{16}O$, 260.1201).

Decompositions of Alcohol 1b.—The reactions described in parts A–C were carried out in nmr tubes. All reactions were run under nitrogen.

A. With Trifluoroacetic Acid.—Trifluoroacetic acid (25 mg, 0.22 mmol) was added to a solution of **1b** (12 mg, 0.033 mmol) in dry C_6D_6 (0.48 ml), and the nmr spectrum of the dark mixture was recorded at frequent intervals until all of the alcohol had been consumed. The only detectable products were benzaldehyde and **7**; they were formed quantitatively within 0.6 hr. Product identifications were based on chemical shifts, vpc retention times, and spectral analyses of trapped vpc fractions, using pure reference compounds for comparison.

B. With Trifluoroacetic Acid-*d* Using 1b-*O*-*d*.—Alcohol **1b** underwent partial conversion to **1b-*O*-*d*** when it was kept for several days in warm (50°) benzene–CH_3OD solution. Continued repetition of the exchange procedure eventually gave **1b-*O*-*d*** containing 84 ± 1 atom % deuterium (according to nmr analysis). A solution of this material (24 mg, 0.065 mmol) in dry C_6D_6 (0.45 ml) was added under nitrogen to 89 mg (0.78 mmol) of CF_3CO_2D (see "Materials," above), and the progress of the reaction was followed by nmr. Quantitative formation of benzaldehyde and **7** occurred within 12 min, and careful expanded-scale integration showed that the PhCHO and Ph_2ArCH signals were of equal intensity (within the probable limits of experimental error, which were ±5–10%). Calculations based on these signals yielded the correct (measured) value for the total aromatic area.

C. With Trifluoroacetic Acid in the Presence of Alcohol 17.—Trifluoroacetic acid (35 mg, 0.31 mmol) was added to a solution of **1b** (19 mg, 0.052 mmol) and **17** (18 mg, 0.15 mmol) in dry C_6D_6 (0.46 ml), and the mixture was allowed to stand at room temperature with occasional analysis by nmr. No metastable intermediates were detected spectrally during the course of the reaction. After 8 hr the conversions of **1b** and **17** were *ca.* 91 and 79%, respectively, but further conversion of **1b** was quite slow. No **1b** remained after 8 days of reaction, and nmr analysis then gave the following result (yields are given in moles/moles of **1b**): **7**, 0.84 ± 0.02; benzaldehyde, 0.84 ± 0.02; **18**, 0.16 ± 0.02; *p*-tolualdehyde, 0.16 ± 0.02; **19**, 2.60 ± 0.07; **17**, 0.11 ± 0.01. All of the aliphatic proton resonances were resolved to a degree sufficient to allow their separate integration and identification by means of spectral reruns following the addition of authentic samples. The CHO protons originally had identical chemical shifts, but this degeneracy was easily removed by dropwise addition of triethylamine, and the downfield CHO peak was then shown to be that due to *p*-tolualdehyde by using the pure material for comparison. A similar comparison established the absence of **14**, and the presence of **7** and **18** was verified by comparing their vpc retention times and the ir and nmr spectra of trapped vpc fractions *vs.* those of authentic specimens.

D. With Formic Acid.—In close conformity with the procedure employed by Kauffmann and Pannwitz for reduction of (*o*-methoxyphenyl)diphenylmethanol,[26a] a solution of **1b** (1.00 g, 2.73 mmol) in formic acid (8.15 ml of "98–100%" material, *ca.* 215 mmol) was heated under reflux, with stirring, until the original dark red color had disappeared. After 30 min the pale rose-colored solution was evaporated *in vacuo*, and the residue was examined by nmr and vpc. A complete quantitative analysis was not attempted; however, comparisons with pure reference compounds showed that **1b** and **18** were absent and that benzaldehyde and **7** were the major products of the reaction (yields were roughly equivalent and were estimated to be at least 70–80%).

Benzyl α,α-Diphenyl-o-tolyl Ether (18).—This preparation was carried out under nitrogen. Phenol **7** (4.40 g, 16.9 mmol) was dissolved in 1 *N* aqueous sodium hydroxide (40 ml) by stirring and heating to 100°. Benzyl chloride (3.00 g, 23.7 mmol) was added to the hot solution, and after 40 min of heating (93–100°) and stirring, more of the benzyl halide (2.00 g, 15.8 mmol) was introduced. Stirring was continued for an additional 65 min at 92–93°; then the mixture was cooled to room temperature and extracted with benzene (100 ml in three portions). Evaporation of the dried extracts gave a semisolid residue, which was crystallized twice from methanol. The second crystallization afforded 2.22 g (38%) of **18** as small snow-white needles: mp 168.5–169.5°; ir (CS_2) no OH or C=O; nmr (CCl_4) δ 6.7–7.3 (m, 19, aromatic H), 5.85 (s, 1, methine H), and 4.88 ppm (s, 2, CH_2); mass spectrum (70 eV) *m/e* 350.1659 (medium; calcd for $C_{26}H_{22}O$, 350.1671).

Anal. Calcd for $C_{26}H_{22}O$: C, 89.11; H, 6.33. Found: C, 89.15; H, 6.45.

Reactions of (*o*-Hydroxyphenyl)diphenylmethanol (6) with Ester 14 and Benzyl Alcohol in the Presence of Trifluoroacetic Acid.—Trifluoroacetic acid (36 mg, 0.32 mmol) was added to an nmr tube containing a solution of **6** (8.9 mg, 0.032 mmol) and **14** (7.5 mg, 0.037 mmol) in dry C_6D_6 (0.48 ml). The reaction mixture was allowed to stand at room temperature under nitrogen with occasional analysis by nmr. After 68 hr, none of **14** had reacted, and neither **16** nor benzaldehyde had been formed. However, **7** was present (0.37 ± 0.02 mol/mol of starting **6**), and several unidentified peaks were detected in the aromatic region of the spectrum. Compound **7** was identified by chemical shift comparisons made *vs.* authentic material in two different solvent media (C_6D_6 and CCl_4). In a parallel experiment, **14** was omitted, and similar results were obtained.

A solution of **6** (7.5 mg, 0.027 mmol) and benzyl alcohol (3.7 mg, 0.034 mmol) in dry C_6D_6 (0.79 ml) was prepared in an nmr tube. Trifluoroacetic acid (46 mg, 0.40 mmol) was added, and the resulting dark mixture was allowed to stand at room temperature under nitrogen. Analysis by nmr showed that the initial reaction was quite rapid. However, the rate soon decreased, and an nmr spectrum taken after 16.7 hr indicated the following composition (moles/moles of starting **6**): **7**, 0.50 ± 0.03; **14**, 0.78 ± 0.04; **16**, 0.33 ± 0.02; benzaldehyde, 0.17 ± 0.01; **6**, 0.17 ± 0.01. The value for **6** could be in error, since it was calculated by difference using the total aromatic area. All other constituents were identified by comparisons of chemical shifts. These were made with solutions of the product mixture in C_6D_6 or CCl_4, following the addition of authentic specimens.

A similar experiment was performed using 55 mg (0.20 mmol) of **6**, 22 mg (0.20 mmol) of benzyl alcohol, 0.79 ml of dry C_6D_6, and 41 mg (0.36 mmol) of trifluoroacetic acid. In this case the rate of disappearance of **6** was slow even at the outset, and diol conversions were estimated to be only *ca.* 34 ± 3 and 65 ± 3% after reaction times of 10 and 34 days, respectively. The following compounds (moles/moles of starting **6**) were also present after 34 days: **7**, 0.34 ± 0.02; **14**, 0.58 ± 0.03; **16**, 0.31 ± 0.02; benzaldehyde, 0.03 ± 0.01; benzyl alcohol, 0.05 ± 0.01.

The preceding experiment was repeated on a larger (tenfold) scale, using ordinary dry benzene as solvent. After 14 days of standing, the mixture was shaken with 1 *N* aqueous sodium hydroxide and filtered with suction. The precipitate was washed several times with fresh benzene, and after the washings had been combined with the original filtrate, the benzene layer was removed and washed with two additional 15-ml portions of the caustic solution. Clarification of the combined aqueous layers was achieved by extraction with two 25-ml portions of ether. The extracts and the benzene solution were then combined, washed several times with water, dried, and evaporated. Extraction of the residue with 20 ml of warm (50°) 1 *N* sodium hydroxide, followed by two recrystallizations of the insoluble material from petroleum ether, gave 40 mg (6%) of **16**, mp 167–168°. The identity of the product was confirmed by a mixture melting point determination and an ir spectral comparison.

2,4,4-Triphenyl-1,3-benzodioxane (16).—Trifluoroacetic acid (0.69 g, 6.1 mmol) was added dropwise during 0.2 hr to a stirred solution of diol **6** (0.55 g, 2.0 mmol) and benzaldehyde (0.21 g, 2.0 mmol) in dry benzene (20 ml). After 1.8 hr of standing under nitrogen, the solution was evaporated to give an off-white solid residue which, in view of its melting point (166–168°), was presumed to be an essentially pure material. Recrystallization of the solid from petroleum ether afforded silky snow-white needles (0.51 g, 71%) of **16**: mp 168–169°; ir (CS_2) no OH

or C=O; nmr (CCl_4) δ 6.7–7.6 (m, 19, aromatic H) and 5.87 ppm (s, 1, aliphatic H).

Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53; mol wt, 364. Found: C, 85.85; H, 5.51; mol wt (benzene), 377.

Registry No.—**1a**, 30316-41-7; **1b**, 30316-42-8; **7**, 4970-23-4; **9**, 30309-97-8; **10**, 30309-98-9; **16**, 30309-99-0; **18**, 30310-00-0.

Acknowledgment.—The author is indebted to Mr. H. J. Tarski for excellent general technical assistance, to Mr. T. Hines for meticulous performance of nmr experiments, and to Dr. R. Pettit for comments on the manuscript. Analytical assistance was generously provided by several other colleagues in the analytical section of this laboratory.

Chemical Syntheses with Bergmann–Schlenk Adducts. VII.[1] Benzil Dianil

E. J. MacPherson and James G. Smith*

Department of Chemistry, University of Waterloo, Waterloo, Ontario

Received December 23, 1970

The reduction of benzil dianil (**1**) with sodium in tetrahydrofuran produced the *N,N'*-disodio-*N,N'*-diphenyl-α,α'-stilbenediamine (**2**). Chemical reactions of this compound with ethyl chloroformate, diethyl oxalate, methyl iodide, allyl bromide, 1,3-dihalopropanes, and water were examined. A cis configuration is suggested for **2**.

In continuing our study[1] of the synthetic utility of Bergmann–Schlenk adducts of conjugated bisimines, a compound in which the azomethine groups were united through the carbon atoms rather than the nitrogens was selected. The natural choice was benzil dianil (**1**) but the preparation of this venerable compound offered some difficulties. Julian's procedure,[2] utilizing benzil as starting material, proved adequate but required careful control of the reaction conditions. The seemingly more convenient procedure[3] for the preparation of **1** using *N*-benzylideneaniline as starting material was, in our hands, only sporadically successful. However, as Becker has recently shown,[4] this reaction depends on the initial formation of α,α'-dianilinostilbene and its subsequent oxidation to benzil dianil (**1**). By slightly modifying Becker's procedure, a convenient synthesis of **1** was obtained.

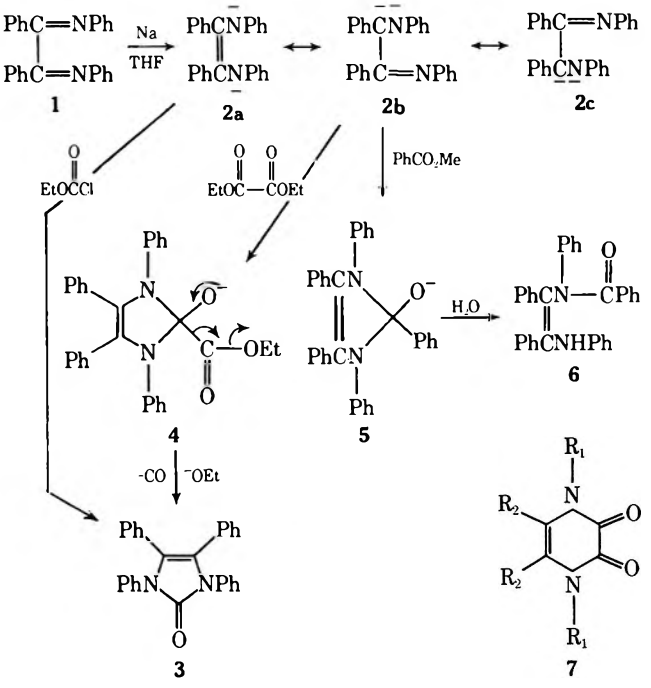
With tetrahydrofuran as solvent and sodium metal as reducing agent, benzil dianil (**1**) was rapidly converted to an adduct **2**, containing 2 g-atoms of sodium per mole of dianil. The initially formed radical anion provided an opaque red-brown solution which changed to a transparent red as the formation of the dianion **2** neared completion.

As observed earlier,[1] the reaction of only one of the two azomethine groups would appear to reflect stabilization of the dianion by the remaining azomethine group participating in the delocalization of the added electrons. Resonance structures involving an azaallylic[5] anion (**2a–c**) can be formulated.

Acylation.—Several reactions were used to characterize the dianion **2** and those employing esters are summarized in Scheme I. With either 1 or 2 mol of ethyl chloroformate, an excellent yield of the known compound 1,3,4,5-tetraphenyl-1,3-imidazolin-2-one (**3**) was isolated. Surprisingly, this same product was isolated when diethyl oxalate was used. Since the expected amount of carbon monoxide was evolved, the

Scheme I

Acylation of the Benzil Dianil Disodium Adduct



initially formed product **4** readily decarbonylates to provide **3**. The unstable intermediate has been formulated as **4** rather than the alternative **7** (R_1 = R_2 = Ph, which might conceivably be formed and suffer a base-catalyzed benzil–benzilic acid rearrangement to **4**) since the known compounds[6,7] **7** (R_1 = Ph, R_2 = H and R_1 = Me, R_2 = H) appear quite stable.

Diethyl dimethylmalonate failed to react with the dianion **2**.

With methyl benzoate the dianion **2** provided *N*-benzoyl-α,α'-dianilinostilbene (**6**) identical with an authentic sample.[8,9] Formation of only a monobenzoyl derivative is reminiscent of the behavior of the diastereomeric *N,N'*-disodio-*N,N'*-1,2-tetraphenylethylenediamines.[9] The explanation offered there applies equally

(1) E. J. MacPherson and J. G. Smith, *Can. J. Chem.*, **48**, 1904, 1915 (1970), papers V and VI of this series.

(2) P. L. Julian, E. W. Meyer, A. Magnani, and W. Cole, *J. Amer. Chem. Soc.*, **67**, 1203 (1945).

(3) J. S. Walia, J. Singh, M. S. Chattha, and M. Satyanarayana, *Tetrahedron Lett.*, 195 (1969).

(4) H.-D. Becker, *J. Org. Chem.*, **35**, 2099 (1970).

(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 187.

(6) J. Honzl, *Collect. Czech. Chem. Commun.*, **25**, 2651 (1960).

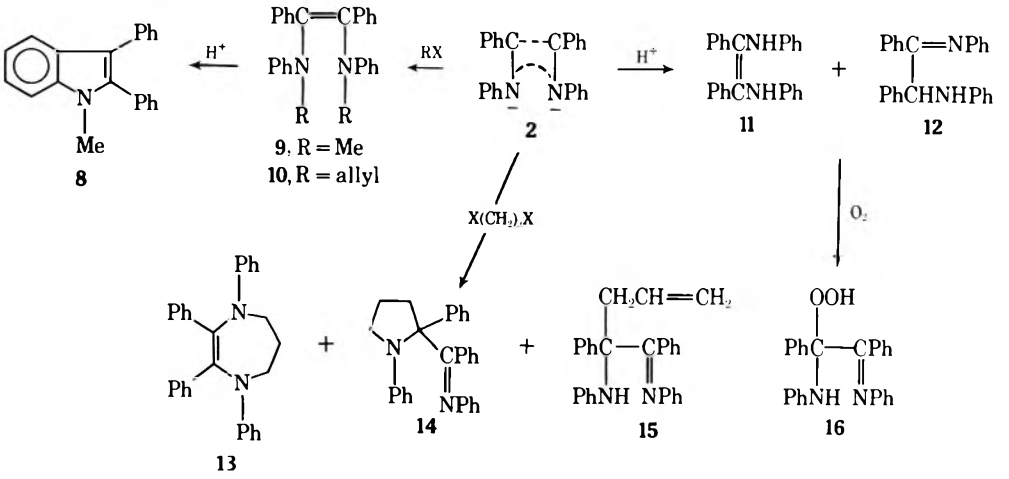
(7) G. W. H. Cheeseman and E. S. G. Torzs, *J. Chem. Soc.*, 6681 (1965).

(8) A. E. Everest and H. McCombie, *ibid.*, **99**, 1752 (1911).

(9) J. G. Smith, *Can. J. Chem.*, **44**, 59 (1966).

SCHEME II

ALKYLATION AND PROTONATION OF THE BENZIL DIANIL-DISODIUM ADDUCT



well here; after the introduction of one benzoyl group, the remaining anion "protects" itself by reacting with the carbonyl group forming **5**.

Alkylation.—In the acylation reactions, only substitution on the nitrogens was observed. Such a behavior is not unexpected for esters, a similar pattern having been noted for the dianion generated from benzophenone anil.[10] In an attempt to encourage substitution at the potential carbanionic center of **2**, several alkylation reactions were studied.

Both methyl iodide and allyl bromide effected alkylation on the nitrogen forming *N*,*N*′-dimethyl-α,α′-dianilinostilbene (**9**) and the analogous *N*,*N*′-diallyl compound **10**. Both **9** and **10** possessed uv spectra reflecting their similar conjugated systems and neither showed absorption in the ir spectrum due to a C=N group. Equivalent allyl and methyl groups were indicated by the nmr spectrum although in the case of **9** the methyls became nonequivalent in $CDCl_3$. The inability to form a dinitrophenylhydrazone from **9** also supported the absence of a C=N group. A final structure proof for **9** was obtained by converting it in refluxing[11] methanolic HCl to 1-methyl-2,3-diphenylindole (**8**) and *N*-methylaniline.

Both methylene iodide and 1,2-dibromoethane were examined in an attempt to prepare imidazoline and tetrahydropyrazine derivatives. No definite products could be isolated from the reaction mixtures (Scheme II).

A more successful reaction occurred with 1,3-diiodo- and 1,3-dibromopropane. Although the reaction mixtures were complex, 4,5,6,7-tetrahydro-1,2,3,4-tetraphenyl-1*H*-1,4-diazepine (**13**) and 1,2-diphenyl-2-(*N*-phenylbenzimidoyl)pyrrolidine (**14**) were isolated. The former compound showed no NH or C=N absorption in the ir spectrum; the uv spectrum resembled that of **9** and **10** and, similar to these last two, **13** fluoresced under ultraviolet radiation. The nmr spectrum showed a triplet for the two NCH_2 groups and a quintet for the remaining CH_2, and the mass spectrum gave a strong parent ion. The pyrrolidine derivative **14** showed absorption in the ir due to C=N; the uv spectrum resembled that of *N*-benzylideneaniline and it did not fluoresce in ultraviolet radiation. Its mass spectrum showed a weak parent ion, the chief fragmentation being cleavage of the bond joining the benzylic carbons forming ions of *m*/*e* 222 and 180.

Accompanying **13** and **14** were a number of other products from which the *N*,*N*′-diallyl derivative **10** and a monoallyl compound believed to be **15** were obtained. Isolation of these compounds was complicated by the instability of their solutions to light and oxygen. At least one of the unidentified compounds decomposed during short periods of storage to form isolable quantities of benzanilide and benzil monoanil.

Obviously this last alkylation is accompanied by appreciable amounts of dehydrohalogenation. Further complicating the reaction is the competitive alkylation on the carbanionic center and on the amino anionic center of the azaallylic anion, the former producing **14** while the latter, **13**. The more reactive 1,3-diiodopropane is the less discriminating and produces more of the carbon–nitrogen dialkylation product **14**.

Protonation.—Treatment of the dianion **2** with water, methanol, or acetic acid generated a reaction mixture which by tlc consisted of two components. The minor component, which fluoresced yellow-green under uv light, was isolated by crystallization and proved to be identical with the α,α′-dianilinostilbene **11** described by Becker.[4] Attempts to isolate the major (nonfluorescent) component by recrystallization or chromatography led either to the regeneration of benzil dianil or to the formation of a hydroperoxide.

This hydroperoxide was more conveniently generated by oxygenating the protonated mixture. Its ir spectrum showed absorption for amino, hydroxyl, and azomethine groups and satisfactory analyses, peroxide titrations, and mass spectra for the structure **16** were obtained. On thermal decomposition, **16** formed benzil dianil.

The sensitivity of enamines (*cf.* **11**) to oxidation is well known[4,12] and imines (*cf.* **12**) have frequently been reported to form hydroperoxides.[13,14] However, **16** cannot be considered as evidence for the existence of

(10) J. G. Smith and C. D. Veach, *Can J. Chem.*, **45**, 1785 (1967).

(11) The ease of this reaction lends credence to Julian's suggestion[2] that compounds such as **9** are intermediates in the Bischler synthesis of indoles from benzoins and arylamines.

(12) A. G. Cook, Ed., "Enamines," Marcel Dekker, New York, N. Y., 1969, p 285.

(13) C. L. Stevens and R. J. Gasser, *J. Amer. Chem. Soc.*, **79**, 6057 (1957).

(14) L. A. Cohen and B. Witkop, *ibid.*, **77**, 6595 (1955).

12 in the protonation mixture since the hydroperoxide 16 can be formed from 11 itself.

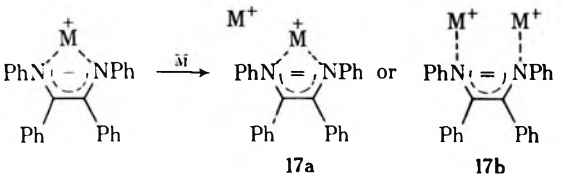
The major product formed on protonation must be either the imine 12 or the geometric isomer of 11. We favor the former possibility for two reasons. First, the major product can be partially isomerized to 11 by sodium cyanide in dimethylformamide. Such an isomerization has been observed for a related pair of compounds[4] whose oxidative stabilities were sufficiently great that their structural relationship could be established. Secondly, the major product showed no fluorescence on irradiation with uv light. Fluorescence would be expected for compounds such as 11 which are related to stilbene and indeed is observed for 9, 10, and 13. However, for compounds 14 and 16 which are related to *N*-benzylideneaniline, no fluorescence is observed.

Discussion

As might be expected, the charge density of the dianion 2 is concentrated on the more electronegative nitrogen atoms. Thus acylation, and to a large extent alkylation, occurs at these centers producing derivatives of α,α'-dianilinostilbene. Only in the case of the 1,3-dihalopropanes is carbon alkylation observed as well. Here, dialkylation at the nitrogens is sterically unfavorable due to formation of the seven-membered ring and formation of the more favorable five-membered ring occurs in detectable amounts. However, the reactivity of the dihalide is an important factor. In the case of 1,3-dibromopropane, the slower alkylation reaction allows side reactions, presumably dehydrohalogenation, to dominate with a consequent formation of unstable by-products.

We favor the view that the dianion 2 is predominantly in a cis configuration. Such a formulation explains most simply the easy formation of the imidazolinone ring from both ethyl chloroformate and diethyl oxalate, the formation of only a monobenzamide with methyl benzoate, and the remarkably facile cyclodehydrogenation of the analogous dilithio dianion to a phenanthrene ring.[15] The possibility of a rapid isomerization of a trans dianion to a cis, followed by a subsequent slow reaction with the added reagent cannot be excluded. However, it would be surprising if such a sequence did not produce mixtures of trans and cis products and this has not been observed.

Indeed, the existence of a cis 1,4 dianion is not without precedence. Bauld[16] has demonstrated that the radical anion and the dianion of benzil both favor a cis configuration, especially in nonpolar solvents. His explanation is applicable here. The radical anion first formed adopts the cis configuration in order that the two nitrogen atoms which bear most of the negative charge density may coordinate efficiently with the counterion. Isomerization of the radical ion to a trans configuration is slower than the rate of electron transfer from metals. Consequently, the dianion which arises then has the cis configuration as represented in 17a or 17b.



17a 17b

(15) E. J. MacPherson and J. G. Smith, *Chem. Commun.*, 1552 (1970).
(16) N. L. Bauld, *J. Amer. Chem. Soc.*, **87**, 4788 (1965).

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-10 and uv spectra on a Cary spectrometer. Nmr spectra were determined with a Varian T60 or 100-Mc spectrometer with tetramethylsilane as internal standard. Tlc was performed with Eastman chromagram precoated silica gel sheets with fluorescent indicator and visualized with uv light. Mass spectra were determined on a Perkin-Elmer RMU6 spectrometer. For several of the compounds it was found necessary to use degassed solvents and to operate as much as possible under nitrogen.

Benzil Dianil (1). The procedure of Julian[2] provided benzil dianil (1) in 50% yield, mp 140–145°.

In a more convenient procedure, α,α'-dianilinostilbene[4] (11) (36.2 g, 0.1 mol) suspended in 250 ml of chloroform and 50 ml of anhydrous methanol was treated with a stream of dry oxygen until all the solid had dissolved. The solvent was evaporated, the residue washed with a small amount of ethanol, and the residue recrystallized from ethanol to give 33 g (90%) of 1, mp 143–145°.

Preparation of Benzil Dianil Disodium Adduct 2.—The sodium adduct was prepared by shaking a solution of 1.8 g (0.005 mol) of benzil dianil in 100 ± 10 ml of anhydrous tetrahydrofuran with an excess of sodium in a modified Schlenk tube for 8 hr. Details of similar reactions and the measurement of sodium uptake have been described elsewhere.[1,9,10]

Initiation of reaction occurred almost immediately as indicated by an opaque brown-red color developing in the solution. After 2 hr the solution became red and transparent and titration indicated 2 g-atoms of sodium per mole of initial dianil. No further change was detected in the next 24 hr.

For subsequent reactions, the solution was drained from the excess metal into a nitrogen-filled flask to which the second reagent was injected through a septum.

Preparation of 1,3,4,5-Tetraphenyl-4-imidazolin-2-one (3).—The adduct 2, cooled to −60°, was treated with 0.54 g (0.005 mol) of ethyl chloroformate. After warming to room temperature and stirring for 24 hr, the reaction was quenched with water and the product isolated by ether extraction. Evaporation of the solvent gave 1.92 g of crude product, mp 195–203°. Recrystallization from cyclohexane gave 1.54 g (80%) of 3, mp 206–207°, undepressed on admixture with an authentic sample:[4] ir (KBr) 1705 cm^{-1} (C=O); uv max (95% EtOH) 295 mμ (ε 10,600); mass spectrum (70 eV) *m/e* (rel intensity) 389 (30), 388 (100, M^+), 387 (15), 180 (31), 77 (26).

Repetition of this experiment with 1.08 g (0.01 mol) of ethyl chloroformate gave 1.95 g (100%) of 3, mp 203–206°.

The adduct 2 was treated with 0.73 g (0.005 mol) of diethyl oxalate in a closed system so that any evolved gases could be collected. Over the next 12 hr, 104 ml (corrected to STP, 93%) of carbon monoxide was evolved and identified by its ir spectrum.

The solution was treated with water and the product isolated by ether extraction. The residue obtained on evaporating the extracts was treated with *n*-hexane and filtered giving 1.8 g (93%) of 3, mp 190–200°. Recrystallization from ethanol–water raised the melting point to 205°, undepressed on admixture with an authentic sample.

Preparation of *N*-Benzoyl-α,α'-dianilinostilbene (6).—The adduct 2 was treated with 1.36 g (0.01 mol) of methyl benzoate at −60° and allowed to warm to room temperature. After 5 hr the color had changed from red to pale yellow. The product was isolated by adding water and extracting with ether. Evaporation of the extracts gave 2.1 g (91%) of a yellow solid, mp 215–219° (sealed tube). Recrystallization from degassed acetonitrile under nitrogen gave 6, mp 222–223° (sealed tube), undepressed on admixture with an authentic sample,[8,9] whose ir spectrum was identical with that of the authentic sample: uv max (95% EtOH) 255 mμ (ε 21,300) 355 (15,800); mass spectrum (70 eV) *m/e* (rel intensity) 467 (21), 466 (53, M^+), 449 (37), 362 (26), 361 (88), 270 (20), 269 (90), 180 (100), 105 (26), 77 (84).

Preparation of *N,N'*-Dimethyl-α,α'-dianilinostilbene (9).—The dianion **2** at −60° was treated with 1.42 g (0.01 mol) of methyl iodide. Rapid decolorization occurred and, after warming to room temperature, the product was isolated by quenching in water and extracting with ether. Evaporation of the ether gave 1.94 g of residue, mp 146–152°, showing a green fluorescence under uv. Recrystallization from degassed acetone under nitrogen gave 1.2 g (62%) of **9**: mp 173–175.5° (sealed tube); uv max (95% EtOH) 272 mμ (ε 18,700), 302 (16,000), 382 (10,200); ir (KBr) 2810 (NCH_3), 2900 and 2915 cm^{-1} (aliphatic CH), no absorption for C=N; nmr (C_6D_6, degassed and sealed) δ 2.50 (s, 6, NCH_3), 6.6–7.3 (m, 20, aromatic CH); nmr ($CDCl_3$ degassed and sealed) δ 2.62 and 3.0 (singlets, 6, NCH_3), 6.5–7.4 (m, 20, aromatic CH); mass spectrum (70 eV) *m/e* (rel intensity) 391 (63), 390 (M^+, 100), 375 (34), 270 (20), 269 (57), 195 (23), 180 (70), 77 (20).

Anal. Calcd for $C_{28}H_{26}N_2$: C, 86.30; H, 6.72; N, 7.19. Found: C, 86.43; H, 6.55; N, 7.19.

Preparation of *N,N'*-Diallyl-α,α'-dianilinostilbene (10).—The sodium adduct **2** was treated with 1.21 g (0.01 mol) of allyl bromide at −60°. After being warmed to room temperature and stirred for 8 hr, the product was isolated by adding water and extracting with ether. Evaporation of the extracts gave 2.1 g of an oily yellowish solid which on recrystallization from *n*-hexane gave 1.55 g (70%) of **10**: mp 165–166°; uv max (95% EtOH) 278 mμ (ε 18,900), 302 (shoulder, 14,800), 382 (12,000); ir (KBr) 2860, 2905, 2920, 2980 cm^{-1} (aliphatic CH); nmr (degassed C_6D_6) δ 3.8 (m, 4, CH_2) 4.9 (m, 4, CH_2=), 5.7 (m, 2, CH=), 6.9 (m, 20, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 443 (22), 442 (58, M^+), 401 (31), 372 (24), 269 (26), 180 (93), 77 (100).

Anal. Calcd for $C_{32}H_{30}N_2$: C, 86.82; H, 6.85; N, 6.33. Found: C, 86.99; H, 6.79; N, 6.72.

Preparation of 1-Methyl-2,3-diphenylindole (8).—*N,N'*-Dimethyl-α,α'-dianilinostilbene (**9**) (0.90 g, 0.0023 mol) was dissolved in 75 ml of methanol containing 1 ml of concentrated HCl and refluxed under nitrogen for 5 hr. On tlc (*n*-hexane–benzene, 10:3) the fluorescent green spot of **9** was gradually replaced by a fluorescent blue spot of lower R_f.

After being cooled and neutralized (Na_2CO_3), the product was isolated by an ether extraction. Evaporation gave an oily white solid which on recrystallization from methanol gave 0.56 g (85%) of **8**, mp 138°, undepressed on admixture with an authentic sample.[17] Evaporation of the filtrate gave an oil identified as *N*-methylaniline by its ir spectrum.

Reaction with 1,3-Dihalopropanes.—The dianion **2** was treated at −60° with 1.48 g (0.005 mol) of 1,3-diiodopropane. Decolorization occurred within 10 min and, after being warmed to room temperature, the product was isolated by adding water and extracting with ether. Evaporation of the solvent provided an oily solid which was triturated with anhydrous ether and the white solid filtered off giving 0.94 g (≤7%) of 1,2-diphenyl-2-(*N*-phenylbenzimidoyl)pyrrolidine (**14**): mp 201–202° [recrystallization from degassed diethyl ether (under N_2) did not raise the melting point]; no fluorescence under uv radiation; uv max (95% EtOH) 250 mμ (ε 14,100) 293 (4600); ir (KBr) 2850, 2960, 2980 (aliphatic CH), 1635 cm^{-1} (C=N); nmr (C_6D_6) δ 1.7 (m, 2, CH_2), 2.4 (m, 2, CH_2), 3.5 (m, 2, NCH_2), 6.9 (m, 20, aromatics); mass spectrum (70 eV) *m/e* (rel intensity) 402 (0.5, M^+), 223 (74), 222 (100), 180 (52), 103 (20), 91 (35), 78 (30), 77 (66), 51 (37).

Anal. Calcd for $C_{29}H_{26}N_2$: C, 86.52; H, 6.52; N, 6.96. Found: C, 86.67; H, 6.56; N, 7.05.

The filtrate was evaporated and the residue chromatographed on silica gel with hexane–benzene 10:3 as eluent. The first fraction (90 mg) was crystallized from *n*-hexane to give 30 mg (1.5%) of *N,N'*-diallyl-α,α'-dianilinostilbene (**10**), mp 165–166°, identified by mixture melting point.

The second fraction, 0.33 g (16.5%), mp 222–224°, was 4,5,6,7-tetrahydro-1,2,3,4-tetraphenyl-1*H*-1,4-diazepine (**13**) (recrystallization from anhydrous diethyl ether did not raise the melting point): fluoresced blue in uv radiation; uv max (95% EtOH) 286 mμ (ε 20,700) 370 (30,600); ir (KBr) 2860, 2895, 2925, 2960 cm^{-1} (aliphatic CH), no absorption for C=N; nmr (C_6D_6) δ 1.67 (quartet, 2, J = 5 Hz, CH_2), 3.85 (t, 4, J = 5 Hz, NCH_2), 6.8 (m, 20, aromatics); mass spectrum (70 eV) *m/e* (rel intensity) 403 (30), 402 (100, M^+) 374 (22), 180 (32), 77 (31).

Anal. Calcd for $C_{29}H_{26}N_2$: C, 86.52; H, 6.52; N, 6.96. Found: C, 86.25; H, 6.49; N, 7.11.

The third fraction (320 mg) proved to be a mixture (tlc) and was rechromatographed on a preparative tlc silica gel plate giving 145 mg (3.6%) of a white solid, mp 132–135°. Three recrystallizations from ethanol gave 25 mg, mp 143–144°, tentatively identified as 2-anilino-*N*-1,2-triphenyl-4-penten-1-imine (**15**): ir (KBr) 2920, 2990 (aliphatic CH), 1640 (C=N), 3350 cm^{-1} (NH); nmr (C_6D_6) δ 1.1 (s, 1, NH), 5.2 (m, 2, CH=), 6.7 (m, 20, aromatics), and two overlapping quartets centered at 3.35 (the AB portion of an ABX pattern with $J_{AX} = J_{BX}$,[18] J_{AB} = 15 Hz, 2 protons, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 402 (3.5, M^+), 361 (12), 269 (16), 223 (33), 222 (100), 221 (33), 181 (14), 180 (75), 77 (48).

Anal. Calcd for $C_{29}H_{26}N_2$: C, 86.51; H, 6.52; N, 6.96. Found: C, 86.25; H, 6.62; N, 6.92.

The fourth fraction (240 mg) was crystallized with ethanol giving 200 mg (7%) of benzil monoanil, mp 98–100°, identified by a comparison of the ir spectrum with an authentic sample and by mixture melting point.

A fifth fraction was eluted from the column with chloroform and proved to be benzanilide (50 mg, mp 160°) by comparison with an authentic sample.

This reaction was repeated using the adduct from 3.6 g (0.01 ml) of benzil dianil in 200 ml of THF and 2.01 g (0.01 mol) of 1,3-dibromopropane. The reaction mixture stood overnight at room temperature before decolorization was complete. The crude reaction product was isolated by an ether extraction of the water-quenched mixture and the entire product chromatographed on silica gel. The following products were eluted: 65 mg (1.5%) of **10**, mp 167–168°; 2.32 g of yellow oil which deposited 0.42 g (10%) of **13**, mp 222–224° (on treatment with ether and cooling, no further material could be isolated from this oil which decomposed on standing); 0.30 g of an oil which yielded 50 mg (1.2%) of **15**, mp 141–142° on preparative tlc; 0.83 g of a solid which on recrystallization from ether gave 0.64 g (16%) of **14**, mp 201–202°; 0.47 g (16%) of benzil monoanil, mp 95°; 0.31 g of an oily solid which on recrystallization from benzene gave 0.12 g of benzanilide, mp 161–163°.

Protonolysis of Disodium Adduct 2.—Treatment of the adduct **2** at −60° with 0.5 ml (0.012 mol) of methanol (or 0.6 g, 0.01 mol of acetic acid) effected immediate decolorization. A tlc using 10:3 *n*-hexane–benzene as developing solvent showed 2 spots, the larger appearing dark blue on visualization while the smaller lead spot fluoresced blue-green. If isolation of the product was attempted using the normal procedures of extracting the water-quenched mixture with ether, only benzil dianil (1.8 g, 100%), mp 138–140°, was obtained and identified by mixture melting point.

The isolation was repeated using degassed water and degassed ether, and the ether extraction was performed under nitrogen. Drying the extracts was accomplished by filtering through a filter stick containing $MgSO_4$ into a nitrogen-filled flask. Evaporation on a vacuum line gave a yellow-green oil and a solution of this oil in degassed anhydrous ether deposited, on refrigeration, 0.20 g (11%) of **11**, identified by its ir spectrum. This material gave the same behavior on tlc as the smaller lead spot of the reaction mixture.

In a repetition of this experiment the yellow green oil was dissolved in 30 ml of 1:1 degassed ether–*n*-hexane. Cooling and filtering under nitrogen provided 1.46 g of a yellow-green solid:[19] mp 145–147° (sealed tube); ir (KBr) indicated formation of the hydroperoxide **16** during the preparation of the disk.

An attempt to purify the material by recrystallization from ether gave a solid, mp 120–121°, whose ir spectrum identified it as the hydroperoxide **16**.

Preparation of Hydroperoxide 16.—The adduct **2** was protonated at −60° with 0.6 g (0.01 mol) of glacial acetic acid. After being warmed to room temperature dry oxygen was bubbled through the solution for 5 hr. Water was added and the product was isolated by ether extraction, drying ($MgSO_4$), and evaporating (no heat) the extracts. The residue was triturated with *n*-hexane and the white solid filtered, 1.6 g, mp 110–120°, with

(17) E. Ritchie, *J. Proc. Roy. Soc. N. S. W.*, **80**, 33 (1946).

(18) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Elmsford, N. Y., 1965, p 364.

(19) Julian[2] described desylaniline anil of uncertain purity, mp 160–185°.

gas evolution. Titration[20] of this material showed it to be 83% hydroperoxide **16**.

It was purified by dissolving in anhydrous ether at 20°, filtering, adding *n*-hexane, and cooling to 0°. The solid, mp 119–120°, with gas evolution, analyzed as 98.6% hydroperoxide **16**: ir (KBr) 3470, 3450 (OH, NH), 1640 cm^{-1} (C=N); mass spectrum (70 eV) *m/e* (rel intensity) 394 (1, M^+), 361 (32), 360 (80), 197 (22), 186 (32), 181 (64), 180 (100), 149 (25), 105 (35), 93 (37), 77 (72).

Anal.[21] Calcd for $C_{26}H_{22}N_2O_2$: C, 79.15; H, 5.63; N, 7.10. Found: C, 78.92; H, 5.84; N, 7.00.

A 100-mg sample of **16** heated under vacuum at 150° for a few minutes decomposed with gas evolution. The product, recrystallized from methanol, gave 50 mg (55%) of benzil dianil identified by mixture melting point.

A solution of 1.56 g (0.0043 mol) of α,α′-dianilinostilbene (**11**) and 0.66 g (0.0086 mol) of anhydrous sodium acetate in 75 ml of THF was stirred overnight by a stream of dry O_2. Isolation of the hydroperoxide **16** was accomplished as previously described, 1.3 g, mp 110–120°, with gas evolution, identified by the ir spectrum.

Isomerization[4] of the Protonation Product.—The adduct **2** was protonated at −60° with 0.6 g (0.01 mol) of acetic acid and warmed to room temperature, and 35 ml of anhydrous DMF containing 100 mg of sodium cyanide was added. Nitrogen was bubbled through the mixture and the THF permitted to distil. The remaining solution was stirred by the nitrogen stream for 48 hr. The reaction was monitored by tlc (1:1 benzene–*n*-hexane) and during this time the fluorescent spot increased in size relative to the nonfluorescent spot.

Addition of water and extraction with ether and evaporation of the extracts provided the crude reaction product. Methanol (50 ml) was added and after 4 hr at 0°, 0.34 g (19%) of α,α′-dianilinostilbene were deposted and identified by its ir spectrum. Attempts to isolate anything further from the filtrates by evaporation and crystallization provided only 1.2 g (67%) of benzil dianil identified by mixture melting point.

Registry No.—**1**, 7510-33-0; **9**, 29954-13-0; **10**, 29954-14-1; **13**, 29954-15-2; **14**, 29954-16-3; **15**, 29954-17-4; **16**, 29954-18-5.

Acknowledgment.—The financial support of the National Research Council of Canada is gratefully acknowledged. The award of a Province of Ontario Graduate Fellowship to one of us (E. J. M.) is also appreciated.

(20) R. L. Augustine, Ed., "Oxidation," Vol. 1, Marcel Dekker, New York, N. Y., 1969, p 222.

(21) We are grateful to Mr. W. Boos of the Uniroyal Research Laboratories, Guelph, Ontario, who arranged for the immediate analysis of this compound.

Reactions of Aryl Azides with Carbonyl-Stabilized Sulfonium Ylides

E. VAN LOOCK, G. L'ABBÉ,* AND G. SMETS

Department of Chemistry, Laboratory of Macromolecular Chemistry, University of Louvain, Louvain, Belgium

Received February 12, 1971

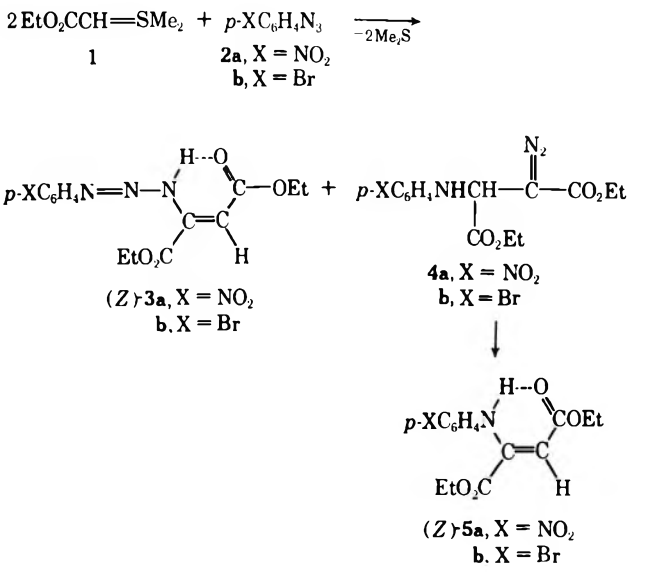
Aryl azides have been found to react with 2 equiv of carbethoxymethylenedimethylsulfurane to give a mixture of aryltriazenofumarates and anilinodiazosuccinates in various amounts depending on the solvent. Reaction of aryl azides with phenacylidenesulfuranes at room temperature produces 1-anilino-1,2-dibenzoylethylenes in addition to small amounts of 1-triazeno-1,2-dibenzoylethylenes (in equilibrium with the cyclic Δ^2-triazolines) and *trans*-1,2,3-tribenzoylcyclopropane. The stereochemistry of the reaction products is discussed as well as the mechanism of their formation.

Although phosphonium and sulfonium ylides are similar in structure, they have been found to react differently on several occasions. Johnson,[1] in reviewing the chemistry of both classes of ylides, clearly pointed out that the formation of a P=O bond (128 kcal/mol^{-1}) is the driving force in most *P*-ylide reactions, whereas *S*-ylides benefit from the sulfide leaving group. This principle is best illustrated by the synthesis of olefins and oxiranes by treating carbonyl compounds respectively with *P*- and *S*-ylides.

Different behavior is also observed in the reactions of nonstabilized phosphonium and oxysulfonium ylides with aryl azides, the former leading to imines[2] and the latter to triazenes and Δ^2-triazolines.[3] In recent studies, the reactions of carbonyl-stabilized phosphonium ylides with aryl azides led to triazoles or diazo compounds.[4] For comparison, in this paper we have investigated the reactions of the corresponding sulfonium ylides with aryl azides.[5]

Results

Carbethoxymethylenedimethylsulfurane (**1**) reacts smoothly with aryl azides **2a,b** at room temperature to give a mixture of aryltriazenofumarates (*Z*)-**3a,b**[6]



(1) A. W. Johnson, "Ylid Chemistry," A. T. Blomquist, Ed., Academic Press, New York, N. Y., 1966, p 331.

(2) H. Hoffmann, *Chem. Ber.*, **95**, 2563 (1962).

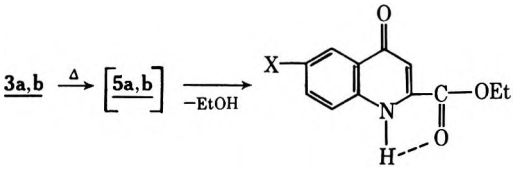
(3) G. Gaudiano, C. Ticozzi, A. Umani-Ronchi, and P. Bravo, *Gazz. Chim. Ital.*, **97**, 1411 (1967).

(4) G. R. Harvey, *J. Org. Chem.*, **31**, 1587 (1966). P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron*, **25**, 5421 (1969); **27**, 845 (1971).

(5) For a preliminary report on this topic, see E. Van Loock, G. L'abbé, and G. Smets, *Tetrahedron Lett.*, 1693 (1970); see also Y. Hayashi, T. Watanabe, and R. Oda, *ibid.*, 605 (1970). This research was presented in part at the International Symposium on Ylides, Leicester, England, July 1970.

(6) (*Z*) and (*E*) are used to designate cis–trans isomers according to the sequence rule procedure; see "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry," *J. Org. Chem.*, **35**, 2849 (1970).

and anilinodiazosuccinates **4a,b**. Their structures were assigned on the basis of elemental analysis and spectral evidence. In particular, the ir and nmr spectra of (*Z*)-**3a,b** indicated intramolecular chelation as shown by the weak N–H absorption at 3190–3210 cm^{-1}, the two distinct C=O bonds at 1730 and 1670 cm^{-1}, and the large nmr δ value (*ca.* 12) for the N–H proton. The mass spectra of (*Z*)-**3a,b** displayed fragments corresponding to $M\cdot^+ - N_2$, $M\cdot^+ - CO_2Et$, $(XC_6H_4N_2)^+$, and $(XC_6H_4)^+$ in addition to the molecular ion peak $M\cdot^+$. Thermolysis of **3a** and **3b** in refluxing diphenyl ether affords the quinolones **6a** and **6b**, presumably



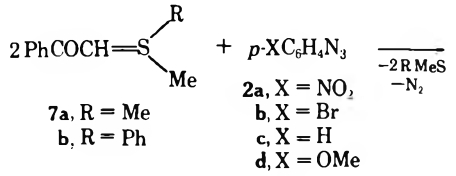
6a, X = NO_2
b, X = Br

via (*Z*)- and/or (*E*)-**5a,b**, and thus provides an extension of the Conrad–Limpach quinolone synthesis.[7]

The diazo compounds **4a,b** showed in the ir spectra a strong N–H band at *ca.* 3400 cm^{-1} and a diazo band at 2100 cm^{-1}. Their nmr spectra were also consistent with structure **4** and showed, *inter alia*, doublets at δ 5.58 and 5.10 (J = 6.5 Hz) for the N–H and tertiary protons. Deuterium exchange resulted in the disappearance of the former and collapse of the latter to a broad singlet at δ 5.10.

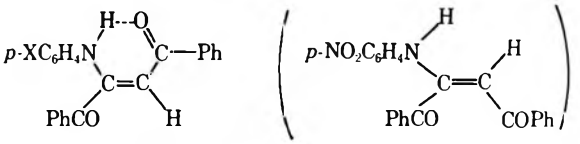
The nature of the solvent influences strongly the relative amounts of products **3a** and **4a**. A ratio of 80:20 (determined by nmr) is obtained in benzene solution, while this ratio is practically reversed in dichloromethane. In DMF, **3a** is formed in less than 10% yield and, furthermore, **4a** decomposes partially to (*Z*)-**5a** under the basic polar reaction conditions. An independent experiment showed that pure **4a** remained unchanged when treated with **1** in benzene or dichloromethane solution, but decomposed to (*Z*)-**5a** in DMF upon addition of a base such as **1** or diethylamine.

The reactions of the phenacylidenesulfuranes **7a** and **7b** with aryl azides **2a–d** in benzene at room temperature proceed with nitrogen evolution and produce enamines **8a–d** as the major products. They were isolated in the chelated (*Z*)-**8** form, with the exception



7a, R = Me
b, R = Ph

2a, X = NO_2
b, X = Br
c, X = H
d, X = OMe



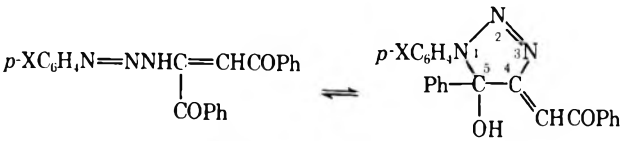
(*Z*)-**8a**, X = NO_2
b, X = Br
c, X = H
d, X = OMe

(*E*)-**8a**

(7) M. Conrad and L. Limpach, *Ber.*, **20**, 994 (1887); **21**, 523, 1649 (1888). See also N. D. Heindel, P. D. Kennewell, and V. B. Fish, *J. Heterocycl. Chem.*, **6**, 77 (1969), and references cited therein.

of the reaction of **7a,b** with **2a** where both isomers of **8a** [60% of (*E*)-**8a** and 30% of (*Z*)-**8a**] were obtained. During the recrystallization process in ethanol or benzene, (*E*)-**8a** was transformed into (*Z*)-**8a**. Structural elucidation of the enamines **8a–d** was accomplished by spectral analysis (see Experimental Section) and confirmed by an independent synthesis from dibenzoylacetylene and arylamines. It is worthwhile to note here that the mass spectra showed a simple fragmentation pattern with characteristic peaks for $M\cdot^+$, $M\cdot^+ -$ COPh, $PhCO^+$, and Ph^+.

In addition to the enamines **8a,b** the reactions of **7a,b** with **2a,b** furnish small amounts (2–5%) of triazenes **9a,b** in equilibrium with Δ^2-triazolines **10a,b**.

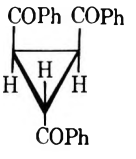


9a, X = NO_2
b, X = Br

10a, X = NO_2
b, X = Br

This type of ring–chain equilibrium has been described previously,[8] and it was shown that the equilibrium position depends on the nature of the substituents and the solvent used. In our particular case, the ir spectra (KBr) of the compounds in the solid state were interpretable in terms of **9a,b** and/or **10a,b** with a broad absorption in the region 3000–3500 cm^{-1} and further bands at 1665, 1620, 1380, and 945. The mass spectra were also consistent with **9a,b** and/or **10a,b** and showed peaks for $M\cdot^+$, $M\cdot^+ - N_2$, and $M\cdot^+ -$ COPh. In DMSO solution, on the contrary, the nmr spectra indicated only one product consistent with the cyclic structure **10a,b**. Indeed, the phenyl protons in the 5 position of the Δ^2-triazolines **10a,b** gave rise to a singlet absorption as expected. Furthermore, the absorption pattern in the phenyl region resembled benzoin (PhCHOHCOPh) and not benzil (PhCOCOPh) or the enamines **8**.

A second side product isolated in the reactions of the keto ylides **7a,b** with aryl azides is *trans*-tribenzoylcyclopropane (**11**). Its structure was substantiated



11

by spectral analysis (see Experimental Section) and its melting point.[9] Table I gives a summary of the reaction products.

Mechanism

A mechanism accounting for all observed products is outlined in Scheme I and involves three main intermediates **12**, **13**, and **14**. They result from the azide by successive addition of one, two, and three molecules of ylide. Stable products derived directly from intermediate **12** have not been isolated. For

(8) C. E. Olsen and C. Pedersen, *Tetrahedron Lett.*, 3805 (1968); R. Fusco and P. D. Croce, *ibid.*, 3061 (1970).

(9) G. Maier, *Chem. Ber.*, **95**, 611 (1962), and references cited therein.

SCHEME I

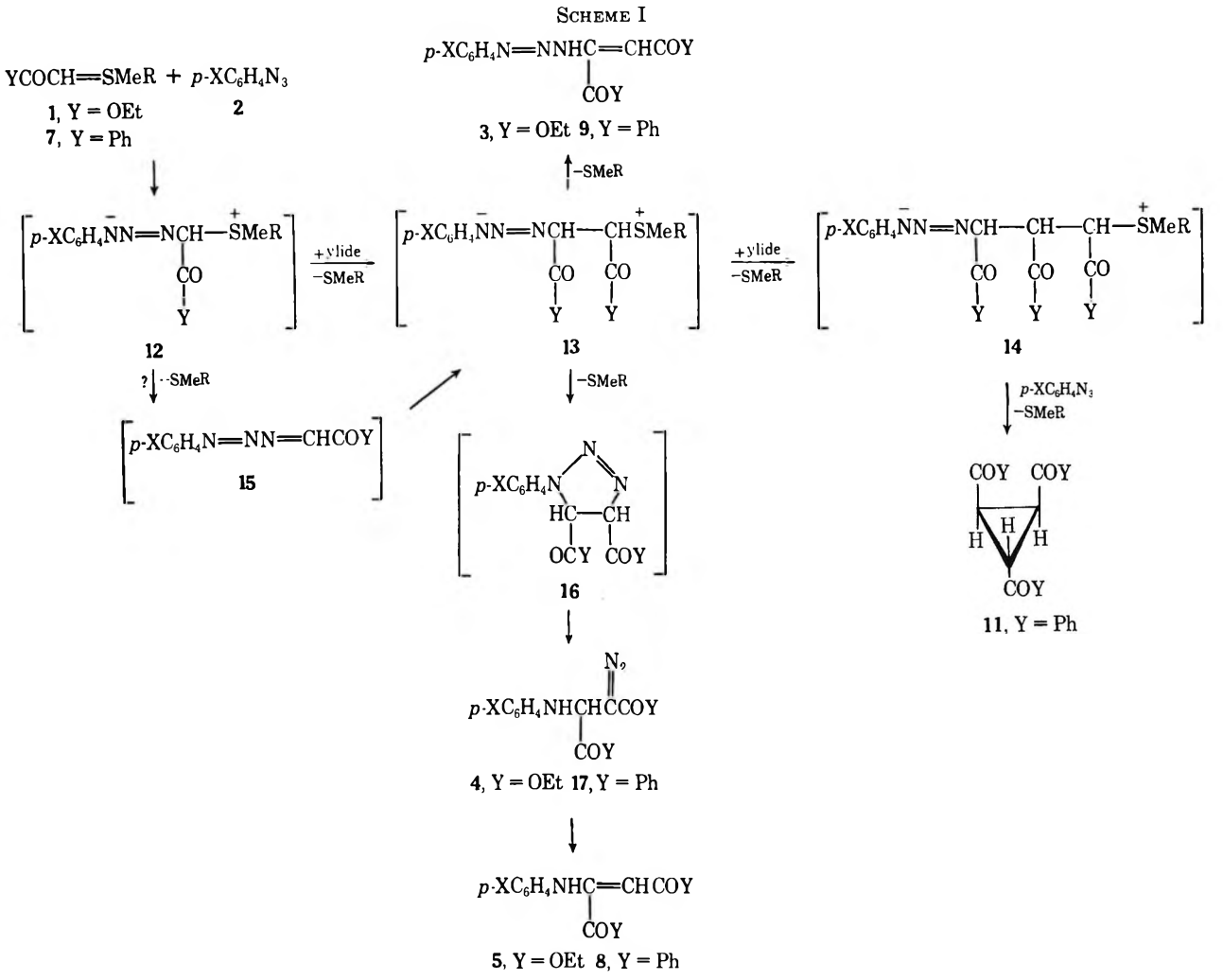


TABLE I
PRODUCT YIELDS FROM THE REACTIONS OF 7a,b WITH 2a–d IN BENZENE AT ROOM TEMPERATURE

Reagents	Enamine 8, %	Triazene 9, %	*trans*-Tribenzoylcyclopropane, %
7a,b + 2a	90	4–5	
7a,b + 2b	81	2–3	8–9
7a,b + 2c	72		8–9
7a + 2d	85		
7b + 2d	40		20

instance, the reaction of equimolar amounts of ylide and azide failed to give the azoimine **15** but furnished instead products derived from intermediate **13** in addition to unreacted azide. Thus, if **15** is formed during the reaction, it must react immediately with another molecule of ylide in a manner analogous to imines.[10]

Stabilization of the intermediate **13** can occur in two ways, leading either to olefinic triazenes **3** and **9** by hydrogen shift, or to Δ^2-triazolines **16** by cyclization. The Δ^2-triazolines of type **16** are expected to be unstable in basic medium[11] and would decompose to diazo compounds **4** and **17**, and enamines **5** and **8**. This view is supported by our observation that, upon addition of ylide **7b**, triazoline **16c** underwent a fast and complete isomerization in less than 5 min to 3-benzoyl-3-anilino-2-diazopropiophenone (**17c**) followed by a slow decomposition (within 5 days) to 1-anilino-1,2-dibenzoylethylene (**8c**). (Triazoline **16c** was prepared from phenyl azide and dibenzoylethylene). By use of Et_2NH, a stronger base than **7b**, the process **16c** → **17c** → **8c** was too fast to be followed by nmr. Note also that the diazo esters **4a,b** were found to decompose by base to the enamines **5a,b** however, at much slower rate than the diazo ketones.[12]

The proposed mechanism *via* the intermediates **12** and **13** is believed to give a cis–trans mixture of the olefinic triazenes and the enamines. Isomerization to the most stable chelated (*Z*) configuration thus occurs in a later stage of the reaction. This is consistent with the isolation of (*E*)-**8a** and its subsequent conversion to (*Z*)-**8a** upon recrystallization.

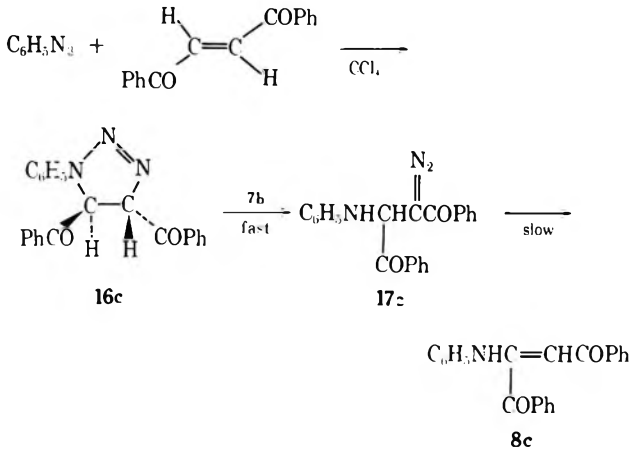
The formation of *trans*-tribenzoylcyclopropane in *S*-ylide reactions has been the subject of several discussions in the literature.[13] The *S*-ylides **7a** and **7b**, namely, are stable at room temperature or on warming

(10) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).

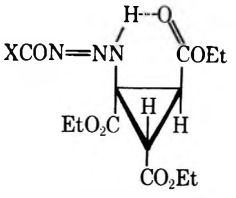
(11) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966); G. Szeimies and R. Huisgen, *ibid.*, **99**, 491 (1966); W. Broeckx, N. Overbergh, C. Samyn, G. Smets, and G. L'abbé, submitted for publication.

(12) The alternative and attractive possibility that the enamines **8** arise from decomposition of the triazenes **9** is excluded by the fact that the latter are stable under the reaction conditions. For recent reviews on triazenes, see C. Suling in "Houben-Weyl. IV. Methoden der Organischen Chemie," Georg Thieme, Stuttgart, 1965, p 699; P. A. S. Smith "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, 1966, p 336.

(13) (a) F. Krollpfeiffer and H. Hartmann, *Chem. Ber.*, **83**, 90 (1950); (b) H. Nozaki, K. Kondô, and M. Takaku, *Tetrahedron Lett.*, 251 (1965); *Tetrahedron*, **22**, 2145 (1966); (c) B. M. Trost, *J. Amer. Chem. Soc.*, **88**, 1587 (1966); **89**, 138 (1967); (d) A. W. Johnson and R. T. Amel, *J. Org. Chem.*, **34**, 1240 (1969).



in the pure state, but decompose to **11** when some other product, such as phenacyl bromide or the sulfonium salt, is present. The same phenomenon seems to occur sometimes in the presence of azides. We interpret the formation of **11** in our reactions by Scheme I. Indeed, the intermediate **14**, produced from **13** by attack of a third molecule of ylide, can regenerate the azide and eliminate sulfide to yield the cyclopropane **11**. We were led to this interpretation by the observation that acyltriazenocyclopropanes **18** were isolated from the reactions of the *S*-ylides with acyl azides,[14] thereby proving the existence of an intermediate analogous to **14**.



18, X = OEt, *p*-MeOC$_6$H$_4$

Experimental Section

All melting points were obtained on a Leitz apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer 521 spectrometer. Nmr spectra were recorded with a Varian A-60 spectrometer using TMS as an internal reference. Mass spectra were obtained with an AEI MS-12 instrument operating at an ionizing potential of 70 eV.

Sulfonium Ylides 1, 7a, and 7b.—The ylides were prepared by standard procedures[15] *via* the corresponding sulfonium salts. Carbethoxymethylenedimethylsulfurane (**1**) was obtained as a viscous pale yellow oil.[15] Benzoylmethylenedimethylsulfurane (**7a**) was recrystallized from benzene and dried carefully, mp 82–82.5° (lit.[13c] 78–79). Benzoylmethylenemethylphenylsulfurane (**7b**) was recrystallized repeatedly from benzene, mp 112–114° (lit.[13b] 113–114°).

Diethyl 2-(*p*-Nitrophenyltriazeno)fumarate [(*Z*)-3a].—Ylide **1** (0.02 mol) and *p*-nitrophenyl azide (0.01 mol) were allowed to react in benzene (100 ml) at room temperature, and the reaction was followed spectroscopically, being finished after 6 min. Removal of the solvent *in vacuo* left a red oil composed of **3a** and **4a** in a ratio of 80:20 (%) by nmr. The oil which solidified upon standing was washed with pentane and recrystallized from methanol (25 ml) to give yellow crystals of pure **3a** in 68% yield: mp 107–109°; ir (KBr) 3195 (chelated NH), 1730 (ester C=O), 1670 (chelated C=O), 1620 (C=C), 1515, and 1340 cm^{-1} (NO$_2$); nmr (CCl$_4$) δ 12.17 (1 H, NH), 8.27 (d, 2 H, J = 9 Hz, meta phenyl protons), 7.62 (d, 2 H, J = 9 Hz ortho phenyl protons), and 5.45 (s, 1 H, C=CH); mass spectrum m/e (%) 336 (13, M·$^+$), 308 (1.4, M·$^+$ − N$_2$), 263 (13, M·$^+$ − CO$_2$Et), 189 (9, 263 − EtOH) 150 (100, NO$_2$C$_6$H$_4$N$_2^+$), and 122 (100, NO$_2$C$_6$H$_4^+$).

Anal. Calcd for C$_{14}$H$_{16}$N$_4$O$_6$ (336): C, 50.00; H, 4.76; N, 16.66; O, 28.57. Found: C, 49.90; H, 4.75; N, 17.15; O, 28.35.

Diethyl 2-(*p*-Nitroanilino)-3-diazosuccinate (4a).—When ylide **1** (0.02 mol) and *p*-nitrophenyl azide (0.01 mol) were allowed to react in dichloromethane (100 ml) at room temperature and the solvent was removed *in vacuo*, the residual red oil was composed of 80% **4a** and 20% **3a** by nmr. The oil was triturated with pentane (25 ml) and fractionally crystallized from methanol to yield yellow crystals of pure **4a**: mp 92.5–94.5°; ir (KBr) 3400 (NH), 2100 (diazo), 1735 and 1690 (C=O), 1520 and 1320 cm^{-1} (NO$_2$); nmr (CDCl$_3$) δ 8.15 (d, 2 H, J = 9 Hz, meta phenyl protons), 6.70 (d, 2 H, J = 9 Hz, ortho phenyl protons), 5.58 (d, 1 H, J = 6.5 Hz, NH), and 5.10 (d, 1 H, J = 6.5 Hz, CH).

Anal. Calcd for C$_{14}$H$_{16}$N$_4$O$_6$ (336): C, 50.00; H, 4.76; N, 16.66; O, 28.57. Found: C, 50.00; H, 4.75; N, 16.70; O, 28.35.

Diethyl 2-(*p*-Nitroanilino)fumarate [(*Z*)-5a].—When ylide **1** (0.02 mol) was allowed to react with *p*-nitrophenyl azide (0.01 mol) in DMF solution (100 ml) and the reaction followed by ir, the diazo compound **4a** was observed first but decomposed partially to **5a**. The nmr spectrum indicated a mixture of **3a**, **4a**, and **5a** in a ratio of 10:45:45. Compound **5a** was identical in all respects with an authentic sample prepared from diethyl acetylenedicarboxylate and *p*-nitroaniline.[16] Thus equimolar amounts (0.02 mol) of both substances were refluxed in methanol (40 ml) for 2 days. Cooling to −20° provided yellow crystals of (*Z*)-**5a**, yield 60%: mp 49.5–51.5°; ir (KBr) 3250 (chelated NH), 1730 (C=O), 1660 (chelated C=O), and 1610 cm^{-1} (C=C); nmr (CDCl$_3$) δ 9.8 (NH), 8.17 (d, 2 H, J = 9 Hz, meta phenyl protons), 6.90 (d, 2 H, J = 9 Hz, ortho phenyl protons), and 5.70 (s, 1 H, C=CH); mass spectrum, m/e (%) 308 (2, M·$^+$), 262 (2, M·$^+$ − EtOH), 235 (8, 263 − 28), 207 (14, 235 − 28), 189 (35, 207 − H$_2$O), 162 (14, M·$^+$ − 2CO$_2$Et).

Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_6$ (308): C, 54.54; H, 5.19; N, 9.09; O, 31.16. Found: C, 54.60; H, 5.20; N, 9.05; O, 31.35.

Diethyl 2-(*p*-Bromophenyltriazeno)fumarate [(*Z*)-3b].—A solution of ylide **1** (0.02 mol) and *p*-bromophenyl azide (0.01 mol) in benzene (100 ml) was kept in the dark at room temperature. The reaction, followed spectroscopically, was finished after 3 hr. Removal of the solvent left a red oil composed of **3b** and **4b** in a ratio of 80–90:10–20 (%) by nmr. The oil solidified upon standing and was recrystallized from methanol to give pale yellow crystals of pure (*Z*)-**3b**: mp 83–84°; ir (KBr) 3205 (chelated NH), 1730 (ester C=O), 1665 (chelated C=O), and 1610 cm^{-1} (C=C); nmr (CDCl$_3$) δ 12.0 (1 H, NH), 7.60 (d, 2 H, J = 9 Hz, meta phenyl protons), 7.40 (d, 2 H, J = 9 Hz, ortho phenyl protons), 5.45 (s, 1 H, C=CH); mass spectrum, m/e (%) 369 and 371 (3, M·$^+$), 341 and 343 (5, M·$^+$ − N$_2$) 324 and 326 (1, M·$^+$ − OEt), 296 and 298 (3, M·$^+$ − CO$_2$Et), 183 and 185 (62, BrC$_6$H$_4$N$_2^+$), 155 (100), and 157 (95, BrC$_6$H$_4^+$).

Anal. Calcd for C$_{14}$H$_{16}$BrN$_3$O$_4$ (370): C, 45.40; H, 4.32; Br, 21.62; N, 11.35; O, 17.29. Found: C, 45.00; H, 4.30; Br, 21.90; N, 11.75; O, 17.45.

2-Carbethoxy-6-nitro-4(1*H*)-quinolone (6a).—This compound crystallized out in 40% yield when a solution of **3a** (0.5 g) in diphenyl ether (5 ml) was refluxed for 5 min and then cooled to room temperature. Recrystallization from methanol gave an analytical product: mp 296–297°; ir (KBr) 1725, 1630, and 1600 cm^{-1}; nmr (DMSO-d_6) δ 12.15 (1 H, NH) and 6.66 (s, 1 H, C=CH); mass spectrum, m/e (%) 262 (85, M·$^+$), 216 (17, M·$^+$ − EtOH), 189 (14, M·$^+$ − CO$_2$Et), 188 (100, 216 − CO), 142 (31, 188 − NO$_2$).

Anal. Calcd for C$_{12}$H$_{10}$N$_2$O$_5$ (262): C, 54.96; H, 3.81; N, 10.68; O, 30.53. Found: C, 54.95; H, 3.72; N, 10.65; O, 30.25.

2-Carbethoxy-6-bromo-4(1*H*)-quinolone (6b).—Triazene **3b** (0.1 g) was refluxed in diphenyl ether (5 ml) for 5 min. The solution was cooled to room temperature and treated with petroleum ether (5 ml) to crystallize the quinolone **6b**, yield 50%. Recrystallization from methanol and vacuum sublimation at 220° gave pure material: mp 249–251°; ir (KBr) 1730, 1620, and 1590 cm^{-1}; nmr (DMSO-d_6) δ 12.25 (1 H, NH) and 6.68 (s,

(14) The reactions of acyl azides with carbonyl-stabilized sulfonium ylides will be reported in a forthcoming paper.

(15) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966); G. B. Payne, *ibid.*, **32**, 3351 (1967).

(16) See, for instance, R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966), and references cited therein.

1 H, C=CH); mass spectrum, *m/e* (%) 295 and 297 (70, $M\cdot^+$), 249 and 251 (12, $M\cdot^+ - EtOH$), 221 and 223 (100, $M\cdot^+ - CO_2Et$), 193 and 195 (10, 223 − CO), 142 (34, 223 − Br), and 114 (80, 142 − CO).

Anal. Calcd for $C_{12}H_{10}BrNO_3$ (296): C, 48.64; H, 3.37; Br, 27.02; N, 4.72; O, 16.21. Found: C, 48.77; H, 3.25; Br, 27.20; N, 4.70; O, 16.30.

Reaction of the Phenacylidenesulfuranes 7a and 7b with *p*-Nitrophenyl Azide.—Ylide **7a** or **7b** (0.02 mol) was treated with *p*-nitrophenyl azide (0.01 mol) in benzene (100 ml) at room temperature. A yellow precipitate was collected after 1 day and shown to be (*E*)-**8a**, yield 60%: ir (KBr) 3380 (NH), 1660, 1595, and 1575 cm^{-1} (C=O and C=C); nmr (DMSO-d_6) δ 10.10 (1 H, NH) and 7.00 (s, 1 H, C=CH). (*E*)-**8a** isomerized to (*Z*)-**8a** during the melting point determination or recrystallization process.

The mother liquor was left to stand for 1 month, during which period the orange triazene **9a** crystallized out, yield 4–5%: mp 172–175° (methanol); ir (KBr) 1665, 1620, and 1595 (CO and C=C) and 1380 cm^{-1} (N=N); nmr (DMSO-d_6) δ 8.52 (1 H, OH), 7.40 (s, 5 H, Ph), and 6.68 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 400 (0.3, $M\cdot^+$), 372 (6.5, $M\cdot^+ - N_2$), 295 (1.3, $M\cdot^+ - COPh$), 267 (68, 372 − COPh), 150 (6, $NO_2C_6H_4N_2^+$), 122 (17, $NO_2C_6H_4^+$), 105 (100, $PhCO^+$), and 77 (88, Ph^+).

Anal. Calcd for $C_{22}H_{16}N_4O_4$ (400): C, 66.00; H, 4.00; N, 14.00. Found: C, 66.00; H, 3.80; N, 14.45.

The resultant mother liquor was diluted with pentane (200 ml) and provided 30% (*Z*)-**8a**: mp 170–171° (methanol); ir (KBr) 1665, 1590, 1570, and 1555 cm^{-1}; nmr ($CDCl_3$) δ 12.85 (1 H, NH), 7.05 (d, 2 H, ortho phenyl protons), and 6.35 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 372 (27, $M\cdot^+$), 267 (100, $M\cdot^+ - COPh$), 189 (8, 267 − C_6H_6), 105 (64.5, $PhCO^+$), and 77 (52, Ph^+).

Anal. Calcd for $C_{22}H_{16}N_2O_4$ (372): C, 70.96; H, 4.30; N, 7.52; O, 17.20. Found: C, 70.66; H, 4.64; N, 7.31; O, 17.21.

Compound (*Z*)-**8a** was independently prepared in 75% yield by refluxing equimolar amounts (0.01 mol) of dibenzoylacetylene[17] and *p*-nitroaniline in ethanol (250 ml) for 4 hr.

Reaction of the Phenacylidenesulfuranes 7a and 7b with *p*-Bromophenyl Azide.—A solution of ylide **7a** or **7b** (0.02 mol) and *p*-bromophenyl azide (0.01 mol) in benzene (100 ml) precipitated *trans*-1,2,3-tribenzoylcyclopropane (**11**) within a few min, yield 8–9%, mp 221° (lit.[9] 215°); ir, nmr, and mass spectrum were consistent with the structure.

Anal. Calcd for $C_{24}H_{18}O_3$ (354): C, 81.35; H, 5.08; O, 13.55. Found: C, 81.24; H, 5.08; O, 13.70.

Treatment of the mother liquor with hexane (100 ml) gave a first crop of enamine (*Z*)-**8b**. The remaining enamine was isolated by evaporation of the solvent and treatment of the residue with ether (25 ml), total yield 81%: mp 167–169° (EtOH); ir (KBr) 1660, 1590, 1570, and 1550 cm^{-1}; nmr ($CDCl_3$) δ 12.60 (1 H, NH), 6.80 (d, 2 H, ortho anilino protons) and 6.15 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 405 and 407 (9, $M\cdot^+$), 300 and 302 (59, $M\cdot^+ - COPh$), 155 and 157 (5.5 $BrC_6H_4^+$), 105 (100, $PhCO^+$), and 77 (71, Ph^+).

Anal. Calcd for $C_{22}H_{16}BrNO_2$ (406): C, 65.02; H, 3.94; Br, 19.70; N, 3.44; O, 7.88. Found: C, 65.04; H, 4.01; Br, 19.65; N, 3.26; O, 7.87.

The triazene **9b**, contaminated with some enamine, was finally isolated from the ether solution by cooling to −20°. The crude material was washed with chloroform to remove the enamine and dried, yield 2–3%: mp 160–161°; ir (KBr) 1665, 1620, and 1580 (C=O and C=C) and 1380 cm^{-1} (N=N); nmr (DMSO-d_6) δ 8.50 (s, 1 H, OH) and 6.50 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 433 and 435 (0.5, $M\cdot^+$), 405 and 407 (2, $M\cdot^+ - N_2$), 328 and 330 (0.5, $M\cdot^+ - COPh$), 300 and 302 (4.5, 405 and 407 − COPh), 183 and 185 (7.5, $BrC_6H_4N_2^+$), 155 and 157 (11, $BrC_6H_4^+$), 105 (100, $PhCO^+$), and 77 (54, Ph^+).

Compound (*Z*)-**8b** was independently prepared in 90% yield by treating equimolar amounts (0.01 mol) of dibenzoylacetylene and *p*-bromoaniline in benzene (30 ml) at room temperature for 2 hr.

Reaction of the Phenacylidenesulfuranes 7a and 7b with Phenyl Azide.—Ylide **7a** or **7b** (0.02 mol) was allowed to react with phenyl azide (0.01 mol) in benzene (100 ml) at room temperature. After 24 hr the precipitated **11** was collected by filtration and the mother liquor was left to stand for 1 week. The solvent was then removed to give crude (*Z*)-**8c** in 72% yield. Recrystallization from methanol (40 ml) afforded yellow crystals (60%): mp 126–128°; ir (KBr) 1665, 1605, 1595, 1585, 1575, and 1550 cm^{-1}; nmr ($CDCl_3$) δ 12.5 (1 H, NH) and 6.05 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 327 (21, $M\cdot^+$), 222 (100, $M\cdot^+ - COPh$), 105 (50, $PhCO^+$), and 77 (64, Ph^+).

Anal. Calcd for $C_{22}H_{17}NO_2$ (327): C, 80.73; H, 5.19; N, 4.28; O, 9.78. Found: C, 80.95; H, 5.20; N, 4.20; O, 9.75.

Compound (*Z*)-**8c** was independently prepared in quantitative yield by heating at reflux equimolar amounts (0.01 mol) of dibenzoylacetylene and aniline in benzene (30 ml) for 2 hr.

Reaction of the Phenacylidenesulfuranes 7a and 7b with *p*-Methoxyphenyl Azide.—A solution of ylide **7a** (0.02 mol) and *p*-methoxyphenyl azide (0.01 mol) in benzene (100 ml) was allowed to stand at room temperature for 2 months. The solution was then diluted with hexane (100 ml) and cooled to 0°. The red crystals of (*Z*)-**8d** that precipitated were collected by filtration (85%) and recrystallized from ethanol, yield 50%: mp 127–129°; ir (KBr) 1670, 1585, 1570, 1550, and 1510 cm^{-1}; nmr ($CDCl_3$) δ 12.7 (1 H, NH), 6.98 and 6.68 (2 d, 4 aromatic protons), and 6.08 (s, 1 H, C=CH); mass spectrum, *m/e* (%) 357 (33.5, $M\cdot^+$), 252 (100, $M\cdot^+ - COPh$), 105 (52, $PhCO^+$), and 77 (30, Ph^+).

Anal. Calcd for $C_{23}H_{19}NO_3$ (337): C, 77.31; H, 5.32; N, 3.92; O, 13.44. Found: C, 77.30; H, 5.40; N, 3.90; O, 13.40.

When the ylide **7b** was used instead of **7a**, 20% **11** crystallized out after a few days. After 3 weeks, the solvent was removed and the residual oil was treated with methanol (30 ml) and crystallized at −20° to yield 40% (*Z*)-**8d**.

Compound (*Z*)-**8d** was also obtained in 98% yield by treating equimolar amounts (0.01 mol) of dibenzoylacetylene and *p*-methoxyaniline in benzene (50 ml) at room temperature for 2 hr.

Registry No.—**3a**, 29954-01-6; **3b**, 29954-02-7; **4a**, 30093-87-9; **5a**, 29954-03-8; **6a**, 30093-88-0; **6b**, 29954-04-9; (*E*)-**8a**, 29954-05-0; (*Z*)-**8a**, 29954-06-1; **8b**, 29954-07-2; **8c**, 29954-08-3; **8d**, 29954-09-4; **9a**, 29954-10-7; **9b**, 29954-11-8.

Acknowledgment.—The authors are indebted to Dr. S. Toppet, Dr. M. C. Delvaux de Fenffe, Dr. F. C. Compernolle, and Dr. F. De Schryver for their advice in the interpretation of the spectra. Thanks are also due to the Nationaal Fonds voor Wetenschappelijk Onderzoek (NFWO, Belgium) and to the Instituut tot aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw (IWONL, Belgium) for a postdoctoral (G. L'a.) and doctoral (E. V. L) fellowship, respectively. Financial support from the Ministry of National Education (FKFO) is gratefully acknowledged.

(17) R. E. Lutz, *J. Amer. Chem. Soc.*, **48**, 2905 (1926).

The Oxidation of Organic Divalent Sulfur by Iodine. II. The Equilibrating Thiol–Iodine–Disulfide–Hydrogen Iodide System in Acetic Acid and Evidence for Sulfenyl Iodide Intermediates[1]

JAMES P. DANEHY,* BRENDAN T. DOHERTY,[2] AND CATHERINE P. EGAN[3]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received November 24, 1970

Spectrophotometric observations of solutions consisting initially of thiol and iodine in acetic acid, or of disulfide and hydrogen iodide in acetic acid, give evidence that this is an equilibrating system which probably involves three reactions (eq 3–5). Practical difficulties prevented the determination of the value for the equilibrium constant for the overall system, but the equilibrium constant for reaction 5 in AcOH has been found to be $1.1\ (\pm 0.1) \times 10^6$. Studies on the titration of 3-mercaptopropionic acid with iodine in acetic acid containing increasing amounts of water or anhydrous sodium acetate show that displacement of the equilibrium toward the disulfide side depends on the equilibrating reaction between hydrogen iodide and base.

In its simple, stoichiometric form the reaction for the oxidation of thiols to disulfides by iodine in aqueous so-

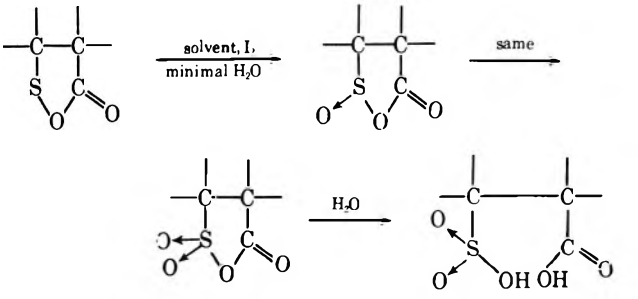
$$2RSH + I_2 \xrightarrow[I^-]{H_2O} RSSR + 2HI \qquad (1)$$

lution has been known for decades. The first comprehensive suggestion concerning the mechanism by which this reaction might take place came, not from studies on simple models, but from a study of the iodination of proteins. Fraenkel-Conrat,[4] employing conditions under which the iodination of tyrosyl residues would be rather slow, observed that tobacco mosaic virus rapidly consumed 2 equiv of iodine for each sulfhydryl group. He attributed this behavior to the formation of sulfenyl iodide groups and successfully tested the assumption by adding cysteine to his modified protein, whereupon the bound iodine was lost and unsymmetrical disulfide was formed. "The observed formation

$$RSH + I_2 \longrightarrow RSI + HI \xrightarrow{R'SH} RSSR' + HI$$

of sulfenyl iodide groups under the influence of iodine suggests a more general hypothesis for the mechanism of oxidation of SH groups, even in cases in which the disulfide group is the only reaction product. Thus, a formulation based on assumption of two consecutive bimolecular reactions, rather than one termolecular reaction, appears now preferable...."[4] More recent work has only served to corroborate his views. Cunningham and Nuenke[5] followed spectrophotometrically the uptake of iodine by a number of proteins and found that the stoichiometry was particularly clean-cut in the case of β-lactoglobulin and that the sulfenyl iodide was remarkably stable in neutral aqueous solution.[6] Much earlier studies[7] demonstrated the relative stability of 2-methyl-2-propanesulfenyl iodide and, quite recently, further studies on the relative stability and spectral characteristics of this compound have been reported.[8]

From a study of the iodometric titration of a variety of thiols as a function of the initial concentration of thiol, we[9] demonstrated that all thiols have at least some tendency to consume more than the stoichiometric amount of iodine as the initial concentration of thiol is decreased and that thiols with a carboxyl group attached to a carbon atom β to the sulfur atom are particularly susceptible to overoxidation. As a possible accounting for the first generalization, we suggested that attack of the sulfenyl iodide by the much less nucleophilic water is gradually favored as the much more nucleophilic thiolate ions become scarcer and that the sulfenic acid thus formed would be further oxidized by iodine. To account for the second generalization we proposed a preferential intramolecular attack by the carboxylate anion on the sulfenyl sulfur to displace an iodide ion and form a five-membered cyclic intermediate[9b] which would then undergo oxidation by iodine after hydrolysis. Consideration of the possibility that further oxidation might precede terminal hydrolysis suggested that it might be possible to isolate the proposed cyclic



(1) Preliminary accounts of this work were presented at the Symposium on Sulfenyl Compounds, Intra-Science Research Foundation, Santa Monica, Calif., Nov 30, 1967 [*Quart. Rep. Sulfur Chem.*, **2**, 325 (1967)], at the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 14, 1968, and at the third Mechanisms Conference, Cork, Republic of Ireland, Oct 2, 1969. The manuscript originally submitted for publication on Jan 15, 1969, was withdrawn when Janice Van Horne and Professor Lamar Field, to whom the authors are deeply indebted, pointed out a serious error of misinterpretation. The present version is the result of a thorough restudy carried out during 1969–1970.

(2) Participant in the National Science Foundation Undergraduate Research Program, 1967–1968.

(3) Postdoctoral Research Associate, 1969–1970.

(4) H. Fraenkel-Conrat, *J. Biol. Chem.*, **217**, 373 (1955).

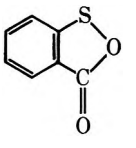
(5) L. W. Cunningham and B. J. Nuenke, *ibid.*, **234**, 1447 (1959); **235**, 1711 (1960).

(6) L. W. Cunningham and B. J. Nuenke, *Biochim. Biophys. Acta*, **39**, 565 (1960).

(7) H. Rheinboldt and E. Motzkus, *Ber. B*, **72**, 657 (1939); H. Rheinboldt and E. Mott, *ibid.*, **72**, 668 (1939).

(8) L. Field, J. L. VanHorne, and L. W. Cunningham, *J. Org. Chem.*, **35**, 3267 (1970).

(9) (a) J. P. Danehy and M. Y. Oester, *ibid.*, **32**, 1491 (1967). (b) L. Field, P. M. Giles, and D. L. Tuleen [*ibid.*, **36**, 623 (1971)] have recently



given evidence that a compound isolated by them, which decomposes in less than 1 hr, has a structure analogous to that shown here.

intermediate, as well as one or more subsequent cyclic oxidation products, if the reaction were carried out in an anhydrous medium, or one containing a minimal amount of water. When, however, an attempt was made to oxidize 3-mercaptopropionic acid in solution in glacial acetic acid by adding to it a solution of iodine in glacial acetic acid, we were surprised to find that the former would not decolorize any increment, however small, of the latter. It was soon found that all other thiols examined behaved in the same way.[10] When the ratio of thiol to iodine is sufficiently high, the absorption due to iodine in acetic acid at 478 nm[11] is all but completely replaced by much more intense absorption with maxima at 293, 360, and 740 nm, corresponding to the triiodide ion.

Starting with this unexpected result, we have made an experimental study of the reaction between 3-mercaptopropionic acid and iodine in acetic acid under anhydrous or predominantly nonaqueous conditions in the hope of shedding more light on the mechanistic pathway by which these species react.

Titration of 3-Mercaptopropionic Acid with Iodine in Anhydrous and Aqueous Acetic Acid.—It appears, then, that, while thiols are oxidized rapidly and quantitatively to disulfides by triiodide in water, in glacial acetic acid triiodide persists even in the presence of a large excess of thiol. How would these same substances behave in acetic acid as the water content of the system is gradually increased from zero?

Stock solutions were prepared of 3-mercaptopropionic acid in acetic acid of known water content and of iodine in the same solvent. Aliquots of the former were titrated to a visible end point with the latter. The results (see Table I) show clearly that the reaction

TABLE I

TITRATION OF 3-MERCAPTOPROPIONIC ACID WITH IODINE IN ACETIC ACID CONTAINING VARYING AMOUNTS OF WATER[a]

ml of water/100 ml of soln	Molarity of water	mequiv of I_2 consumed/mequiv of MPA
4.00	2.22	0.029
8.00	4.44	0.201
12.00	6.66	0.492
16.00	8.88	0.764
20.00	11.10	0.883

[a] 0.0450 N I_2 and 0.0990 M MPA in each case; 30-sec end points, minimally.

of the thiol with iodine does not depend stoichiometrically upon the amount of water present; for the rapid, quantitative oxidation of the thiol to disulfide the concentration of water must be near 14 M. We appear to be dealing with an equilibrating system.

Ignoring for the moment the individual steps which have been postulated, it might be considered that, when iodine is added to thiol in acetic acid under titration conditions in the presence of a limited amount of water, the reaction proceeds rapidly in accord with eq 1. When eventually a point is reached, depending on the concentration of water, at which no more iodine (and triiodide) is consumed, this result cannot be attributed to depletion of water, for the concentration of water does not change significantly during the course of any of the titrations. Rather, it would seem that the system loses its ability to take up any more iodine when the effective concentration of hydrogen iodide reaches a value such that the reductive cleavage of disulfide opposes the forward reaction. The concentration of hydrogen iodide depends not only upon the amount of iodine added but upon the water content of the solvent, in accord with the equilibrium shown in eq 2.

$$HI + H_2O \overset{AcOH}{\rightleftharpoons} H_3O^+ + I^- \quad (2)$$

If it is the basicity of water which promotes the oxidation of the thiol, then a more basic species should fulfill this function even more effectively. Table II presents

TABLE II

TITRATION OF 3-MERCAPTOPROPIONIC ACID WITH IODINE IN ACETIC ACID CONTAINING VARYING AMOUNTS OF SODIUM ACETATE[a]

Molarity of acetate ion	mequiv of I_2 consumed/mequiv of MPA
0.12	0.890
0.24	0.945
0.36	0.970
0.48	0.962
0.60	0.957

[a] 0.0485 N I_2 and 0.0960 M MPA in each case; 30-sec end points, minimally.

data obtained by titrating solutions of the thiol in acetic acid containing known concentrations of anhydrous sodium acetate with standard iodine solutions made up in the same solvents. The results are fully in accord with the expectations based on the superior basicity of the acetate ion over that of water. When 3-mercaptopropionic acid was titrated with iodine in absolute ethanol, 0.87 equiv of iodine was required to reach an end point, corresponding to the intermediate basicity of the solvent, less than that of water, but much more than that of acetic acid.

Spectrophotometric Study of the System Initially. RSH–I_2–AcOH.—It may be helpful to precede a discussion of the experimental results with a summary of the conceptual framework into which the facts can be fitted. One might expect that the mixing of iodine and thiol in acetic acid would initiate reactions 3–5 and

$$RSH + I_2 \rightleftharpoons RSI + HI \quad (3)$$

$$RSH + RSI \rightleftharpoons RSSR + HI \quad (4)$$

$$HI + I_2 \rightleftharpoons HI_3 \quad (5)$$

that all of them would have at least some degree of reversibility. Based on the stoichiometric summation

$$2RSH + 3I_2 \rightleftharpoons RSSR + 2HI_3 \quad (6)$$

(eq 6) an equilibrium expression can be formulated (K_6),

$$\frac{[RSSR][HI_3]^2}{[RSH]^2[I_2]^3} = K_6$$

in which RSI and HI are not present. Alternatively, an equivalent equilibrium expression can be formulated

(10) It has been known for a long time that hydrogen sulfide is not oxidized by iodine in solution in ethyl ether in the absence of appreciable amounts of water: (a) A. A. Noyes and G. V. Sammet, *J. Amer. Chem. Soc.*, **24**, 498 (1902); (b) L. B. Parsons, *ibid.*, **47**, 1820 (1925). Recently, Fava and coworkers have observed that "... in anhydrous hydrocarbon solvent the common oxidation of thiols by iodine fails to take place:" (c) A. Fava, G. Reichenbach, and U. Peron, *ibid.*, **89**, 6699 (1967).

(11) R. E. Buckles and J. F. Mills, *ibid.*, **75**, 552 (1953).

(K_7), based on the stoichiometric summation (eq 7), in which RSI and I_2 are not present.

$$RSSR + 3HI \rightleftharpoons 2RSH + HI_3 \quad (7)$$

$$\frac{[RSH]^2[HI_3]}{[RSSR][HI]^3} = K_7$$

Then

$$K_6K_7 = \frac{[HI_3]^3}{[I_2]^3[HI]^3} = K_5^3 \quad (8)$$

Of the three reactions 3–5, reaction 5 is the only one that can be studied independently, so that K_5 can be determined experimentally. Since reaction 6 corresponds to the situation starting with thiol and iodine, and reaction 7 to that starting with disulfide and hydrogen iodide, it was hoped that K_6 and K_7 could be evaluated experimentally. Verification of expression 8 would support the overall mechanistic view presented in the introduction.

It is necessary to consider in some detail the spectrophotometric observations made on mixtures of 3-mercaptopropionic acid and iodine dissolved in glacial acetic acid (see Table III). As quickly as they can be examined after preparation such solutions show relatively intense absorption, peaking at 293 and 360 nm, and no peak at 478 nm. The λ_{max} value for iodine in acetic acid is at 478 nm.[11] When equivalent amounts of iodine and of potassium iodide or hydrogen iodide in acetic acid solution are mixed, the same pattern of absorption peaking at 293 and 360 nm is observed, with a ratio of $A_{293}/A_{360} = 1.70$. Since the intensity ratios in the solutions originally containing thiol, iodine, and acetic acid are 1.69 ± 0.01 it can be concluded both, that hydrogen triiodide (or triiodide ion) is the absorbing species, and that iodine does not interfere with measurement of triiodide at 360 nm. However, examination of the spectra themselves and knowledge of molar absorptivities show clearly that triiodide ($a_m = 2.6 \times 10^4$ for hydrogen triiodide at 360 nm) would interfere seriously with measurement of iodine ($a_m = 775$ at 478 nm[11]) or of the sulfenyl iodide ($a_m = 64$ at 444 nm for 2-methyl-2-propanesulfenyl iodide in methylcyclohexane[8]).

Considerably less than half of the iodine reacts, even when the initial molar ratio of thiol to iodine is ~4.5:1.[12] Much free iodine, then, must be present in all cases in addition to triiodide. While there is no feasible way of determining the sulfenyl iodide quantitatively, there is some evidence that at least appreciable amounts are present. When solutions are allowed to stand ~24 hr in daylight with strict exclusion of air, the absorption at 293 and 360 disappears and that at 478 increases. The photolytic disproportionation of sulfenyl iodide[7,8] could account for part of this and the extreme sensitivity of

$$2RSI \xrightarrow{h\nu} RSSR + 2HI$$

hydrogen iodide to aerial oxidation could account for the rest of it. Later in this paper we shall present more evidence for the presence of significant amounts of sulfenyl iodide in this system.

Unfortunately, however, the information obtainable from these data, either directly or by calculation, does not permit calculation of a value for K_6. In each case original values are known for [RSH] and for [I_2], and values for [HI_3] are determined spectrophotometrically. Values for [RSH] remaining must be equal to the original [RSH] minus the [HI_3] found since, when an RSH disappears, either by 3 or 4, an HI appears which, in view of the large stability constant of HI_3, is transformed almost quantitatively into the latter. However, values for [I_2] remaining and [RSSR] produced depend not only on the [HI_3] found but also upon how much of the RSI formed is subsequently consumed.

If we assume for the moment that 4 is displaced far to the left, so that very little RSSR is formed, then we may sum 3 and 5 to get

$$RSH + 2I_2 \rightleftharpoons RSI + HI_3 \quad (9)$$

and

$$\frac{[RSI][HI_3]}{[RSH][I_2]^2} \cong K_9$$

Here, as above, original values are known for [RSH] and for [I_2], and values for [HI_3] are determined spectrophotometrically. Values for [RSI] may be taken equal to those found for [HI_3], values for [RSH] remaining may be taken equal to those for the original [RSH] minus those found for [HI_3], and values for [I_2] may be taken equal to those for the original [I_2] minus twice those found for [HI_3]. The calculated values for K_9 are not included in Table III since they obviously do not constitute a constant, although the absence of a drift in one direction offers some support for the idea that relatively small amounts of disulfide are formed, and the magnitude of the values for K_9 suggests that reaction 3 goes appreciably to the right. This last idea is not necessarily at variance with the fact that more than half of the iodine has not reacted in the presence of an excess of thiol when one considers the low concentrations at which the reaction was studied.

The data for an exactly parallel study of the system initially composed of triphenylmethanethiol, iodine, and acetic acid are presented in Table IV. The only apparent

TABLE III

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[I_2]_{initial}$, $M \times 10^4$	$[RSH]_{initial}$, $M \times 10^4$	$\frac{[I_2]_{initial}}{[RSH]_{initial}}$	A_{293}	A_{360}	$[HI_3]$,[a] $M \times 10^4$
1.98	8.42	0.235	0.308	0.181	0.54
4.96	10.53	0.471	1.03	0.611	1.81
3.97	4.21	0.942	0.865	0.509	1.51
4.96	4.21	1.17	0.915	0.538	1.60
4.93	2.68	1.84	0.901	0.530	1.58
9.92	4.21	2.35		0.921	2.73
4.93	1.34	3.68	0.496	0.292	0.86
9.86	2.68	3.68	1.06	0.629	1.87

[a] Values calculated on the assumption that absorption at 293 and 360 nm is attributable to HI_3, and using a value of 2.6×10^4 for a_m at 360 nm (*vide infra*).

(12) If we assume that only insignificant amounts of RSSR are formed, then the pertinent stoichiometry is $RSH + 2I_2 \rightleftharpoons RSI + HI_3$ and the fraction of iodine consumed is $[HI_3]/[I_2]_{original}$. On the alternative assumption that only insignificant amounts of RSI persist, the relevant stoichiometry is $2RSH + 3I_2 \rightleftharpoons RSSR + 2HI_3$ and the fraction of iodine consumed is $1.5[HI_3]/[I_2]_{original}$. For the case in which $[I_2]/[RSH]$ is 0.235, the fraction of iodine consumed is 0.27 on the first assumption and 0.41 on the second assumption.

TABLE IV

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN TRIPHENYLMETHANETHIOL AND IODINE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[I_2]_{initial}$, $M \times 10^4$	$[RSH]_{initial}$, $M \times 10^4$	$\frac{[I_2]_{initial}}{[RSH]_{initial}}$	A_{293}	A_{360}	$[HI_3]$,[a] $M \times 10^4$
8.08	20.4	0.396	0.921	0.496	1.88
10.1	20.4	0.495	1.097	0.602	2.41
10.1	10.2	0.99	0.940	0.553	2.21
20.2	10.2	1.98	1.914	1.126	4.50
4.04	1.63	2.48	0.233	0.122	0.488
10.1	4.08	2.48	0.444	0.233	0.932

[a] Calculated on the basis given in Table III.

difference is a quantitative one: average values for K_9 are approximately 18 times greater for the primary thiol than they are for the tertiary one. This may be considered quite simply as an inductive effect; the three phenyl groups withdraw electrons from the sulfur atom and weaken its effectiveness as a nucleophile.

Spectrophotometric Study of the System Initially. RSSR–HI–AcOH.—Unless special precautions are taken the addition of small amounts of colorless, aqueous ~50% hydriodic acid to glacial acetic acid gives a brown solution within a matter of a few seconds as a result of aerial oxidation of hydrogen iodide to iodine and the transformation of substantially all of the latter to triiodide. In the present study, using freshly purified, oxygen-free acetic acid and preparing solutions in a drybox flushed with nitrogen, a stock solution, 1.44×10^{-2} *M* HI in AcOH, had an absorbance of only 0.016 at 360 nm 1 hr after preparation. The measured absorbances at 360 nm, then, reported in Table V,

TABLE V

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3,3′-DITHIODIPROPIONIC ACID AND HYDROGEN IODIDE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

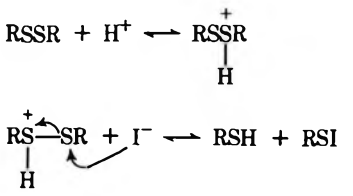
$[HI]_{initial}$, $M \times 10^3$	$[RSSR]_{initial}$, $M \times 10^3$	A_{360}	$[HI_3]$,[a] $M \times 10^4$
3.86	7.20	0.886	3.05
1.54	7.20	0.284	0.97
0.77	7.20	0.125	0.43
3.86	1.44	0.155	0.53
1.54	1.44	0.081	0.28

[a] Calculated on the basis given in Table III.

demonstrate that triiodide is formed in appreciable amounts as a result of the interaction of disulfide and hydrogen iodide, and the simplest way to interpret this fact is to assume that reactions 4, 3, and 5 have taken place in reverse, and in that order. These data corroborate the reversibility of all three reactions which we have already postulated.

The summation of the reverse of reactions 4, 3, and 5, as already shown, leads to the stoichiometric reaction 7 for which the equilibrium expression and constant, K_7, has already been given. However, it is not possible to use these data in Table V to calculate a value for K_7, just as it was not possible to use the data in Table III to calculate a value for K_6, and for exactly the same reason: our inability to determine the concentration of RSI upon which, in this case, both the concentration of thiol formed, and the concentration of hydrogen iodide remaining, depend. Nevertheless, the demonstration that from 5 to 10% of the hydrogen iodide added was converted to hydrogen triiodide is compatible with one or the other of two alternative interpretations. First, the disulfide might indeed be extensively cleaved (the reverse of reaction 4) and sulfenyl iodide would accumulate rather than form much thiol (reverse of reaction 3). Second, it is at least possible (if less likely) that disulfide is not extensively cleaved by hydrogen iodide.

An exactly comparable study was made of the systems consisting initially of hydrogen iodide, acetic acid, and nine other disulfides. Four of them behaved qualitatively like 3,3′-dithiodipropionic acid: 4,4′-dithiodiisobutyric acid, ethyl disulfide, isobutyl disulfide, benzyl disulfide. Four others (phenyl disulfide, *tert*-butyl disulfide, dithiodisuccinic acid, and 2,2′-dithiodipropionic acid) showed no development of absorbance beyond the blank, even after 1 hr. This means that neither triiodide nor sulfenyl iodide was formed in detectable amounts, so that no significant cleavage of these disulfides took place. It seems reasonable that in those cases in which cleavage does take place it does so by a nucleophilic displacement, assisted by electrophilic catalysis, and that one step, probably the second one, may be sterically hindered.



Not surprisingly, the ninth compound, triphenylmethyl disulfide, despite the formal steric hindrance, is extensively cleaved by hydrogen iodide in acetic acid (see Table VI). Both the insensitivity to steric hindrance and the failure to give anything remotely resembling constancy for K_7 indicates that another mechanistic pathway pertains, and the structure suggests free-radical intermediates. Solutions of the disulfide in acetic acid at room temperature give no detectable esr signal, however, so that we have no positive evidence to support this suggestion.[13] It is a fact that this disulfide rapidly equilibrates with hydrogen iodide, as do the others which react, and it is characteristic only of this one that the absorbance developed is

TABLE VI

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN TRIPHENYLMETHYL DISULFIDE AND HYDROGEN IODIDE IN GLACIAL ACETIC ACID AT ROOM TEMPERATURE

$[HI]_{initial}$, $M \times 10^4$	$[RSSR]_{initial}$, $M \times 10^4$	A_{360}	$[HI_3]$,[a] $M \times 10^4$
5.34	4.77	0.041	0.164
10.68	4.77	0.174	0.70
26.70	4.77	1.097	4.38
26.70	9.54	1.46	5.84
5.34	23.85	0.149	0.59
10.68	23.85	0.420	1.70

[a] Calculated on the basis given in Table III.

(13) The failure to demonstrate any esr signal is indeed surprising since F. F. Blicke [*J. Amer. Chem. Soc.*, **45**, 1965 (1923)] has reported that an initially colorless solution of tripheylmethyl disulfide in benzene becomes yellow within a few minutes and that the passage of dry air through the solution is followed by a precipitation of triphenylmethyl peroxide.

TABLE VII

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN CARBON TETRACHLORIDE AT ROOM TEMPERATURE

$[I_2]_{initial}$, $M \times 10^3$	$[RSH]_{initial}$, $M \times 10^3$	$\frac{[I_2]_{initial}}{[RSH]_{initial}}$	Time[a]	A_{511}[b]	A_{293}	A_{360}
0.98	1.047	0.94	5 min	0.084	0.018	0.004
			10 min	0.084	0.018	0.004
			5 hr	0.086	0.027	0.018
			15 hr	0.086	0.013	0.009
1.96	1.047	1.88	5 min	0.164	0.022	0.004
			10 min	0.168	0.022	0.004
			5 hr	0.172	0.022	0.013
			15 hr	0.172	0.011	0.004
4.90	1.047	4.70	5 min	0.426	0.051	0.027
			15 hr	0.423	0.029	0.004
4.90	2.10	2.35	5 min	0.426	0.066	0.029
			15 hr	0.410	0.036	0.004
4.90	4.14	1.17	5 min	0.423	0.113	0.052
			15 hr	0.410	0.078	0.018

[a] Solutions were made up in the dark, and first reading made in the dark; after 5 min solutions were kept in the light in the laboratory. [b] Values for I_2 at the same concentration in the absence of thiol were, respectively, 0.086, 0.174, 0.432, 0.432, and 0.432.

TABLE VIII

SPECTROPHOTOMETRIC OBSERVATIONS OF THE REACTION BETWEEN 3-MERCAPTOPROPIONIC ACID AND IODINE IN CYCLOHEXANE AT ROOM TEMPERATURE

$[I_2]_{initial}$, $M \times 10^3$	$[RSH]_{initial}$, $M \times 10^3$	$\frac{[I_2]_{initial}}{[RSH]_{initial}}$	Time[a]	A_{522}[b]	A_{293}	A_{360}
1.006	1.004	0.10	5 min	0.071	0.046	0.007
2.012	1.004	0.20	5 min	0.146	0.092	0.016
				0.122	0.092	0.015
5.030	1.004	0.50	5 min	0.377	0.168	0.051
			5 hr	0.314	0.161	0.043
4.024	4.016	1.00	5 min	0.328	0.081	0.011
			5 hr	0.319	0.081	0.010

[a] Solutions were made up in the dark, and first reading made in the dark; after 5 min solutions were kept in the light in the laboratory. [b] Values for I_2 at the same concentration in the absence of thiol were, respectively, 0.094, 0.187, 0.469, and 0.382.

proportional to $[HI]^2$, at least when the ratio of [HI]/[RSSR] is relatively high.

The Systems, RSH–I_2, in Nonpolar Solvents.—From the data presented so far one might conclude that acetic acid inhibits the course of reactions made possible by the basicity of water. This, however, would be a mistaken conclusion. Acetic acid actually promotes the reaction, but much less effectively than water. The truth of the latter statement follows consideration of the situation in nonpolar solvents.

From the data in Tables VII and VIII, bearing in mind the high molar absorptivity of triiodide, it is barely possible to demonstrate that any triiodide is present in solutions of 3-mercaptopropionic acid and iodine in either carbon tetrachloride or cyclohexane. In cyclohexane, however, the concentrations of iodine are significantly lower in the presence of thiol than they are in its absence. And in carbon tetrachloride small amounts of a crystalline precipitate, identified as 3,3′-dithiodipropionic acid by melting point (155°) and mixture melting point, eventually appeared.

Determination of the Equilibrium Constant for the Reaction, HI + I_2 ⇌ HI_3 in Acetic Acid.—From previously published values for the dissociation constants of the triiodide ion in water and in alcohols,[14-16] one would expect that the equilibrium constant for reaction 5 in acetic acid would be a large number. Using the "dilution technique" method of Katzin and Gebert,[16] we have found an average value of 1.1 (±0.1) × 10^6 for K_5 in anhydrous acetic acid or in acetic acid containing about 0.1% water (see Table IX) and an average value of 2.6 (±0.1) × 10^4 for the molar absorptivity, a_m, of hydrogen triiodide. When an identical procedure was carried out, using anhydrous potassium iodide instead of hydrogen iodide (data not included in this report), the value of a_m for the triiodide ion was only slightly larger, 2.8 (±0.1) × 10^4, but the value for the dissociation constant of I_3^- was found to be significantly greater than that for HI_3: 2.8 (±0.4) × 10^{-5} for the former, and 9.2 (±0.6) × 10^{-7} for the latter (from Table IX). Recently, Guidelli and Piccardi,[17] from a study of the voltammetric behavior of the iodide–iodine couple in acetic acid at the platinum electrode, calculated values of 2.3–4.0 × 10^{-5} for the dissociation constant, in excellent agreement with our average value.

Experimental Section

Materials.—3-Mercaptopropionic acid and 2-mercaptopropionic acid, 99.2 and 99.1% thiol, respectively, by titration with aqueous potassium triiodide, and mercaptosuccinic acid, mp 154°, were gifts from Evans Chemetics, New York, N. Y. Triphenylmethanethiol, mp 107–109°, was purchased from Frinton Laboratories, Vineland, N. J. The preparation of 3,3′-dithiodipropionic acid, mp 155–156°, was described previously,[18]

(14) G. Jones and B. B. Kaplan, *J. Amer. Chem. Soc.*, **50**, 1845 (1928).
(15) A. D. Awtrey and R. E. Connick, *ibid.* **73**, 1842 (1951).
(16) L. I. Katzin and E. Gebert, *ibid.*, **76**, 2049 (1954).
(17) R. Guidelli and G. Piccardi, *Anal. Lett.*, **1**, 779 (1968).
(18) J. P. Danehy and J. A. Kreuz, *J. Amer. Chem. Soc.*, **83**, 1109 (1961).

TABLE IX

DETERMINATION OF THE EQUILIBRIUM CONSTANT FOR THE REACTION, $HI + I_2 \rightleftharpoons HI_3$, IN ACETIC ACID[a]

$[I_3^-]$, $M \times 10^4$	Dilution factor, V	A_{360}[d]	r	F	$K \times 10^7$	$1/K \times 10^{-6}$	$a_m \times 10^{-4}$
4.61[b]	1	1.097					
	2	0.538	2.039	0.959	8.10	1.23	2.48
	5	0.208	5.274	0.958	8.49	1.18	2.48
	10	0.099	11.058	0.954	10.2	1.02	2.49
5.51[c]	1	1.425					
	2	0.699	2.039	0.959	9.65	1.03	2.69
	5	0.270	5.276	0.957	10.6	0.94	2.70
	10	0.128	11.13	0.962	8.27	1.21	2.68

[a] For definitions of V, r, and F, and the rationale for the method, see Katzin and Gebert.[15] $K = [HI][I_2]/[HI_3]$ so that $1/K = K_5$ in this paper. [b] Sufficient acetic anhydride was introduced to consume the water introduced with hydrogen iodide. [c] Contained ~0.1% water. [d] Values obtained with Cary spectrophotometer, 1-mm path.

and 4,4′-dithiodibutyric acid, mp 108°. 2,2′-dithiodipropionic acid, mp 110°, and dithiodisuccinic acid, mp 171–173°, were prepared in exactly the same way. The other disulfides were purchased from Distillation Products Industries, Rochester, N. Y., with the exception of triphenylmethyl disulfide. This compound, originally prepared by Vorländer and Mittag[19] by the addition of sulfuryl chloride to an alkaline alcoholic solution of triphenylmethanethiol, has apparently never been prepared by direct oxidation of the latter. That it is not feasible to oxidize the latter to the corresponding disulfide by iodine in acetic acid is obvious from the data in Table IV. But the data in Table II provided the basis for a simple and effective procedure. Triphenylmethanethiol (0.281 g) was dissolved in 100 ml of acetic acid, 0.5 M in sodium acetate. This solution rapidly consumed 1 equiv of iodine (97 ml of 1.05 N iodine) when the latter was added from a buret. The bulk of the acetic acid was removed by flash evaporation *in vacuo*, water was added, and the mixture extracted with ethyl ether. Evaporation of the ether left 0.28 g of white solid which recrystallized from chloroform, mp 160°. The highest previously reported melting point was 158°.[20]

Acetic acid was purified by the method of Tomiček and Heyrovsky.[21]

Methods.—Both a Beckman DB-G spectrophotometer and a Cary recording spectrophotometer were used, with a 1-mm light path in each case. Stable absorbance values were attained in all cases as soon as solutions were prepared.

Registry No.—Iodine, 7553-56-2; hydrogen iodide, 10034-85-2; acetic acid, 64-19-7; 3-mercaptopropionic acid, 107-96-0; triphenylmethanethiol, 3695-77-0; 3,3′-dithiodipropionic acid, 1119-62-6; triphenylmethyl disulfide, 15446-31-8; hydrogen triiodide, 30228-79-6.

Acknowledgment.—We are grateful to the National Science Foundation whose support of B. T. D. during the summers of 1967 and 1968 and of C. P. E. during 1969–1970 made this investigation possible. We also acknowledge the contribution of Mr. John Bachmann, a Notre Dame undergraduate, who made the initial observation that 3-mercaptopropionic acid could not be titrated with iodine in glacial acetic acid.

(19) D. Vorländer and E. Mittag, *Ber.*, **46**, 3453 (1913).

(20) H. Rheinboldt, M. Dewald, and O. Diepenbruck, *J. Prakt. Chem.*, [2], **130**, 133 (1931).

(21) O. Tomiček and A. Heyrovsky, *Collect. Czech. Chem. Commun.*, **15**, 984 (1950).

The Oxidation of Organic Divalent Sulfur by Iodine. III. Further Evidence for Sulfenyl Iodides as Intermediates and for the Influence of Structure on the Occurrence of Cyclic Intermediates in the Oxidation of Thiols

JAMES P. DANEHY,* CATHERINE P. EGAN,[1a] AND JURGEN SWITALSKI[1b]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received November 30, 1970

Further support for the view that the overoxidation of certain thiols by iodine in aqueous iodide proceeds *via* a cyclic intermediate formed by the intramolecular displacement of an iodide ion from a sulfenyl iodide by a carboxylate ion is provided by the study of the oxidation of 19 selected primary and secondary thiols. Only those thiols which have a free carboxyl group on a carbon atom β or γ to the thiol sulfur atom show the marked tendency to overoxidize with decreasing initial concentration of thiol and increasing pH previously reported. 2,5-Dimercaptoadipic acid and 3-mercapto-2-(mercaptomethyl)propionic acid, in which a second mercapto group can make an intramolecular attack on the sulfenyl iodide, show a minimal tendency to be overoxidized. The view that a sulfenyl iodide is the first product of the nucleophilic attack of a thiol on iodine is strengthened by observations on two tertiary thiols, 2-mercapto-2-methylpropanoic acid and penicillamine. Though each is oxidized only to the corresponding disulfide, the deep-orange sulfenyl iodide can be seen unless the iodine is added very slowly, and significantly higher I/SH ratios are observed when iodine is added rapidly. The sulfenyl iodide corresponding to 2-mereapto-2-methylpropanoic acid has been trapped at −40° with 4-chlorothiophenol. The product of trapping, 2-(4′-chlorophenyldithio)-2-methylpropanoic acid, has been characterized.

The question of the mechanism of the oxidation of thiols by iodine has recently been reexamined in conjunction with an attempt to explain the anomalous, excessive consumption of iodine by a few thiols.[2] It was suggested that in all cases the initiating event is the nucleophilic attack of thiol (or thiolate ion) on iodine to displace an iodide ion and to form a sulfenyl iodide,

(1) (a) Postdoctoral Research Associate, 1969–1970. (b) Undergraduate student, Indiana University, South Bend campus.

(2) J. P. Danehy and M. Y. Oester, *J. Org. Chem.*, **32**, 1491 (1967).

as originally suggested by Fraenkel-Conrat.[3] The fate of the latter depends upon its structure. In the great majority of cases an attack of thiol on sulfenyl iodide, which displaces iodide from sulfur and forms disulfide, completes the oxidation. But, in those cases in which thiols are sensitive to overoxidation, all of which have carboxyl groups on the carbon β to the sulfur, it was suggested that the carboxylate anion displaces iodide from the sulfenyl iodide and forms a cyclic, five-membered intermediate. Formation of a sulfenic acid by hydrolysis of the cyclic intermediate is followed by further uptake of iodine, which leads to higher oxidation products: sulfinic and sulfonic acids. Evidence in support of these views was obtained both by product analysis and elementary kinetic considerations.

The present paper offers further support for these views based on three groups of experimental data. First, a number of other thiols which do *not* undergo overoxidation, as well as three more β-mercaptocarboxylic acids which do, are reported. Second, the tendency for some γ- and δ-mercaptocarboxylic acids to be overoxidized by iodine has been measured. Third, the peculiar behavior of two water-soluble tertiary thiols toward iodine is interpreted as favoring the reality of a sulfenyl iodide as the first intermediate in the oxidation of thiols by iodine.

Since the alternative pathways are competitive, the second one, which leads to overoxidation, is favored over the first one, as the initial concentration of thiol is decreased. Over a wide range of concentration the following thiols show only that slight tendency to overoxidation which is always present: thiophenol, 2-mercaptophenol, 4-mercaptophenol, 4-mercaptobenzenesulfonic acid, 3-mercaptobenzoic acid, and 4-mercaptobenzoic acid. It is interesting to note that the favorably rigid structure of 2-mercaptobenzoic acid, which is extremely sensitive to overoxidation, is matched by the unfavorably rigid structures of the 3 and 4 isomers just reported. Because of solubility limitations, the titrations of these aromatic thiols were carried out only in acetate buffer (~pH 5.6). This fact does not in any way qualify the results, since lowering the pH value in the range of 3–2 almost always reduces any tendency to overoxidation. It has never been observed to increase the tendency.

Quantitative data are given in Table I for the extent of overoxidation, as a function of initial concentration of thiol and of pH, for eight β-mercaptocarboxylic acids. The compounds are arranged, very roughly, in the order of decreasing sensitivity to overoxidation. It must be remembered that in the case of cysteine (and perhaps *N*-acetylcysteine as well?) the maximal value for the I/SH ratio is four rather than six. The effect of structural variation on sensitivity is neither very marked nor subject to any rationalization that has occurred to us. In five cases there is at least some support for the generalization that sensitivity increases with the pH value of the medium, which was previously illustrated graphically.[2] The unique insensitivity to pH of cysteine has been shown previously.[2]

The last compound listed in Table I, a β-mercaptocarboxylic acid (doubly so, in fact) which exhibits negligible tendency to overoxidation, requires special consideration. Jansen[4] isolated from concentrates of asparagus a disulfide which could not be crystallized because of its polymeric character although it was readily reduced to 3-mercapto-2-(mercaptomethyl)propionic acid, melting at 61–62°. Schotte and Ström[5] prepared the disulfide by aerial oxidation of the dithiol, successfully separated the 1,2-dithiolane-4-carboxylic acid component from the polymeric one by taking advantage of the solubility of the former one in benzene, and showed by recovery that the monomer constitutes at least 62% of the crude disulfide. We have now found that oxidation of the dithiol with potassium triiodide also gives a mixture of monomer and polymer. Quantitative data on the distribution will be reported elsewhere. Here our interest is limited to the extent of overoxidation observed. That it is negligible may be attributed to the facts that not only the carboxylate ion, but a second mercapto group as well, is in a position to make an intramolecular attack on the sulfenyl iodide moiety to give a five-membered ring, and that the mercapto group is more nucleophilic than the carboxylate ion. Since, as Schotte and Ström pointed out, the 1,2-dithiolane system readily undergoes spontaneous cleavage of sulfur–sulfur bonds and subsequent formation of polymer, it may be that all of the dithiol passes through the dithiolane form upon oxidation by iodine.

The possible overoxidation of γ- or δ-mercaptocarboxylic acids could be explained by an exactly analogous scheme, invoking a six- or seven-membered cyclic intermediate, respectively. Relevant experience in this area indicates that the formation of six-membered, and particularly seven-membered, cyclic intermediates is less facile than the formation of five-membered ones. Quantitative data for five compounds are found in Table II. γ-Mercaptobutyric acid and its substitution product, *N*-acetylhomocysteine, do fit this pattern; while their sensitivity to overoxidation is more than minimal, it is considerably less than that of any of the β-mercaptocarboxylic acids. But the data for homo-

TABLE I

EXTENT OF OVEROXIDATION OF β-MERCAPTOCARBOXYLIC ACIDS BY AQUEOUS POTASSIUM TRIIODIDE AS A FUNCTION OF INITIAL CONCENTRATION OF THIOL AND OF pH

Compd	Registry no.	Initial [RSH]	I/SH at pH 3.0–3.5	I/SH at pH 5.6–6.0
o-HSC_6H_4COOH	147-93-3	0.20		1.85
		0.0001		5.90
HSCHCOOH CH_2COOH	70-49-5	0.100	1.10	
		0.001	4.50	5.21
$HSCH_2CH_2COOH$	107-96-0	0.100	1.00	
		0.001	4.21	4.55
$HSCH_2C(N^+H_3)HCOO^-$	52-90-4	0.100	1.00	
		0.006	1.63	
		0.001		2.58
$HSCH_2CHCOOH$ CH_2COOH	28525-49-7	0.102		2.07
		0.056	1.04	
		0.006	1.87	3.06
		0.003	2.51	3.38
$HSCH_2CHCOOH$ NHAc	616-91-1	0.010	1.04	2.11
		0.005	1.09	2.45
$HSC(CH_3)HCH_2COOH$	26473-49-4	0.090		1.47
		0.024	1.00	1.71
		0.006		2.23
$(HSCH_2)_2CHCOOH$	7634-96-0	0.100		1.00
		0.009		1.01
		0.004		1.01

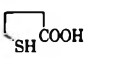
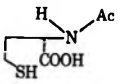
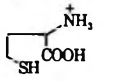
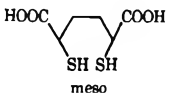
(3) H. Fraenkel-Conrat, *J. Biol. Chem.*, **217**, 373 (1955).

(4) E. F. Jansen, *ibid.*, **176**, 657 (1948).

(5) L. Schotte and H. Ström, *Acta Chem. Scand.*, **10**, 687 (1956).

TABLE II

EXTENT OF OVEROXIDATION OF γ- AND δ-MERCAPTOCARBOXYLIC ACIDS BY AQUEOUS POTASSIUM TRIIODIDE AS A FUNCTION OF INITIAL CONCENTRATION OF THIOL AND OF pH

Compd	Registry no.	Initial [RSH]	I/SH (pH)	I/SH (pH)
	13095-73-3	0.050	1.00 (2.4)	1.00 (5.18)
		0.0033	1.01 (2.4)	1.17 (5.18)
	7378-21-4	0.013	1.00 (2.00)	1.00 (5.4)
		0.0039	1.04 (2.0)	1.11 (5.4)
	454-28-4	0.058		2.12 (6.5)[a]
		0.015	1.00 (1.5)	2.51 (6.5)
		0.0044	1.03 (1.5)	2.79 (6.5)
δ-Mercapto valeric acid	30247-98-4	0.048		1.07 (6.0)
		0.029		1.09 (6.0)
		0.015		1.10 (6.0)
		0.0075		1.14 (6.0)
		0.0029		1.18 (6.0)
 meso	30318-69-5	0.0060	1.00 (1.9)	1.02 (6.0)

[a] Fleeting end points. In one case, I/SH = 2.81, direct analysis gave 0.26 mmol of RSSR and 0.53 mmol of RSO_2H. Since RSSR/RSO_2H = [4 − (I/SH)]/[2 (I/SH) − 2], 0.26/0.53 should equal (4 − 2.81)/[2(2.81) − 2]; actually, 0.49 = 0.33.

cysteine itself provides an anomaly for which we have not yet been able to account. While low pH (predominantly cationic species) effectively represses overoxidation, at higher pH (predominantly dipolar ionic species) the tendency to overoxidation is just as pronounced as with the β-mercaptocarboxylic acids. The I/SH ratios given for homocysteine are for fleeting end points which correspond to the disappearance of thiol and little oxidation beyond the sulfinic acid stage, so that the maximum value would be four rather than six. Comparison with the behavior of the *N*-acetyl derivative suggests that the positively charged nitrogen atom interacts with the carboxylate anion to produce a sterically favored conformation which potentiates the intramolecular attack. But examination of models has not yet revealed plausibly specific details.

The data for δ-mercaptovaleric acid reveal that its tendency to overoxidation is quite comparable to that of the two "normal" γ-mercaptocarboxylic acids. It is not surprising that the only other δ-mercaptocarboxylic acid investigated, 2,5-dimercaptoadipic acid, shows even less tendency to overoxidation for not only the carboxyl groups, but a second mercapto group as well, is in the δ position. Fredga[6] has shown that only cyclic disulfide, no trace of polymer, is formed by the oxidation of this dithiol with iodine. On the basis of relative nucleophilicity, carboxylate ion would not be expected to be competitive with thiol when both of them can participate in intramolecular attack.

Finally, it should be noted that glutathione is not overoxidized significantly over the pH range of 2–6. While this tripeptide, γ-glutamylcysteinylglycine, has two carboxyl groups, participation of one of them in an intramolecular reaction would involve an eight-membered cyclic intermediate and of the other one, a ten-membered ring.

During the titration of an aqueous solution of 2-mercapto-2-methylpropanoic acid, an orange color appears when little more than 5–10% of the equivalent amount of iodine has been added.[7] The color, which is quite different from that of aqueous triiodide, is neither intensified nor otherwise changed in the presence of starch. If the addition of iodine is stopped as soon as this color appears, the solution becomes colorless within a few moments. Further addition of iodine restores the color, which takes a little longer to disappear each time. If the titration is continued in this cautious fashion a stable, true iodine end point is eventually reached, and the I/SH ratio is 1.0, independent of the initial concentration of thiol. When, however, to a suitably dilute solution iodine is added as rapidly as possible from a buret, ignoring the orange color, no difficulty is encountered in seeing the starch-sensitized iodine end point, corresponding to an I/SH ratio of 1.15–1.20 at room temperature. Titrations carried out near 0° give I/SH ratios near 1.30. During the few minutes following the attainment of the end point the solution becomes much darker. Back-titration with standard thiosulfate after 15 min shows that the iodine which develops by "backing up" corresponds exactly to the observed excess of the I/SH ratio over 1.0. 2,2′-Dithiodiisobutyric acid is recovered quantitatively. More limited experiments carried out with penicillamine (2-amino-3-mercapto-3-methylbutanoic acid, another tertiary thiol) gave parallel results.

These observations can be reasonably interpreted in the following manner. The tertiary sulfenyl iodide, formed instantly by the reaction of iodine with thiol, is appreciably more resistant to attack by thiol than are primary or secondary sulfenyl iodides. This is consistent with the data and interpretation of Kolthoff and Harris[8] on the nonaqueous titration of tertiary thiols, and, less directly, with the relative stability of 2-methyl-2-propane sulfenyl iodide reported by Rheinboldt and Motzkus,[9] who prepared it by the reaction of silver or

(6) A. Fredga, *Ber. B*, **71**, 289 (1938).

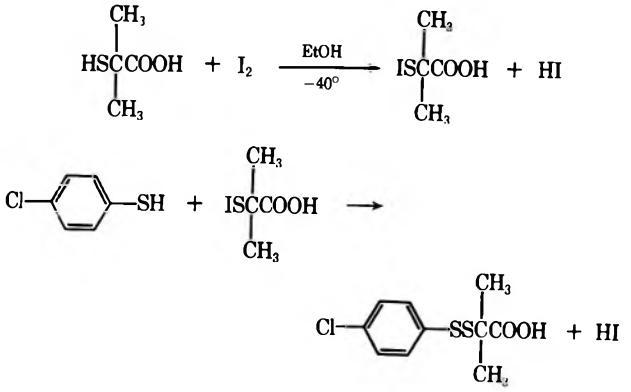
(7) It may be that the appearance of this color misled Schöberl into concluding that aqueous acidic solutions of this thiol cannot be titrated with iodine: A. Schöberl, *ibid.*, **70**, 1186 (1937).

(8) I. M. Kolthoff and W. E. Harris, *Anal. Chem.*, **21**, 963 (1949).

(9) H. Rheinboldt and E. Motzkus, *Ber.*, **72**, 657 (1939).

mercury *tert*-butyl mercaptide with iodine in ethyl ether. Nevertheless, the half-life of these tertiary sulfenyl iodides in the presence of thiols is only a few seconds, so that if iodine is added slowly enough sulfenyl iodide does not accumulate. But, if iodine is added as rapidly as possible, or tertiary thiol is added to iodine, formation of sulfenyl iodide is maximized. The facts shows that sulfenyl iodide (at least, tertiary sulfenyl iodide) does not undergo nucleophilic attack by water in the absence of thiol. Rather, dismutation takes place, with disulfide and iodine as the products.

The tertiary sulfenyl iodide corresponding to 2-mercapto-2-methylpropanoic acid has been trapped by the following sequence.



The mixed disulfide, 2-(4′-chlorophenyldithio)-2-methylpropanoic acid, was obtained in 36% yield, after separation from the corresponding symmetrical disulfides. In view of the demonstrated resistance of dithiodiisobutyric acid to alkaline hydrolysis[10] (nucleophilic displacement of sulfur from sulfur by hydroxide ion) and the fact that the 4-chlorophenylmercapto group is a good leaving group but a relatively poor nucleophile *vis-à-vis* the dithiodiisobutyric acid,[11] it is extremely unlikely that any of the mixed disulfide was formed by the reaction of 4-chlorothiophenol with the symmetrical disulfide.

Experimental Section

Materials.—*o*-Mercaptobenzoic acid, mercaptosuccinic acid, 3-mercaptopropionic acid, and L-cysteine were identified in paper I.[2] Mercaptomethylsuccinic acid and 3-mercaptobutanoic acid were prepared exactly as specified by Holmberg and Schjånberg.[12] Thiophenol and *N*-acetylcysteine were purchased from Distillation Products Industries, Rochester, N. Y. 4-Mercaptophenol, 3-mercaptobenzoic acid, and 4-mercaptobenzoic acid were identified in another paper.[11] 2-Mercaptophenol was a gift from Hooker Chemical Corp., Niagara Falls, N. Y. *meso*-2,5-Dimercaptoadipic acid was a gift from the Toni Co., Chicago, Ill. 2-Mercapto-2-methylpropanoic acid was purchased from Pierce Chemical Co., Rockford, Ill. γ-Butyrothiollactone, DL-homocysteinethiollactone, and *N*-acetyl-DL-homocysteinethiollactone were purchased from Aldrich Chemical Co., Milwaukee, Wis. 3-Mercapto-2-(mercaptomethyl)propanoic acid was a gift from Dr. Daniel L. Klayman, Walter Reed Army Medical Center, for whom it had been prepared by the Regis Chemical Co. 4-Mercaptobenzenesulfonic acid was prepared exactly as specified by Gorin.[13] Glutathione and penicillamine were purchased from California Biochemicals, Los Angeles, Calif.

δ-Mercaptovaleric Acid.—δ-Bromovaleronitrile (10.0 g) was refluxed for 3 hr with 50 ml of 9 *N* H_2SO_4, the solution was cooled and extracted with ethyl ether, and the combined ethereal extracts were dried over $MgSO_4$ and evaporated to give 6.5 g of oil. The latter, without purification, was refluxed for 3 hr with 2.8 g of thiourea in 30 ml of ethanol. Then 25 ml of 4 *N* NaOH was added and refluxing was continued for another 2 hr. The solution was concentrated *in vacuo*, extracted with ether (ether extract discarded), acidified with 6 *N* HCl, and extracted with ether, the ethereal extract dried over $MgSO_4$, the ether evaporated, and the residue distilled *in vacuo* to give 4.7 g of δ-mercaptovaleric acid, 73% pure by determination of thiol content with Folin's reagent, and 74% pure by electrometric titration of the carboxyl group.

Alkaline Hydrolysis of γ-Thiollactones.—Since γ-mercaptobutyric acid undergoes lactonization spontaneously, it is not practical to obtain and store samples of this compound in the pure state. For our purpose it seemed reasonable to dissolve a known weight of γ-butyrothiollactone in a volume of standard aqueous alkali whose equivalence slightly exceeded that of the lactone. This procedure seemed justified by the statement of Schjånberg[14] that "· · · alkaline hydrolysis of the thiollactone is very rapid and complete," although he did not specify details. Only after we had collected a considerable quantity of confusing and misleading data did we realize that complete and rapid hydrolysis depends on a very substantial excess of alkali. The definitive data in Table II were obtained by dissolving 1.0201 g of γ-butyrothiollactone in 12 ml of water in which 5.0 g of NaOH had already been dissolved, holding 10 min before diluting to 25 ml with water, and mixing 2-ml aliquots with sufficient HCl and AcOH, or acetate buffer, to give the pH values shown, before titrating with standard potassium triiodide. From constant I/SH ratios at higher initial concentrations than those given in the table, the purity of the thiollactone was calculated to be 89%.

N-Acetyl-DL-homocysteinethiollactone (93% pure) was found to require the same treatment so that the data for *N*-acetyl-DL-homocysteine in Table II were obtained by the same procedure.

This resistance to hydrolysis by a thiollactone was recently quantified for DL-homocysteinethiollactone by Duerre and Miller,[15] who showed spectrophotometrically that 5 min of exposure at room temperature to 2 *N*, but not 1.5 *N*, NaOH was sufficient to cleave the ring quantitatively. Our experience has shown that 2-ml aliquots of 0.5 *M* homocysteinethiollactone (93% pure) must be mixed with 2-ml aliquots of 5 *N* NaOH and held for 5 min in order that, when neutralized, maximum iodine titers can be obtained.

Trapping of *S*-Iodo-2-mercapto-2-methylpropanoic Acid with 4-Chlorothiophenol.—In four separate experiments 2 equiv of iodine in ethanol at −40° was added to 0.5–1.0-g samples of 2-mercapto-2-methylpropanoic acid in ethanol at −40° in a darkened flask. In one of the cases inverse addition was employed. Within 5 min or less 1 equiv of 4-chlorothiophenol in ethanol at −40° was added and the solution was allowed to warm to room temperature. The slight excess of iodine was reduced by addition of aqueous sodium bisulfite dropwise, the solution was neutralized with sodium bicarbonate, evaporated to small volume, water was added, and the solution was acidified and filtered to yield a solid residue (80–90% of the weight of the initial thiols) A. Suspension of A in water with excess sodium bicarbonate and filtration gave an insoluble residue B which, after a single recrystallization from ethanol, was readily identified by melting point and ir spectrum as 4-chlorophenyl disulfide, corresponding to about 25% of the initial 4-chlorothiophenol. Acidification of the filtrate gave a precipitate C, mp 125–135°. Limited extraction of C with CCl_4 or $HCCl_3$ and evaporation of the extract gave D, mp 137–138°, an equivalent weight of 249. *Anal.* Calcd for $ClC_6H_4SSCMe_2CO_2H$ (263): C, 45.71; H, 4.23; Cl, 13.47; S, 24.40. Found: C, 46.82; H, 4.57; Cl, 13.01; S, 21.48. The ir spectrum of D closely resembled that of a superposition of those of authentic specimens of 2,2′-dithiodiisobutyric acid and 4-chlorophenyl disulfide. The simple nmr spectrum of D in $CDCl_3$ (TMS) shows a singlet (6 H) at δ 1.52 and a quartet (4 H) centering at δ 7.28. For reference, 2,2′-dithiodiisobutyric acid melts at 197° and has an equivalent weight of 119; 4-chlorophenyl disulfide melts at 72°. D appears

(10) J. P. Danehy and W. E. Hunter, *J. Org. Chem.*, **32**, 2047 (1967).
(11) J. P. Danehy and K. N. Parameswaran, *ibid.*, **33**, 568 (1968).
(12) B. Holmberg and E. Schjånberg, *Ark. Kemi, Mineral. Geol.*, **14A** (7), 22 pp (1940).
(13) H. A. Smith, G. Doughty, and G. Gorin, *J. Org. Chem.*, **29**, 1484 (1964).
(14) E. Schjånberg, *Ber.*, *B*, **75**, 468 (1942).
(15) J. A. Duerre and C. H. Miller, *Anal. Biochem.*, **17**, 310 (1966).

to be 2-(4′-chlorophenyldithio)-2-methylpropanoic acid contaminated with a small amount of 2,2′-dithiodiisobutyric acid.

Registry No.—4-$ClC_4H_4SSCMe_2CO_2H$, 30247-81-5; 4-chlorophenyl disulfide, 1142-19-4.

Acknowledgment.—We are grateful to the National Science Foundation for the support of C. P. E. and to the Toni Company, Chicago, Ill., for the support of J. S. during the summers of 1968 and 1969.

Notes

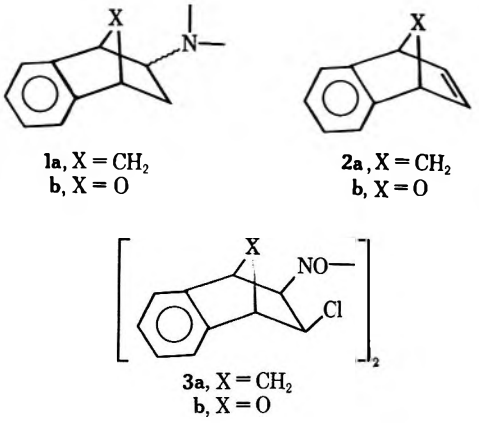
Lithium Aluminum Hydride Reduction of Bridged Bicyclic Nitroso Chloride Dimers

S. J. DOMINIANNI* AND P. V. DEMARCO

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received December 7, 1970

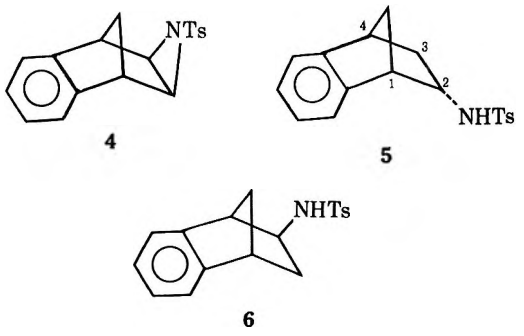
In connection with synthetic routes to amino compounds of type **1**, we have examined the $LiAlH_4$ reduction of the nitrosyl chloride adducts **3** derived from the olefins **2**. Thus, treatment of **2a** with nitrosyl chloride in chloroform followed by dilution with methanol afforded the white dimer **3a**[1] in 68% yield. Reaction of **3a** with $LiAlH_4$ in dioxane (heterogeneous mixture) followed by acylation with *p*-toluenesulfonyl chloride in pyridine provided a mixture from which two compounds could be isolated. The major product (*ca.* 45%), mp 153–154°, was shown to be the *exo*-aziridine **4** by comparison with authentic material prepared from **2a** and tosyl azide.[2] The minor product (*ca.* 5%), mp 142–144°, is assigned the endo structure **5** on the basis of its composition and the following nmr (100 MHz, C_6D_6) evidence: δ 1.82 (doublet of quartets, J = 12.3, 9.8, 4.0 Hz, H_3 exo), 2.73 (broad singlet, H_4), 3.11 (doublet of triplets, J = 1.0, 1.0, 4.0 Hz, H_1), 3.59 (broad doublet, J = 9.8, 4.0, and *ca.* 0.9 Hz, H_3 endo). The presence of a 4-Hz coupling between H_1 and H_2 dictates the exo configuration for H_2 (and thus the endo configuration for the *N*-tosyl group) since it is well established that coupling of significant magnitude between such protons in bicyclic systems is observed only when H_2 is exo.[3] Further, **5** is isomeric with **6**, mp 123–125°, which was prepared by treatment of **2a** with sodium azide–mercuric acetate–sodium borohydride in THF–H_2O,[4] followed by $LiAlH_4$ reduction of the azide and tosylation (60% overall yield). This sequence would be expected to lead to the exo product **6**; that this is indeed the case is supported by the apparent absence of coupling between H_1 and H_2 in the nmr spectrum (100 MHz, C_6D_6) of **6**. Careful comparison of the nmr spectra of **4**, **5**, and **6** with the spectrum of the mixture from reduction of **3a** showed the composition to be 60% **4**, 25% **5**, and 15% **6**.



1a, X = CH_2
b, X = O

2a, X = CH_2
b, X = O

3a, X = CH_2
b, X = O



Prior thermal isomerization of **3a** followed by $LiAlH_4$ reduction and tosylation, as before, led to a mixture of **4**, **5**, and **6** in approximately the same ratio. It thus seems reasonable to suppose that the reduction of **3a** occurs *via* a prior isomerization to a chloro oxime (which could not be isolated). Recent work has shown that $LiAlH_4$ reduction of bridged oximes gives predominantly aziridines.[5]

The 7-oxa analog **3b** behaved differently. Treatment of **2b** with nitrosyl chloride provided **3b** (61%).[1] Reduction of **3b** with $LiAlH_4$ (either directly or after thermal isomerization) followed by tosylation afforded a mixture from which two isomeric, chlorine-containing tosyl amides could be isolated by fractional crystallization from 2-propanol. The less soluble isomer, mp 185–187° (*ca.* 20% yield), is assigned the exo-cis structure **9**; the more soluble isomer, mp 196–198° (*ca.* 20% yield), was assigned the endo-trans structure **9**. Careful examination of the nmr spectrum of the crude mix-

(1) Exo-cis stereochemistry is based on analogy with other NOCl additions [*e.g.*, J. B. Miller, *J. Org. Chem.*, **26**, 4905 (1961); J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Amer. Chem. Soc.*, **86**, 4074 (1964)] and subsequent transformations.

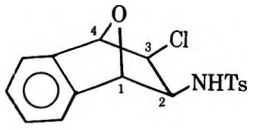
(2) M. M. Martin and R. A. Koster, *J. Org. Chem.*, **33**, 3428 (1968).

(3) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

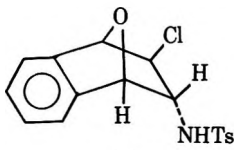
(4) C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).

(5) For a recent summary, see K. Kotera and K. Kitahonoki, *Org. Prep. Proced.*, **1**, 305 (1969).

ture showed that **8** and **9** accounted for at least 80% of the products.



8



9

The configurational assignments for **8** and **9** rest on nmr (100 MHz) arguments analogous to those presented for **5** and **6**. Thus in **9**, H_1 and H_2 are coupled by *ca.* 2.1 Hz as shown by double resonance. Irradiation of the doublet at δ 3.36 (H_1) causes collapse of the H_2 quartet at δ 4.22 to a doublet (values at 100 MHz, $CdCl_3$). No such coupling exists between H_1 and H_2 in **8**. Further nmr shift values are presented in Table I.

TABLE I

Compd	H_1	H_2	H_3	H_4	NH
5	3.18	3.59	4.10	3.18	
6	3.25	3.25	1.8	3.25	5.85
9	3.36	4.22	5.21	5.26	3.91
8	5.12	3.76	4.06	5.28	5.38

The most conspicuous distinguishing feature between the endo pairs (**5** and **9**) and the exo pairs (**6** and **8**), which further supports our configurational assignments made on the basis of coupling constants, is the very low field resonance position for the H_3 endo protons in **5** and **9**. This is obviously a result of the more proximal location of these protons in the endo orientation to the highly anisotropic sulfonamide and/or aromatic moieties of the *N*-tosyl function. The considerably smaller shift for H_1 on proceeding from **5** to **6** than from **9** to **8** is, however, troubling. This anomalous observation could possibly be rationalized if, in the exo compound **8**, the tosyl NH proton is intramolecularly hydrogen bonded to the bridge oxygen. This would have the effect of fixing the tosyl amide in close proximity to H_1, thereby exerting a deshielding influence upon this proton *via* a syn-diaxial mechanism.[6] In support of this explanation are two observations: (a) the lower field resonance position for the tosyl NH in **8** (δ 5.38) relative to **9** (δ 3.91) is strongly indicative of hydrogen bonding,[7] and (b) the presence of a 1.0-Hz coupling between H_1 and H_4 in **8** but not in **9** suggests some modification of the bridgehead molecular orbitals through which spin information is transmitted from H_1 to H_4. However, we see no evidence for hydrogen bonding in the ir spectrum of **8**.

The difference in behavior between **3a** and **3b** can be rationalized if it is assumed that in **3b** the organometallic reagent complexes on the bridgehead oxygen (and the nitroso group) rather than displacing chloride ion.

Experimental Section

Benzonorbornadiene Nitroso Chloride Dimer 3a.—A stirred solution of 2.84 g (0.020 mol) of benzonorbornadiene in 30 ml of chloroform was cooled to 0° and purged with nitrosyl chloride for 5 min. After an additional 30 min at 0°, the green solution (containing some white solid) was diluted with 30 ml of methanol and filtered to afford 2.82 g (68.2%) of **3a** as fine white needles, mp 167–169° dec. Attempted recrystallization of this material led to extensive decomposition.

Anal. Calcd for $(C_{11}H_{10}ClNO)_2$: C, 63.62; H, 4.85; Cl, 17.07; N, 6.75. Found: C, 63.42; H, 5.03; Cl, 17.28; N, 6.83.

7-Oxabenzonorbornadiene Nitroso Chloride Dimer 3b.—The procedure described for **3a** afforded **3b** as a white powder, mp 153–154° dec, in 73% yield.

Anal. Calcd for $(C_{10}H_8ClNO)_2$: C, 57.29; H, 3.84; Cl, 16.91; N, 6.68. Found: C, 57.09; H, 3.97; Cl, 16.63; N, 6.82.

Reduction of 3a.—A stirred mixture of 2.07 g (0.010 mol) of **3a**, 3.8 g of $LiAlH_4$, and 100 ml of dioxane was cautiously heated to *ca.* 70° when a vigorously exothermic reaction set in. The source of heat was removed and the reaction allowed to subside. The mixture was then refluxed 1 hr and let stand overnight. Excess $LiAlH_4$ was destroyed by dropwise addition of 4 ml of H_2O, 3 ml of 20% NaOH, and 14 ml of H_2O. The mixture was extracted with ether and the ether solution washed with cold H_2O. Removal of solvent *in vacuo* from the dried (K_2CO_3) solution afforded a pale yellow oil (1.58 g) which rapidly darkened on exposure to air. An ice cold solution of this oil in 20 ml of ether was treated with 5 ml of pyridine and then, in one portion, with 1.90 g (0.010 mol) of *p*-toluenesulfonyl chloride. The resulting yellow-green mixture was stirred at 0° for 2 hr and then at room temperature overnight. The mixture was diluted with H_2O (100 ml) and extracted with ether. The ether layer was washed with 50-ml portions of cold H_2O, cold 5% $NaHCO_3$, cold H_2O, cold 0.5 *N* HCl, and cold H_2O and dried (Na_2SO_4). Removal of the solvent *in vacuo* provided 2.50 g of a yellow-green gum, a portion of which was reserved for the nmr spectrum. The remainder was dissolved in 15 ml of hot 2-propanol and the solution allowed to cool. The solid which precipitated was removed and the mother liquor concentrated portionwise, each crop of solid being collected separately. The less soluble product amounted to 1.40 g (45%) and, after recrystallization from 2-propanol, had mp 153–154°. Its spectra were superimposible on those of authentic exo-aziridine **4**. The more soluble product **5** amounted to 0.16 g (5%) of white needles and had mp 142–144° after recrystallization from 2-propanol.

Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.99; H, 6.11; N, 4.47; S, 10.23. Found: C, 68.84; H, 6.01; N, 4.65; S, 10.51.

Thermal Isomerization and Reduction of 3a.—A stirred mixture of 2.07 g (0.010 mol) of **3a**, 50 ml of dioxane, and 1 drop of triethylamine was heated to reflux. Within 5 min all of the solid dissolved forming a pale green solution. After an additional 10 min the color faded. No precipitate formed when the solution was cooled. This solution was added dropwise to a slurry of 3.8 g (0.10 mol) of $LiAlH_4$ and 50 ml of THF (exothermic reaction). After the addition was complete, the mixture was stirred at reflux 1 hr and then at room temperature overnight. Work-up and tosylation were as described for **3a**. Nmr examination of the crude product showed approximately 65% **4**, 20% **5**, and 15% **6**.

Reduction of 3b.—The procedure described for **3a** afforded from 2.10 g (0.010 mol) of **3b**, 2.32 g of a mixture of **8** and **9**. Fractional crystallization from small volumes of 2-propanol provided the less soluble **8** as white needles, mp 185–187°, after further recrystallizations from 2-propanol (20% isolated yield).

Anal. Calcd for $C_{17}H_{16}ClNO_3S$: C, 58.36; H, 4.61; N, 4.00; S, 9.17; Cl, 10.14. Found: C, 58.21; H, 4.59; N, 3.95; S, 8.92; Cl, 10.23.

The more soluble **9** was isolated from the mother liquors in *ca.* 20% yield. Recrystallization from 2-propanol afforded white needles of **9**, mp 196–198°.

Anal. Found: C, 58.20; H, 4.52; N, 4.17; S, 9.07; Cl, 10.30.

***exo*-1,2,3,4-Tetrahydro-2-(*p*-tolylsulfonamido)1,4-methanonaphthalene (6).**—A stirred solution of 6.36 g (0.020 mol) of mercuric acetate in 20 ml of H_2O was treated, in order, with 20 ml of THF, 3.72 g (0.060 mol) of NaN_3, and 2.84 g (0.020 mol) of **2a**. The resulting curdy white mixture was heated to 50–55° for 18 hr, cooled, and treated with 20 ml of 15% aqueous KOH followed by a solution of 0.40 g $NaBH_4$ in 20 ml of 15% aqueous KOH. The resulting black mixture was stirred in an ice bath, treated with excess solid NaCl, and extracted with several portions of ether. The combined ether extracts were quickly washed with three 30-ml portions of ice–H_2O and dried (Na_2SO_4, 0°). The resulting pale yellow solution was added dropwise to a stirred mixture of 3.8 g of $LiAlH_4$ and 100 ml of ether (exothermic

(6) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 759 (1966); P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

(7) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, Chapter 4.

reaction). After the addition was complete, the mixture was stirred at reflux 1 hr and at room temperature overnight. Work-up and tosylation as described for **3a** afforded 3.77 g (60%) of **6** as a chalky solid, mp 119–124°. Several recrystallizations from 2-propanol afforded pure **6** as white needles, mp 123–125°.

Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.99; H, 6.11; N, 4.47; S, 10.23. Found: C, 68.74; H, 6.32; N, 4.73; S, 10.50.

Registry No.—**3a**, 30135-80-9; **3b**, 30135-81-0; **5**, 30166-89-3; **6**, 30166-90-6; **8**, 30166-91-7; **9**, 30166-92-8.

Acknowledgment.—We are grateful to Professors J. E. Baldwin (MIT) and E. Wenkert (Indiana) for helpful discussions.

trans-1-Aryl-2-(arenesulfonyl)ethenes. Copper-Catalyzed Addition of Sulfonyl Chlorides to Substituted Styrenes[1]

WILLIAM E. TRUCE* AND CHRISTIAN T. GORALSKI[2]

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received January 21, 1971

trans-1-Phenyl-2-(benzenesulfonyl)ethene (**2**, R = R′ = C_6H_5) has been prepared by (a) the condensation of benzenesulfonylacetic acid with benzaldehyde,[3] (b) the addition of benzenethiol to phenylacetylene followed by oxidation of the resulting *trans*-1-phenyl-2-(phenylmercapto)ethene with hydrogen peroxide,[4] and (c) the copper-catalyzed addition of benzenesulfonyl chloride to styrene followed by dehydrohalogenation of the resulting 1-chloro-1-phenyl-2-(benzenesulfonyl)ethane (**1**, R = R′ = C_6H_5) with triethylamine.[5] In this paper we would like to describe our studies on the synthetic utility of method c.

Arenesulfonyl chlorides can be added to styrenes to give 1-chloro-1-aryl-2-(arenesulfonyl)ethanes [**1**, R,R′ = aryl (eq 1)] in good to excellent yields (see Table I).

$$RCH{=}CH_2 + R'SO_2Cl \xrightarrow[Et_3N\cdot HCl,\ CH_3CN]{CuCl_2} \underset{\displaystyle Cl}{\overset{\displaystyle |}{RCHCH_2SO_2R'}} \quad (1)$$

1

The reaction appears to be little affected by substituent electronic effects or by steric effects of substituents in the 2 and 6 positions of either the sulfonyl chloride or the styrene. Treatment of the 1-chloro-1-aryl-2-(arenesulfonyl)ethanes (**1**) with triethylamine in benzene afforded the corresponding *trans*-1-aryl-2-(arenesulfonyl)ethenes [**2**, R, R′ = aryl (eq 2)] in excellent yield (see Table II).[6]

TABLE I.—SULFONYL CHLORIDE ADDUCTS **1**

Registry no.	R	R′	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % S	Found, % C	Found, % H	Found, % Cl	Found, % S
6461-58-1	C_6H_5	C_6H_5	88–90[a]	75								
30158-41-9	C_6H_5	2,4,6-$[CH(CH_3)_2]_3C_6H_2$	119–120	89	67.87	7.68	8.71	7.88	68.02	7.86	8.90	8.13
30158-42-0	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	98–99	84	63.24	5.93	10.98	9.93	63.15	6.15	11.08	9.96
30158-43-1	C_6H_5	2-$C_{10}H_7$	124.5–125	89	65.34	4.57	10.72	9.69	65.16	4.55	10.95	9.45
30158-44-2	C_6H_5	4-FC_6H_4[b]	88–90	82	56.28	4.05	11.87	10.73	56.28	3.84	11.70	10.95
30158-45-3	C_6H_5	4-BrC_6H_4[c]	90.5–91	96	46.75	3.36	9.86	8.91	47.02	3.55	9.90	9.01
30158-46-4	C_6H_5	4-$O_2NC_6H_4$[d]	136–137	78	51.61	3.72	10.88	9.84	51.85	3.93	10.76	9.80
30158-47-5	C_6H_5	2-$O_2NC_6H_4$[e]	106–107	82	51.61	3.72	10.88	9.84	51.38	3.86	11.00	9.73
30158-48-6	C_6H_5	2-O_2N-4-ClC_6H_3[f]	135–137	82	46.69	3.05	19.69	8.90	46.85	3.26	19.44	8.97
30158-49-7	4-$CH_3C_6H_4$	C_6H_5	91–93	65	61.11	5.13	12.03	10.88	61.35	5.06	12.01	10.68
30158-50-0	4-$C_6H_5C_6H_4$	C_6H_5	130–132	46[g]	67.31	4.80	9.94	8.98	67.58	4.68	9.66	9.09
30158-51-1	2,6-$(CH_3)_2C_6H_3$	C_6H_5	75–77	73	62.24	5.51	11.49	10.37	62.35	5.57	11.69	10.49
30158-52-2	4-ClC_6H_4	C_6H_5	80.5–82	68	53.34	3.84	22.50	10.17	53.56	4.09	22.63	10.39
30158-53-3	3-$O_2NC_6H_4$[h]	C_6H_5	86–88	74	51.61	3.72	10.88	9.84	51.53	3.70	11.00	9.75
6038-47-7	C_6H_5	CH_3	70.5–72	66	49.42	5.07	16.22	14.66	49.53	5.11	15.94	14.43
30158-39-5	C_6H_5	$C_6H_5CH_2$	121–122	6[i]	61.11	5.13	12.03	10.88	61.23	5.10	11.76	10.87
30158-56-6	C_6H_5	$BrCH_2$[j]	101–102	80	36.32	3.39	11.91	10.77	36.21	3.15	11.99	10.72

[a] M. Asscher and D. Vofsi [*J. Chem. Soc.*, 4962 (1964)] report mp 89–90°. [b] *Anal.* Calcd for $C_{14}H_{12}ClFO_2S$: F, 6.36. Found: F, 6.45. [c] *Anal.* Calcd for $C_{14}H_{12}BrClO_2S$: Br, 22.22. Found: Br, 22.30. [d] *Anal.* Calcd for $C_{14}H_{12}ClNO_4S$: N, 4.30. Found: N, 4.58. [e] *Anal.* Calcd for $C_{14}H_{12}ClNO_4S$: N, 4.30. Found: N, 4.28. [f] *Anal.* Calcd for $C_{14}H_{11}Cl_2NO_4S$: N, 3.86. Found: N, 3.87. [g] A large amount of polymerization of 4-vinylbiphenyl occurred. [h] *Anal.* Calcd for $C_{14}H_{12}ClNO_4S$: N, 4.30. Found N, 4.35. [i] Most of the α-toluenesulfonyl chloride decomposed to benzyl chloride and sulfur dioxide (see text and Experimental Section) resulting in a low yield of 1:1 adduct. [j] *Anal.* Calcd for $C_9H_{10}BrClO_2S$: Br, 26.85. Found: Br, 26.70.

(1) Unsaturated Sulfones and Suitable Precursors. III. For previous papers in this series, see W. E. Truce, C. T. Goralski, L. W. Christensen, and R. H. Bavry, *J. Org. Chem.*, **35**, 4217 (1970); W. E. Truce and C. T. Goralski, *ibid.*, **35**, 4220 (1970).

(2) Halogens Research Laboratory, The Dow Chemical Co., Midland, Mich. 48640.

(3) V. Baliah and M. Seshapathirao, *J. Org. Chem.*, **24**, 867 (1959).

(4) H. G. Klein, Ph.D. Thesis, Purdue University, 1961.

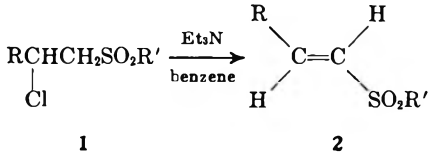
(5) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 4962 (1964).

(6) The vinyl sulfones **2** were identified as the trans isomers by their nmr (J_{vinyl} = 14–16 cps) and infrared (ω_{vinyl} = 10.2–10.5 μ) spectra which are typical of trans 1,2-disubstituted olefins. We earlier described the reaction of these vinyl sulfones (Table II) with dimethylsulfonium methylide to give the corresponding *trans*-1-(arenesulfonyl)-2-arylcyclopropanes: W. E. Truce and C. T. Goralski, *J. Org. Chem.*, **34**, 3324 (1969).

TABLE II.—UNSATURATED SULFONES 2

Registry no.	R	R′	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
16212-06-9	C_6H_5	C_6H_5	75–76[a]	94						
30166-82-6	C_6H_5	2,4,6-$[CH(CH_3)_2]_3C_6H_2$	125–126	88	74.55	8.16	8.65	74.56	8.00	8.46
30166-83-7	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	89.5–90.5	96	71.30	6.33	11.20	70.90	6.20	11.06
30166-84-8	C_6H_5	2-$C_{10}H_7$	143.5–144	87	73.44	4.79	10.90	73.38	5.02	11.02
30166-85-9	C_6H_5	4-FC_6H_4[b]	83.5–84	97	64.10	4.23	12.23	64.08	4.37	12.32
30166-86-0	C_6H_5	2-$O_2NC_6H_4$[c]	123.5–124	93	58.13	3.83	11.08	58.13	4.11	11.18
30166-87-1	C_6H_5	2-O_2N-4-ClC_6H_3[d]	170–170.5	89	51.93	3.11	9.91	52.14	3.40	9.85
30166-88-2	4-$CH_3C_6H_4$	C_6H_5	137–138[e]	78						
30166-77-9	4-$C_6H_5C_6H_4$	C_6H_5	172–173	84	74.97	5.03	10.01	74.70	5.20	9.77
33166-78-0	2,6-$(CH_3)_2C_6H_3$	C_6H_5	120–121	89	70.55	5.92	11.78	70.71	5.96	11.50
30246-73-2	2-$C_{10}H_7$	C_6H_5	103–104	19[f]	73.44	4.79	10.97	73.38	5.02	11.02
20605-52-1	4-ClC_6H_4	C_6H_5	131–132[g]	80						
15436-11-0	C_6H_5	CH_3	80–81[h]	87						

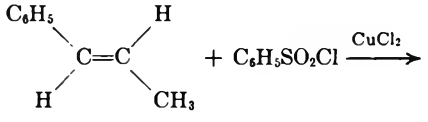
[a] M. Asscher and D. Vofsi [*J. Chem. Soc.*, 4962 (1964)] report mp 75–76°. [b] *Anal.* Calcd for $C_{14}H_{11}FO_2S$: F, 7.24. Found: F, 7.23. [c] *Anal.* Calcd for $C_{14}H_{11}NO_4S$: N, 4.84. Found: 4.55. [d] *Anal.* Calcd for $C_{14}H_{10}ClNO_4S$: Cl, 10.95; N, 4.33. Found: Cl, 10.69; N, 4.27. [e] V. Baliah and M. Seshapathirao [*J. Org. Chem.*, 24, 867 (1959)] report mp 135.5–136.5°. [f] This represents the total overall yield from 2-vinylnaphthalene. A large amount of polymerization of the 2-vinylnaphthalene occurred, and the initial sulfonyl chloride adduct could not be isolated in pure form. [g] V. Baliah and M. Seshapathirao [*ibid.*, 24, 867 (1959)] report mp 129–130°. [h] W. E. Parham, F. D. Blake, and D. R. Theissen [*ibid.*, 27, 2415 (1962)] report mp 77–78°.



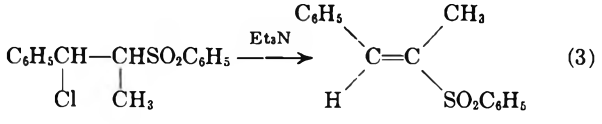
(2)

1 2

The reaction of *trans*-β-methylstyrene (**3**) with benzenesulfonyl chloride gave 1-chloro-1-phenyl-2-(benzenesulfonyl)propane (**4**) as a thick, viscous oil which, on treatment with triethylamine in benzene, was converted to β-(benzenesulfonyl)-*cis*-β-methylstyrene (**5**, eq 3).[7] In contrast, an attempt to react *trans*-stilbene



3

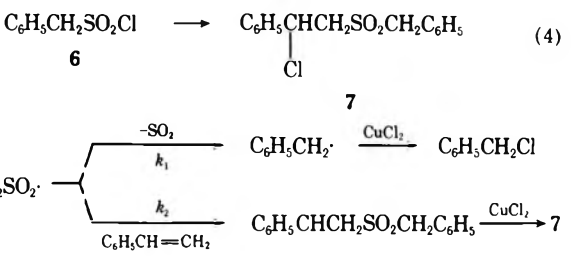


(3)

4 5

with benzenesulfonyl chloride gave only a 95% recovery of the starting olefin.

A brief study of the reaction of alkanesulfonyl chlorides with styrene was made. Methanesulfonyl chloride and bromomethanesulfonyl chloride added to styrene to give 1:1 adducts (Table I) in 66 and 80% yield, respectively, but α-toluenesulfonyl chloride (**6**) gave mainly benzyl chloride and sulfur dioxide and only a 6% yield of 1-chloro-1-phenyl-2-(α-toluenesulfonyl)-ethane (**7**, eq 4). Apparently the intermediate α-toluenesulfonyl radical loses sulfur dioxide to give a



(4)

6 7

benzyl radical at a faster rate than it is trapped by styrene to give a 1-phenyl-2-(α-toluenesulfonyl)ethyl radical ($k_1 > k_2$).[8]

In conclusion, the copper-catalyzed addition of sulfonyl chlorides to styrenes followed by elimination of hydrogen chloride from the resulting β-chloro sulfones represents an excellent, high-yield synthesis of *trans*-1-aryl-2-(arenesulfonyl)ethenes and other unsaturated sulfones.

Experimental Section[9]

General Procedure for the Addition of Sulfonyl Chlorides to Styrenes.—Typically, in a 100-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet, and a reflux condenser fitted with a calcium chloride drying tube were placed 0.10 mol of the styrene, 0.10 mol of the sulfonyl chloride, 0.13 g (1.0 mmol) of anhydrous cupric chloride, 0.206 g (1.5 mmol) of triethylamine hydrochloride, and 4.00 g of acetonitrile. The above mixture was then heated at 100–130°, with stirring, under the nitrogen for 2 hr and then cooled. Methanol (40 ml) was added to the cooled reaction mixture, and the β-chloro sulfone separated as a white, crystalline solid. The solid was filtered, washed with water, and recrystallized from 95% ethanol to give analytically pure **1**.

β-(Benzenesulfonyl)-*cis*-β-methylstyrene.—A mixture of 10.0 g (0.085 mol) of *trans*-β-methylstyrene, 15.0 g (0.085 mol) of benzenesulfonyl chloride, 0.110 g (0.85 mmol) of anhydrous cupric chloride, 0.175 g (1.27 mmol) of triethylamine hydro-

(7) The structural assignment of **5** is based on the observation that the vinyl proton signal overlaps the ortho aromatic protons of the benzenesulfonyl group (δ 7.80) as observed for the proton geminal to the phenyl group (δ 7.67) in the nmr spectra of *trans*-1-phenyl-2-(benzenesulfonyl)-ethene. In contrast, the signal for the proton geminal to the phenyl group in *cis*-1-phenyl-2-(benzenesulfonyl)ethene occurs at δ 6.90 [A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *J. Amer. Chem. Soc.*, **86**, 2877 (1964)].

(8) A similar mechanism has been proposed to explain the results of the reaction of chloromethanesulfonyl chloride with 1-octene and styrene in the presence of cupric chloride (ref 5).

(9) All reactions were carried out in a nitrogen atmosphere. Reagent grade cupric chloride was used in all addition reactions and was dried at 140° prior to use. All compounds gave nmr spectra consistent with their assigned structures (recorded on a Varian A-60A spectrometer with tetramethylsilane as an internal standard). All melting points are uncorrected. The elemental analyses were performed by Dr. C. S. Yeh and the staff of the Purdue Microanalytical Laboratory.

chloride, and 3.4 g of acetonitrile was heated with stirring at 110° for 2 hr and then cooled. Methanol (34 ml) was added to the cooled reaction mixture and the resulting solution was refrigerated. After standing under refrigeration for several days, no solid separated from the solution. The methanol was removed *in vacuo* leaving a thick, viscous, yellow oil. The oil was dissolved in a minimum amount of dry benzene and 12.87 g (0.127 mol) of triethylamine was added. The reaction mixture was stirred for 1 hr and then filtered to remove the triethylamine hydrochloride which had precipitated. The triethylamine hydrochloride was washed with several portions of dry benzene. The benzene was removed *in vacuo* from the combined benzene filtrates leaving a yellow oil which crystallized on addition of a small amount of 95% ethanol. The solid was filtered, dried, and recrystallized from 95% ethanol to give 9.90 g (45% yield) of β-(benzenesulfonyl)-*cis*-β-methylstyrene: mp 94.5–95.5°; nmr δ 2.10 (d, 3), 7.33 (s, 5), 7.45–7.70 (m, 3), 7.75–8.05 (m, 3).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.68; H, 5.23; S, 12.53.

Attempted Reaction of Benzenesulfonyl Chloride with *trans*-Stilbene.—A mixture of 18.00 g (0.10 mol) of *trans*-stilbene, 17.67 g (0.10 mol) of benzenesulfonyl chloride, 0.130 g (1.0 mmol) of anhydrous cupric chloride, 0.206 g (1.5 mmol) of triethylamine hydrochloride, and 4.00 g of acetonitrile was heated, with stirring, at 120° for 2 hr and then cooled. Methanol (40 ml) was added to the cooled reaction mixture and unreacted *trans*-stilbene separated as a pale yellow, crystalline solid. The recovered *trans*-stilbene was filtered, dried, and recrystallized from 95% ethanol to give 17.10 g (95% recovery), mp 125–126° (lit.[10] mp 124°).

General Procedure for the Preparation of Unsaturated Sulfones (2).—To a saturated solution of the sulfonyl chloride adduct 1 in dry benzene was added 1.5 equiv of triethylamine. The reaction mixture was allowed to stir for 45 min and then filtered to remove the triethylamine hydrochloride produced. The triethylamine hydrochloride was washed with several portions of dry benzene. The benzene was removed *in vacuo* from the combined benzene filtrates leaving an oil which crystallized on addition of a small amount of ethanol. The solid was recrystallized from 95% ethanol to give analytically pure 2.

Reaction of α-Toluenesulfonyl Chloride (6) with Styrene.—In a 100-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet tube, and a reflux condenser with a drying tube were placed 10.41 g (0.10 mol) of styrene, 19.06 g (0.10 mol) of α-toluenesulfonyl chloride, 0.130 g (0.0010 mol) of anhydrous cupric chloride, 0.206 g (0.0015 mol) of triethylamine hydrochloride, and 4.00 g of acetonitrile. The reaction mixture was heated, with stirring, at 125° for 2 hr and then cooled. During the entire 2-hr reaction period the evolution of sulfur dioxide (SO_2) was noted. Methanol (40 ml) was added to the cooled reaction mixture, and the resulting solution was refrigerated. A small amount of a white solid separated from the cold solution. The solid was filtered, dried, and recrystallized from 95% ethanol to give 0.85 g of 1-chloro-1-phenyl-2-(α-toluenesulfonyl)ethane, mp 121–122°.

Anal. Calcd for $C_{15}H_{15}ClO_2S$: C, 61.11; H, 5.13; Cl, 12.03; S, 10.88. Found: C, 61.23; H, 5.10; Cl, 11.76; S, 10.87.

The methanol was removed from the recrystallization liquor *in vacuo* leaving a yellow oil which was distilled under reduced pressure. The distillation yielded 7.18 g of a colorless liquid which was shown by nmr to be a mixture consisting of 65% benzyl chloride and 35% styrene. A heavy, dark residue remained after distillation. The residue was dissolved in 95% ethanol and decolorized. The ethanol solution was cooled yielding an additional 1.00 g of 1-chloro-1-phenyl-2-(α-toluenesulfonyl)-ethane, mp 118–119°. The total yield of 1:1 adduct was 1.85 g (6% yield).

Registry No.—5, 30246-74-3; 7, 30158-39-5.

Acknowledgment.—The authors wish to express their appreciation for financial support of this work by the Purdue Research Foundation and the Public Health Service Research Grant No. CA-04536-09 from the National Cancer Institute.

(10) "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Publishing, Cleveland, Ohio, 1964, p C-546.

α,β-Epoxysulfonamides

W. E. TRUCE* AND L. W. CHRISTENSEN

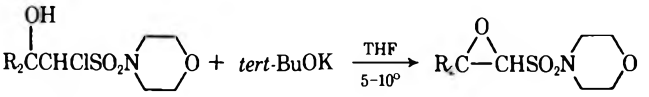
Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received February 17, 1971

Although various electronegatively substituted epoxides are known, considerable current attention is being devoted to the synthesis of new moieties in this classification.[1] Only recently has the preparation of α,β-epoxysulfonyl and sulfinyl systems been reported.[2]

Our own interest in α-substituted sulfonic acid derivatives[3] coupled with the facile synthetic route to β-hydroxy-α-chlorosulfonamides, which we recently reported,[4] suggested the preparation of the novel α,β-epoxysulfonic acid derivatives.

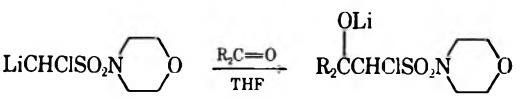
Indeed, when the precursory β-hydroxy-α-chlorosulfonamides **1** were treated with potassium *tert*-butoxide in THF, the α,β-epoxysulfonamides were formed in good to moderate yields (Table I).



1 **2**

This reaction almost certainly proceeds *via* initial formation of the β-alkoxide followed by an intramolecular displacement of the halogen atom. The ease (low temperature, short reaction time) of this displacement is noteworthy since it is in direct contrast to intermolecular S_N2 displacements α to sulfonyl groupings in both sulfones[5] and sulfonamides,[6] which occur only with difficulty. However, a parallel effect is encountered in the Ramberg–Bäcklund reaction, which also involves an intramolecular displacement α to a sulfonyl grouping and can also occur at low temperature.[7] Seemingly, when the nucleophilic center is generated in the proximity of the reaction site, the sulfonyl group exhibits either a highly diminished retarding effect or no retarding effect on α displacements.

It would be useful synthetically if the α,β-epoxide could be generated directly from the condensation of the α-chloroalkyllithium sulfonamide **6** with a ketone, thereby bypassing the isolation and subsequent ring closing of the β-hydroxy-α-chlorosulfonamide. However, allowing a solution of **6** and a ketone, *e.g.*, acetone,



6 **7**

(1) (a) J Cantacuzene and J.-M. Normant, *Tetrahedron Lett.*, 2947 (1970); (b) H. Newman and R. B. Angier, *Tetrahedron*, **26**, 825 (1970).

(2) (a) P. F. Vogt and D. F. Tavares, *Can. J. Chem.*, **47**, 2875 (1969); (b) F. Bohlmann and G. Haffer, *Chem. Ber.*, **102**, 4017 (1969); (c) T. Durst and K.-C. Tin, *Tetrahedron Lett.*, 2369 (1970); (d) D. F. Tavares, R. E. Estep, and M. Blezard, *ibid.*, 2373 (1970).

(3) (a) W. E. Truce and L. W. Christensen, *Tetrahedron*, **25**, 181 (1969); (b) W. E. Truce and D. J. Vrencur, *Can. J. Chem.*, **47**, 860 (1969).

(4) W. E. Truce and L. W. Christensen, *Tetrahedron Lett.*, 3075 (1969).

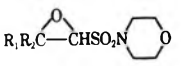
(5) F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

(6) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5184 (1951).

(7) W. E. Truce, T. C. Klingler, J. E. Parr, H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969).

TABLE I

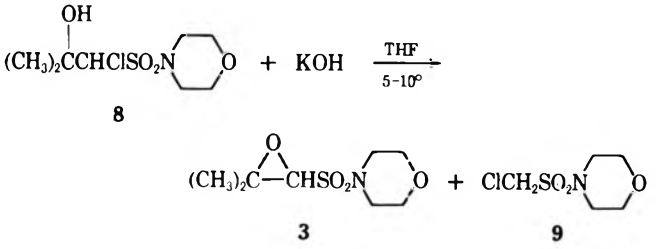
α,β-EPOXYSULFONAMIDES



No.	Substituents	Mp, °C	Yield,[a] %	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
3	$R_1 = CH_3$ $R_2 = CH_3$	67–68	75	43.48	6.84	14.51	43.20	6.90	14.49
4	R_1 = Ph; R_2 = Ph	144–145	57[b]	62.68	5.52	9.29	62.41	5.60	9.16
5	R_1, $R_2 = (CH_2)_5$	86.5–88	66	50.26	7.30	12.25	50.55	7.53	12.06

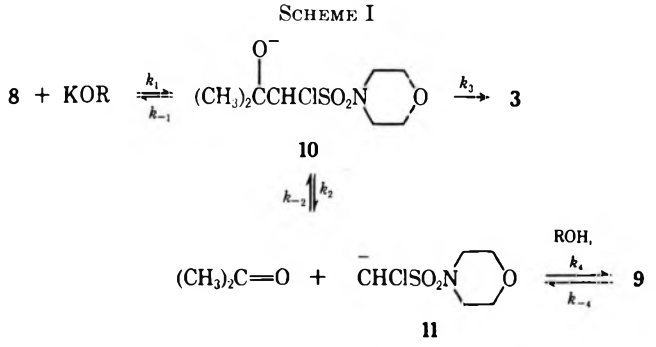
[a] Isolated, purified material, yield not optimized. [b] *Anal.* Calcd for N: 4.06. Found: 3.94.

to warm from −75° to room temperature before hydrolyzing and work-up does not result in epoxide formation. Apparently, when lithium is the cation in the intermediate species **7**, the nucleophilicity of the alkoxide is diminished to such an extent that the displacement will not occur. When potassium is then substituted as cation by interaction of **1** with *tert*-BuOK, the displacement occurs readily. Analogous cation effects in condensations and displacements have been reported previously.[8] In addition to the nature of the cation, it has been found that even the nature of the base itself is crucial for the formation of epoxide. For example, when potassium hydroxide is substituted for potassium *tert*-butoxide, the yield of **3** is greatly diminished (20%) and a large amount (80%) of chloromethylsulfonmorpholide **9** is isolated. Similar results



involving the nature of the base employed have been reported by Bohlmann and Haffer[2] for β-hydroxy-α-chlorosulfones. These results may be rationalized by noting ramifications of the mechanism proposed in Scheme I. Assuming epoxide formation is irreversible,

SCHEME I



i.e., **10** → **3**, then the protonation of **11** is more complete with water as the conjugate acid of the base used (KOH) than with *tert*-butyl alcohol acting as the conjugate acid of the base *tert*-BuOK. Hence, epoxide formation predominates with *tert*-BuOK while fragmentation prodominates when KOH is utilized.

Considering the ease of formation of the precursory β-hydroxy-α-chlorosulfonamides and the facile nature of the ring closure, a useful method is at hand for the preparation of α,β-epoxysulfonic acid derivatives.

(8) E. M. Kaiser and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 4566 (1967).

Experimental Section[9]

General Procedure for Epoxide Formation from β-Hydroxy-α-Chlorosulfonamides.—To 0.01 mol of the 1-chloro-2-hydroxysulfonamide in 20 ml of freshly dried THF under N_2 at 0° was added *tert*-BuOK (0.01 mol) in 15–20 ml of THF. The addition was carried out at such a rate as to maintain the temperature below 15°. After being stirred for 10 min, 100 ml of 3% aqueous NH_4Cl was added and the resultant solution extracted with five 40-ml portions of $CHCl_3$. The chloroform extracts were dried over Na_2SO_4 and then evaporated *in vacuo*, yielding a colorless oil. This oil was taken up in 90% ethanol and cooled, and the resultant solid recrystallized from ethanol to afford pure product.

Epoxide Formation from 1-Chloro-2-hydroxy-2-methylpropanesulfonmorpholide.—1-Chloro-2-hydroxy-2-methylpropanesulfonmorpholide (0.90 g, 3.5 mmol) and potassium *tert*-butoxide (0.393 g, 3.5 mmol) afforded 0.58 g (75%) of α,α-dimethyl-β-sulfonmorpholylethylene oxide: mp 67–68°; nmr δ 1.45 (s, 3), 1.70 (s, 3), 3.40 (m, 4), 3.76 (m, 5).

Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.48; H, 6.84; S, 14.51. Found: C, 43.20; H, 6.90; S, 14.49.

Epoxide Formation from 1-Chloro-2-hydroxy-2,2-diphenylethanesulfonmorpholide.—1-Chloro-2-hydroxy-2,2-diphenylethanesulfonmorpholide (1.30 g, 3.5 mmol) and potassium *tert*-butoxide (0.393 g, 3.5 mmol) yielded 0.69 g (57%) of α,α-diphenyl-β-sulfonmorpholylethylene oxide: mp 144–145°; nmr δ 3.20 (m, 4), 3.60 (m, 4), 4.35 (s, 1), 7.40 (m, 10).

Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.68; H, 5.52; N, 4.06; S, 9.29. Found: C, 62.41; H, 5.60; N, 3.94; S, 9.16.

Epoxide Formation from 1-Chloro-1-(1-hydroxycyclohexyl)-methanesulfonmorpholide.—1-Chloro-1-(1-hydroxycyclohexyl)-methanesulfonmorpholide (1.20 g, 3.41 mmol) and potassium *tert*-butoxide (0.382 g, 3.41 mmol) gave 0.56 g (66%) of the spiral epoxide **5**, mp 86.5–88°. The nmr of the crude reaction mixture also indicated that some fragmentation occurred to afford cyclohexanone and chloromethylsulfonmorpholide: δ 4.51 ($ClCH_2$); nmr δ 1.80 (m, 10), 3.40 (m, 4), 3.70 (m, 5).

Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.26; H, 7.30; N, 5.36; S, 12.25. Found: C, 50.55; H, 7.53; N, 5.57; S, 12.06.

Attempted Formation of α,α-Dimethyl-β-sulfonmorpholylethylene Oxide Using Potassium Hydroxide.—To 1-Chloro-2-hydroxy-2-methylpropanesulfonmorpholide (1.00 g, 3.88 mmol) in 25 ml of THF at 0° under N_2 was added powdered potassium hydroxide (0.244 g, 4.0 mmol). After being stirred for 15 min at 15°, 100 ml of 3% aqueous NH_4Cl was added and the resulting mixture extracted with chloroform. The chloroform extracts were dried over $NaSO_4$ and then evaporated *in vacuo* affording a light yellow semisolid, the nmr of which indicated a 20% yield of epoxide and an 80% yield of chloromethylsulfonmorpholide as determined from the signals at δ 4.51 ($ClCH_2$) and 1.50, 1.70 [$(CH_3)_2CO$-C]. No starting 1-chloro-2-hydroxysulfonamide could be detected in the nmr spectrum of this crude reaction material. Separation *via* column chromatography using silica gel as adsorbent and dichloromethane as eluent afforded 0.65 g (75%) of **3** and 0.13 g (17%) of **9**.

(9) All melting points are uncorrected. The nmr spectra were obtained in $CDCl_3$ using a Varian A-60 spectrometer with TMS = 0. Microanalyses and molecular weight determinations were performed by Dr. C. S. Yeh and staff. *tert*-BuOK was purchased from MSA Corp. and purified by sublimation. Reagent grade THF was distilled from $LiAlH_4$ prior to use. The α-chloro-β-hydroxysulfonamides were prepared *via* a previously reported procedure.[4]

Registry No.—**3**, 30345-08-5; **4**, 30345-09-6; **5**, 30345-10-9.

Acknowledgment.—The authors wish to thank the Public Health Service for financial support of this work under Grant No. CA-04536-13 from the National Cancer Institute.

A Novel Synthesis of β-Keto Sulfides

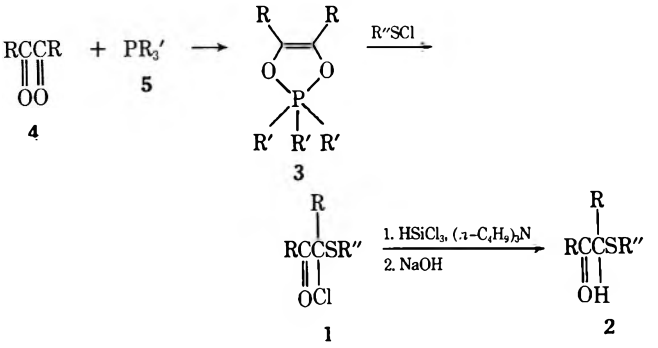
DAVID N. HARPP* AND P. MATHIAPARANAM[1]

Department of Chemistry, McGill University, Montreal, Canada

Received December 31, 1970

The general utility of β-keto sulfides (and their corresponding sulfoxide derivatives) is well documented.[2] These sulfides are most commonly prepared by the action of mercaptides (RS^-) on α-halo ketones,[3a] by reacting sulfenyl halides with ketones[2a] and by the decomposition of dialkylphenacylsulfonium salts with base.[3b] In addition, a number of 3-thianones have recently been prepared *via* a novel intramolecular cyclization reaction.[3c] None of the methods is widely versatile, however, since yields are often low and isomeric products and/or intermediates are encountered. We wish to report a useful new synthesis of β-keto sulfides from simple starting materials. The reactions employed proceed cleanly and in high yield.

The trichlorosilane–tri-*n*-butylamine system[4] reduces α-chloro-β-keto sulfides[5] **1** to β-keto sulfides **2** in nearly quantitative yield. The chloro keto sulfides **1** are



easily prepared[5] by the action of sulfenyl chlorides on substituted 1,3,2-dioxaphospholenes **3**. In addition, the reduction of chloro keto sulfides **1** may be carried out *in situ* from α-diketones **4** and trimethyl phosphite **5** in overall yields of 60–80%. The results are summarized in Table I.

TABLE I

No.	R	R''	Mp or bp (mm), °C	Yield, % from 1 (from 4 + 5)	Nmr data, τ	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2a	C_6H_5	C_6H_4-*p*-CH_3	94–96	98 (80)	1.80–3.10 (14 H, m), 4.12 (H, s), 7.73 (3 H, s)	79.21	5.70	10.07	79.16	5.72	9.98
2b	C_6H_5	$CH_2C_6H_5$	70–72	(60)	2.10–2.80 (15 H, m), 4.62 (H, s), 6.33 (2 H, AB, J = 14 Hz)	79.21	5.70	10.07	79.02	5.75	9.97
2c	C_6H_5	CH_2CH_3	78–80	(62)	1.80–2.90 (10 H, m), 4.37 (H, s), 7.50 (2 H, split AB, J = 7 Hz), 8.83 (3 H, t, J = 7 Hz)	74.96	6.29	12.51	74.85	6.33	12.43
2d	CH_3	C_6H_5	78–80 (0.003)	80 (61)	2.30–2.85 (5 H, m), 6.29 (H, q, J = 7 Hz), 7.80 (3 H, s), 8.63 (3 H, d, J = 7 Hz)			17.79			17.85
2e	CH_3	CH_2CH_3	Dec								

Experimental Section

Reaction of α-Benzoyl-α-chlorobenzyl *p*-Tolyl Sulfide (1a) with Trichlorosilane and Tri-*n*-butylamine.—In a 50-ml flask, fitted with a condenser carrying a drying tube and a dropping funnel, was dissolved α-benzoyl-α-chlorobenzyl *p*-tolyl sulfide (1) (0.70 g, 0.02 mol) in dry dimethoxyethane (10 ml). Tri-*n*-butylamine (0.37 g, 0.02 mol) was added, followed by trichlorosilane (0.36 g, 0.026 mol). The reaction mixture was refluxed for 2–3 hr. At the end of the reflux period, it was cooled and poured into a cold solution of 2 *N* sodium hydroxide[6] with stirring. The sodium hydroxide solution was extracted with several portions of methylene chloride. The methylene chloride extracts were combined and washed successively with water, dilute acid, and then water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residual solid recrystal-

(1) NRCC scholarship recipient, 1967–1970.

(2) (a) C. Rappe, "Mechanisms of Reactions of Sulfur Compounds," Vol. 4, IntraScience Research Foundation, 1969, p 95. (b) M. C. Caserio, W. Lauer, and T. Novinson, *J. Amer. Chem. Soc.*, **92**, 6082 (1970); G. A. Russell and G. Hamprecht, *J. Org. Chem.*, **35**, 3007 (1970), and references cited therein; G. A. Russell and E. T. Sabourine, *ibid.*, **34**, 2336 (1969).

(3) (a) T. C. Whitner and E. E. Reid, *J. Amer. Chem. Soc.*, **43**, 638 (1921); L. M. Long, *ibid.*, **68**, 2159 (1946). (b) H. Böhme and W. Krause, *Chem. Ber.*, **82**, 426 (1949). (c) P. T. Lansbury, E. J. Nienhouse, D. J. Scharf, and F. R. Hilfiker, *J. Amer. Chem. Soc.*, **92**, 5649 (1970).

(4) These reagents have been used to reduce a number of functionalities: see T. H. Chan, J. P. Montillier, W. F. Van Horn, and D. N. Harpp, *ibid.*, **92**, 7224 (1970); R. A. Benkeser, K. M. Foley, J. M. Gaul, and G. S. Li, *ibid.*, **92**, 3232 (1970); R. A. Benkeser and W. E. Smith, *ibid.*, **90**, 5307 (1968).

(5) D. N. Harpp and P. Mathiaparanam, *Tetrahedron Lett.*, 2089 (1970). In addition, α-chloro-β-keto sulfides of the type RCO(R')C(Cl)SR'' have been prepared; see F. Weygand, H. J. Bestmann, and H. Fritzsche, *Chem. Ber.*, **93**, 2340 (1960), and references cited therein.

(6) Alkaline conditions were maintained during work-up in order to eliminate any side reactions arising from the hydrolysis of the following possible intermediate, $RC(OSiCl_3)=CR(SR'')$. The trichlorosilyl anion may well be involved; see R. A. Benkeser, K. M. Foley, J. B. Grutzner, and W. E. Smith, *J. Amer. Chem. Soc.*, **92**, 697 (1970), and S. C. Bernstein, *ibid.*, **92**, 699 (1970). At present, however, it is uncertain as to the exact mechanism of this reaction.

lized from 95% ethanol, affording 0.62 g (98%), mp 91–93°. See Table I for analytical and spectral data.

Reaction of α-Benzoyl-α-chlorobenzyl Benzyl Sulfide (1b) (Prepared *in Situ*) with Trichlorosilane and Tri-*n*-butylamine.—The 1:1 benzil–trimethylphosphite adduct **3** was generated as previously described[7] from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, 0.01 mol). Dry 1,2-dimethoxyethane (10 ml) was added, followed by sulfenyl chloride (0.01 mol) in the same solvent (10 ml). The pale yellow solution was stirred for 15 min. Tri-*n*-butylamine (1.85 g, 0.01 mol) and trichlorosilane (1.80 g, 0.013 mol) were added. The reaction mixture was worked up as in the previous experiment. The product crystallized from 95% ethanol (60%). In a similar manner sulfide **2c** was prepared in 62% yield.

Reaction of α-Acetyl-α-chloroethyl Phenyl Sulfide (1d) with Trichlorosilane and Tri-*n*-butylamine.—As described above, α-acetyl-α-chloroethyl phenyl sulfide (**1d**) (1.20 g, 0.0056 mol) was dissolved in 1,2-dimethoxyethane (10 ml). Tri-*n*-butylamine (1.10 g, 0.006 mol) and trichlorosilane (1.40 g, 0.01 mol) were added and the reaction mixture was refluxed overnight with stirring. Work-up as in the preparation of **2a** from **1a** gave sulfide **2d**: bp 78–80° (0.003 mm); yield 0.80 g (80%); ir 1720 cm^{-1} (CO). Exact mass data: calculated for $C_{10}H_{12}OS$, 180.0609; found, 180.0608.

Attempted Reaction of α-Acetyl-α-chloroethyl Ethyl Sulfide (1e) with Trichlorosilane and Tri-*n*-butylamine.—The procedure described in the previous experiment was repeated with α-acetyl-α-chloroethyl ethyl sulfide (**1e**) (1.66 g, 0.01 mol), trichlorosilane (1.80 g, 0.013 mol), and tri-*n*-butylamine (1.85 g, 0.01 mol). A black tarry mass was obtained and yielded no identifiable products.

Reaction of α-Acetyl-α-chloroethyl Phenyl Sulfide (1d) (Prepared *in Situ*) with Trichlorosilane and Tri-*n*-butylamine.—Benzenesulfenyl chloride (1.45 g, 0.01 mol) was added to a solution of 1:1 biacetyl–trimethyl phosphite adduct **3** (2.10 g, 0.01 mol) in 1,2-dimethoxyethane (10 ml) under nitrogen. Once the exothermic reaction had subsided, trichlorosilane (1.80 g, 0.013 mol) and tri-*n*-butylamine (1.85 g, 0.01 mol) were added and the reaction mixture was refluxed overnight. Usual work-up provided an oil which was chromatographed on Florisil using methylene chloride. Pure α-acetylethyl phenyl sulfide was obtained, yield 1.10 g (61%). Spectroscopic data were identical with the data of the previous sample. When ethanesulfenyl chloride was used instead of benzenesulfenyl chloride in the above procedure, only an intractable tarry oil was obtained.

Registry No.—**2a**, 17527-58-1; **2b**, 23343-23-9; **2c**, 16222-12-1; **2d**, 13023-53-5; **2e**, 19170-22-0.

Acknowledgment.—We wish to thank the Defence Research Board of Canada (Grant No. 9530-97) and the Research Corporation for financial support of this work.

(7) P. Mathiaparanam, Ph.D. Thesis, McGill University, Dec 1970; F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **85**, 3252 (1963), and references cited therein.

Alkylation of Pyridine with *tert*-Butyllithium. Convenient Syntheses of 2,6-Di-*tert*-butylpyridine and 2,4,6-Tri-*tert*-butylpyridine

FRANCIS V. SCALZI* AND NORMAN F. GOLOB

Department of Chemistry, Hiram College, Hiram, Ohio 44234

Received January 21, 1971

A large number of sterically hindered organic bases have been reported.[1] Perhaps most notable among these is 2,6-di-*tert*-butylpyridine (**1**), since it is the only base demonstrated as having the ability to distinguish between Brønsted (protonic) and Lewis acids.[2] We required pure **1** in decigram quantities for the purpose of utilizing this unique property in another investigation. An earlier report[2] of its synthesis described a multistep procedure beginning with 2-ethylpyridine and requiring purification after each step. However, it was suggested in that article that a more direct route from pyridine was feasible. A two-stage method was later employed in the synthesis of 2,6-di-*tert*-butyl-4-alkoxypyridines from 4-alkoxypyridines.[3]

Accordingly, we attempted the most straightforward route, namely, the direct alkylation of pyridine with excess *tert*-butyllithium. This approach met with success, for in one step we could obtain not only **1** in yields up to 30% but also 2,4,6-tri-*tert*-butylpyridine (**2**),[4] both compounds being isolated in the quantities we required. Under proper conditions, **2** was the predominant product (up to 55% yield). Also produced were smaller quantities of the new compound, 2,4-di-*tert*-butylpyridine (**3**), 6,6′-*tert*-butyl-2,2′-bipyridine (**4**),[2] and tarry material formed in some cases. Control over product distribution was accomplished by varying the molar ratio of *tert*-butyllithium to pyridine and the mode of addition. The use of excess *tert*-butyllithium also minimized the yields (max 8%) of monosubstitution product, 2-*tert*-butylpyridine (**5**). The results are summarized in Table I.

TABLE I

REACTION OF PYRIDINE WITH *tert*-BUTYLLITHIUM[a]

tert-BuLi/pyridine[g]	Overall yield, %	Yield, %[b] 1	2	3	4[c]	5
2.5[d]	69	30 (25)	20 (19)	10 (9)	1	8 (6)
5[d]	70	27 (17)	31 (31)	7	1	4 (3)
10[e]	72	6	54 (43)[f]	9	2	1
20[e]	90	5	55 (26)[f]	11	15	4

[a] Addition was carried out at −75° under dry nitrogen followed by 7-hr reflux at 100°. [b] Glpc yields, based on pyridine. Isolated yields are in parentheses. All compounds were isolated in >95% purity by fractional distillation, sublimation, and/or crystallization. [c] Approximately 0.5 g was isolated in pure form from the reaction residue. [d] See Experimental Section, procedure A; scale, 0.2 mol of pyridine. [e] See Experimental Section, procedure B; scale, 0.01 mol or 0.02 mol of pyridine. [f] Low isolated yield is due to small scale with unavoidable mechanical losses. [g] Molar ratio.

The crude product mixture was directly resolved into its components, each >95% pure, by one careful fractionation using a highly efficient distilling apparatus. In those trials in which >50% yield of **2** were realized, this solid could be crystallized out of the crude mixture upon cooling and subsequently purified by vacuum sublimation. This procedure thus constitutes the preferred method for obtaining **1** and **2**.

The identities of compounds **1** and **5** were established by comparison of boiling points, infrared and proton nmr spectra, and melting points of the chloroaurates

(1) See, for example, F. E. Condon, *J. Amer Chem. Soc.*, **87**, 4494 (1965), and reference cited therein.

(2) H. C. Brown and B. Kanner, *ibid.*, **88**, 986 (1966); **75**, 3865 (1953).

(3) H. C. van der Plas and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 841 (1962).

(4) A multistep synthesis (overall yield, 42%) of **2** *via* treatment of 2,4,6-tri-*tert*-butylpyrylium tetrafluoroborate with alcoholic ammonia has been reported: K. Dimroth and W. Mach, *Angew. Chem., Int. Ed. Engl.*, **7**, 460 (1968).

with those of authentic samples.[5] Compound **2** was identified by comparison of its melting point[4] and infrared[6] and proton nmr[4] spectra with literature data. Compound **3** was characterized by elemental analysis and by comparison of its infrared spectrum with literature data.[6] Characteristic bands for β CH and ring breathing vibrational modes were identified in the 1300–1000 cm^{-1} region, as well as diagnostic substitution pattern bands below 1000 cm^{-1} (Table II) and

TABLE II

PHYSICAL PROPERTIES OF PRODUCTS[a]

Compd	Bp, °C (mm)	Mp, °C	Mp of chloroaurate,[b] °C	Ir,[c] cm^{-1}
1	90–93 (20)		184–185[d]	993, 890, 817, 750
2	115–120 (20)	70.9–71.2[e]	277–278 dec	1022, 998, 875
3	100–102 (17)		197.5–199 dec	1150, 995, 887, 839
4		122.5–123[f]		1140, 1083, 990, 805, 757
5	63–67 (20)			

[a] Compounds **1** and **2** were obtained in >99% purity by a single distillation or by sublimation. Compound **3** required a second distillation of combined fractions of >90% purity to achieve >99% purity. No attempt was made to purify **5** beyond 95% purity. Satisfactory analytical values (±0.3% for C, H, N) were reported for compounds **1**, **2**, and **3**: Ed. [b] Prepared according to procedure of Brown.[2] Compounds **1**, **2**, and **3** did not give picrates. [c] Only those bands pertinent to characterization are given. [d] Lit.[2] 184.2–184.5°. [e] Lit.[4] 69°. [f] Crystallized out of the reaction residues. Lit.[2] 122.3–122.8°.

their characteristic overtone patterns in the 2100–1700-cm^{-1} region. In addition, the splitting patterns in the δ 6.5–8.5 region of the proton nmr spectra of **1**, **2**, and **3** are quite comparable to those of 2,6-lutidine, 2,4,6-trimethylpyridine, and 2,4-lutidine, respectively.

Experimental Section

General.—Melting points (Mel-Temp apparatus) are corrected. Boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were determined in spectrograde carbon tetrachloride using tetramethylsilane as reference and measured with a Varian T60 spectrometer. Both infrared and proton nmr spectra have been subsequently published by the Sadtler Research Laboratories, Inc., for compounds **1**, **2**, and **3**.[7] All distillations were performed on a manually operated, 24-in. Teflon annular spinning-band column (Nester-Faust) at approximately 20-mm pressure, which resolved a persistant foaming problem encountered with other columns. Glpc analysis of reagents, crude reaction mixture, and purified products were performed on a Perkin-Elmer Model 800 instrument equipped with thermal conductivity and flame ionization detectors. One or both of the following columns were used throughout this work: column A (11 ft × 0.25 in., 20% Siponate Ds-10 on 45–60 mesh Chromosorb W, 5% NaOH, carrier gas flow 60 ml/min) and column B (6 ft × 0.25 in., 15% Carbowax 6000 on 40–60 mesh Chromosorb W, 5% NaOH, carrier gas flow 60 ml/min). Pyridine (Fisher or Baker reagent grade), *tert*-butyllithium, 2 *M* in pentane (Ventron ALFA), and heptane (Phillips pure grade) were all used without further purification. The microanalyses were performed by Crobaugh Laboratories, Cleveland, Ohio, or on a F & M CHN analyzer Model 185.

General Procedures for Alkylation. A. Addition of *tert*-Butyllithium to Pyridine.—Pyridine (15.8 g, 0.20 mol) in 200 ml of heptane was placed in a flask equipped with magnetic or mechanical stirrer, dewar condenser, alcohol thermometer, pressure-compensated addition funnel, CO_2–acetone cooling bath, and provision for introducing dry nitrogen below the surface of the reaction mixture. With thorough flushing with dry nitrogen, the solution was cooled to −75°. The volume of *tert*-butyllithium, 2 *M* in pentane, necessary to provide the desired molar ratio (Table I) of *tert*-butyllithium to pyridine was introduced to the addition funnel by expelling it with dry nitrogen pressure from a glass wash bottle previously filled in a glove bag under dry nitrogen.[8] Addition required 2 hr and stirring at −75° was continued for 1 hr. The mixture was then allowed to warm to room temperature. Under a dry nitrogen stream, the pentane was removed by distillation and the reaction mixture was refluxed for 7 hr. After being cooled to 10°, the reaction was carefully quenched by dropwise addition of water. The aqueous layer was thoroughly extracted with pentane and the combined organic layers were washed once with water and dried ($MgSO_4$). Removal of solvents left a red-brown oil (*ca.* 44 g) which was distilled and analyzed by glpc. Yields are given in Table I and physical properties in Table II.

B. Addition of Pyridine to *tert*-Butyllithium.—The volume of *tert*-butyllithium, 2 *M* in pentane, necessary to provide the desired molar ratio (Table I) of *tert*-butyllithium to pyridine was carefully introduced into the apparatus as described in procedure A. After the mixture was cooled to −75°, pyridine (1.58 g, 0.02 mol) in 50 ml of heptane was added dropwise (45 min) with dry nitrogen flush and the stirring was continued an additional hour. Procedure A was then followed. The resulting oil (*ca.* 5.8 g) was either distilled or allowed to crystallize at room temperature. Filtration and vacuum sublimation gave pure **2**.

Registry No.—**1**, 585-48-8; **2**, 20336-15-6; **2** chloroaurate, 29930-36-7; **3**, 29939-31-9; **3** chloroaurate, 29930-37-8; **5**, 5944-41-2; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4.

Acknowledgments.—The assistance of a number of Hiram College students is appreciated. In particular, early scouting and development were performed by R. Waller, J. Wansack, W. Toth, C. Brininger, and G. Luteri. The writers also thank Professor Peter Kovacic for discussions and suggestions. Financial support by the Hiram College Faculty Research Assistance Fund is gratefully acknowledged.

(5) We are indebted to Professor H. C. Brown for providing authentic samples of **1** and **5**.

(6) A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, Chapter 10, pp 276–279.

(7) "Sadtler Standard Spectra" references, compound (ir spectrum no, nmr spectrum no): **1** (702339, 9708M); **2** (702340, 9709M); **3** (708021, 10509M).

(8) For an alternative procedure, see S. Farber and R. T. Conley, *J. Chem. Educ.* **45**, 704 (1968).

New General Methods for the Substitution of 5-Chloropyrazoles. The Synthesis of 1,3-Dialkyl-5-chloropyrazol-4-yl Aryl Ketones and New 1,3-Dialkyl-2-pyrazolin-5-ones

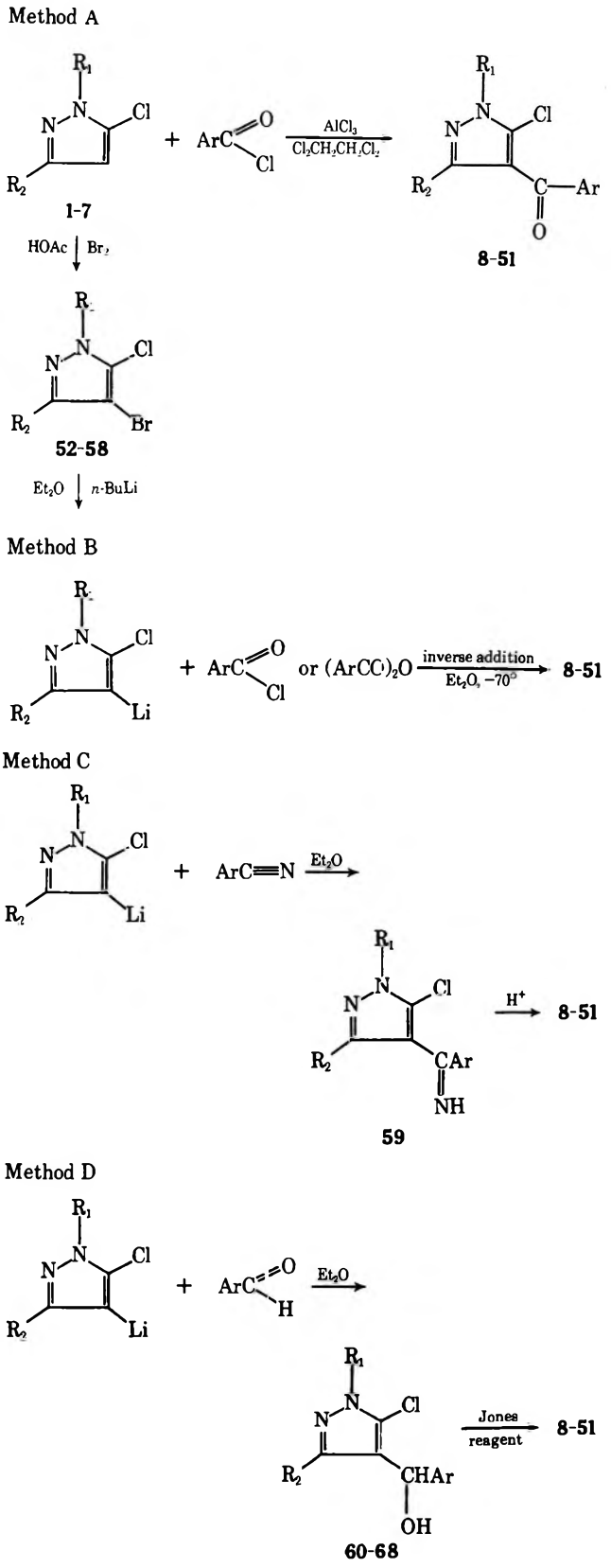
DONALD E. BUTLER* AND HORACE A. DEWALD

Chemistry Department, Medical and Scientific Affairs Division, Parke, Davis and Company, Ann Arbor, Michigan 48106

Received February 3, 1971

In connection with other synthetic studies underway in this laboratory, we required a large variety of the previously unknown 1,3-dialkyl-5-chloropyrazol-4-yl aryl ketones. Based on the ready availability of

SCHEME I

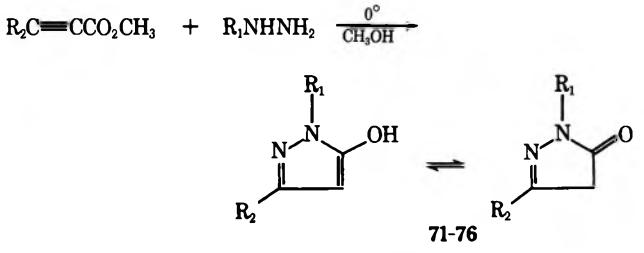


1,3-dialkyl-5-chloropyrazoles[1-4] and aroyl chlorides, the Friedel–Crafts reaction between these components was reinvestigated. Michaelis and Rojahn[5-7] had earlier reported the failure of this reaction with substituted pyrazoles of this type using relatively mild conditions. We have found that the synthesis can be performed easily in high yield in refluxing *s*-tetrachloroethane (Scheme I).

The Friedel–Crafts reaction would be expected to fail when the aroyl chloride is susceptible to the action of aluminum chloride or self aroylation. Therefore, a second approach was developed. Hüttel and Schön[8] have shown that treatment of 4-bromo-1-methylpyrazole with phenyllithium results in a mixture of 4-lithio-1-methylpyrazole and 4-bromo-5-lithio-1-methylpyrazole. We have found that the easily prepared 1,3-dialkyl-4-bromo-5-chloropyrazoles[1] react with *n*-butyllithium resulting in reasonably stable 1,3-dialkyl-5-chloro-4-lithiopyrazoles. These reagents undergo the usual reactions of aryllithiums[9] including those leading to the desired ketones. While extra steps are involved in this sequence, the reactions are simple to perform, result in high yields, and constitute a general approach to the desired compounds. As demonstrations of the versatility of the second approach, a few examples of alkyl, cycloalkyl, and 1- or 3-phenyl-substituted pyrazolyl ketones were prepared and are included with the other new ketones in Table I.

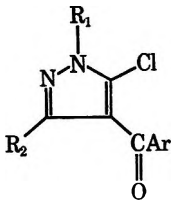
A variety of 1,3-dialkyl-2-pyrazolin-5-ones was also needed. As stated by Büchi, Ursprung, and Lauener,[10] the classical 2-pyrazolin-5-one synthesis of Knorr[11] gives very poor yields when alkylhydrazines other than methylhydrazine are condensed with ethyl acetoacetate. These workers condensed alkyl bromides or iodides in a bomb with 3-methyl-2-pyrazolin-5-one to produce 1-alkyl-3-methyl-2-pyrazolin-5-ones in yields of 10–44% depending on the alkyl group. A large number of workers have condensed acetylenic esters with hydrazine and phenylhydrazine but little or nothing has been done with alkylhydrazines.[12,13] With the commercial availability of methylhydrazine and other alkylhydrazines available by alkylation and other procedures,[14] we investigated the reaction of a number of methyl esters of alkylacetylenecarboxylic acids with alkylhydrazines. Shown in Scheme II, this appears to be

SCHEME II



(1) K. von Auwers and F. Niemeyer, *J. Prakt. Chem.*, **110**, 153 (1925).
(2) L. C. Behr, R. Fusco, and C. H. Jarboe in "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings," Interscience, New York, N. Y., 1967 pp 87, 88.
(3) T. L. Jacobs, *Heterocycl. Compounds*, **5**, 101 (1957).
(4) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidines and Derivatives," Interscience, New York, N. Y., 1964, p 27.
(5) A. Michaelis and C. A. Rojahn, *Ber.*, **50**, 737 (1917).
(6) C. A. Rojahn, *ibid.*, **55**, 291 (1922).
(7) Reference 3, p 100.
(8) R. Hüttel and M. E. Schön, *Justus Liebigs Ann. Chem.*, **625**, 55 (1959).
(9) S. R. Sandler and W. Karo in "Organic Functional Group Preparations," Academic Press, New York, N. Y., 1968, p 170.
(10) J. Büchi, R. Ursprung, and G. Lauener, *Helv. Chim. Acta*, **32**, 984 (1949).
(11) L. Knorr, *Justus Liebigs Ann. Chem.*, **279**, 236 (1894).
(12) Reference 4, p 15.
(13) Reference 3, p 120.
(14) P. A. Smith in "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Chapter 9, pp 139–144, New York, N. Y., 1966, and references therein.

TABLE I



Compd no.	Registry no.	R_1	R_2	Ar	Method[a]	Yield,[b] %	Mp (recrystn solvent[c]) or bp (mm),[d] °C
8	29938-70-3	CH_3	CH_3	C_6H_5	A	79	49–52 (J),
					D	88	128–130 (0.2)
9	29938-71-4	CH_3	CH_3	2-FC_6H_4	A	82	73–75 (F)
10	29938-72-5	CH_3	CH_3	3-FC_6H_4	A	52	44–46 (J),
							156–160 (0.5)
11	29938-73-6	CH_3	CH_3	4-FC_6H_4	A	55	158–160 (0.3)
12	29938-74-7	CH_3	CH_3	2-ClC_6H_4	A	71	70–72 (J)
13	29938-75-8	CH_3	CH_3	3-ClC_6H_4	A	77	81–83 (L)
14	30093-77-7	CH_3	CH_3	4-ClC_6H_4	A	78	65–68 (M)
15	29938-76-9	CH_3	CH_3	2-BrC_6H_4	B	70	135–137 (0.15)
16	30093-78-8	CH_3	CH_3	2-$CF_3C_6H_4$	B	75	77–79 (J),
							105–107 (0.15)
17	29938-77-0	CH_3	CH_3	3-$CF_3C_6H_4$	B	70	64–66 (J)
18	29938-78-1	CH_3	CH_3	2-$CH_3OC_6H_4$	B	62	86–88 (J),
							131–133 (0.15)
19	29938-79-2	CH_3	CH_3	4-$CH_3OC_6H_4$	C	75	128–130 (G)
20	29938-80-5	CH_3	CH_3	2-$CH_3C_6H_4$	B′	70	51–53 (J),
							105–106 (0.15)
21	30093-79-9	CH_3	CH_3	3-$CH_3C_6H_4$	A	76	60–62 (J),
							175–180 (0.5)
22	29938-81-6	CH_3	CH_3	4-$CH_3C_6H_4$	A	54	160–170 (0.3)
23	29938-82-7	CH_3	CH_3	2-Cl,3-$CH_3OC_6H_3$	D	75	108–109 (H)
24	29938-83-8	CH_3	CH_3	C_6H_{11}	B	67	78–80 (J)
25	29938-84-9	C_2H_5	CH_3	C_6H_{11}	B	72	110–111 (0.15)
26	29938-85-0	CH_3	CH_3	2-C_4H_3S	B	71	97–99 (J)
					D	85	
27	29938-86-1	CH_3	CH_3	3-C_4H_3S	D	84	86–88 (J)
28	29938-87-2	CH_3	CH_3	2,3-$(CH_3O)_2C_6H_3$	B	65	75–76 (J),
							146–148 (0.025)
29	29938-88-3	CH_3	CH_3	2,6-$(CH_3O)_2C_6H_3$	B	60	158–160 (I)
30	29938-89-4	CH_3	CH_3	2-(HOOC)C_6H_4	B′	31	150–152 (H)
31	29938-90-7	CH_3	CH_3	2-(5-BrC_4H_2S)	D	71	103–105 (J)
32	29938-91-8	CH_3	C_2H_5	2-ClC_6H_4	A	64	77–79 (J)
33	30093-80-2	CH_3	C_3H_7	2-ClC_6H_4	A	90	180–182 (0.2)
34	30093-81-3	CH_3	i-C_3H_7	2-ClC_6H_4	A	70	148–150 (0.2)
35	29938-92-9	CH_3	C_4H_9	2-ClC_6H_4	A	90	188–190 (0.2)
36	29938-93-0	C_2H_5	CH_3	2-ClC_6H_4	A	68	62–64 (K)
37	29938-94-1	C_3H_7	CH_3	2-$CH_3OC_6H_4$	B	60	153–155 (0.2)
38	29938-95-2	C_3H_7	CH_3	2-$CF_3C_6H_4$	B	78	123–125 (0.2)
39	29938-96-3	C_3H_7	C_2H_5	2-ClC_6H_4	A	94	138–140 (0.15)
40	29938-97-4	C_6H_{11}	CH_3	2-ClC_6H_4	A	90	115–117 (J)
41	29938-98-5	CH_3	C_2H_5	3-FC_6H_4	A	46	160–165 (0.3)
42	30093-82-4	CH_3	C_2H_5	C_6H_5	A	90	55–57 (J)
43	29938-99-6	CH_3	CH_3	3,5-$(CH_3O)_2C_6H_3$	C	72	88–90 (I)
44	29939-00-2	C_6H_{11}	CH_3	2-C_4H_3S	D	70[e,f]	148–150 (0.15)
45	30093-83-5	CH_3	C_3H_7	2-C_4H_3S	D	74	108–110 (0.15)
46	29939-01-3	CH_3	i-C_3H_7	2-C_4H_3S	D	79[e]	128–130 (0.4)
47	29939-02-4	CH_3	C_4H_9	2-C_4H_3S	D	80[e]	128–130 (0.17)
48	30115-50-5	C_6H_5	CH_3	2-C_4H_3S	D	88	84–86 (J)
49	29939-03-5	CH_3	C_6H_5	2-C_4H_3S	D	80	181–183 (J)
50	29939-04-6	C_6H_5	CH_3	2-$CH_3OC_6H_4$	B	60	107–109 (J)
51	29939-05-7	CH_3	C_6H_5	2-$CH_3OC_6H_4$	D	80	112–114 (J)

[a] The methods are those represented by capital letters A–D in Scheme I. [b] The yields on the products using methods C and D are calculated from the amount of 1,3-dialkyl-4-bromo-5-chloropyrazole charged. [c] Recrystallization solvents are represented by the following capital letters: F, ethyl acetate–petroleum ether; C, 95% ethanol; H, anhydrous diethyl ether; I, ethanol; J, benzene–petroleum ether; K, hexane; L, carbon tetrachloride; M, petroleum ether; N, tetrahydrofuran–petroleum ether; O, toluene–petroleum ether. [d] Satisfactory analytical values (±0.4% for C, H, and N) were reported for compounds **8–14**, **16–19**, **21–23**, **26–31**, and **38–51**; values within these limits for C and H were reported for the remaining compounds in the table (not analyzed for N). [e] The intermediate alcohols reacted upon attempted distillation and the reactions were repeated and the alcohols oxidized without purification. [f] The parent alcohol of this compound underwent dehydration to the ether upon attempted distillation. The resulting 4,4′-(oxydi-2-thenylidene)bis[5-chloro-1-cyclohexyl-3-methylpyrazole] had mp 223–225° (purified by boiling with acetone and filtering). *Anal.* Calcd for $C_{30}H_{36}Cl_2N_4OS_2$: C, 59.68; H, 6.02; N, 9.27. Found: C, 59.69; H, 6.08; N, 9.30.

a simple, general, high-yield procedure for the preparation of 1,3-dialkyl-2-pyrazolin-5-ones. This route also avoids the difficulty involved in a crossed Claisen reaction to prepare ω-alkylacetoacetic acid esters.

In summary (a) 1,3-dialkyl-5-chloropyrazol-4-yl aryl ketones can be prepared using the Friedel–Crafts reaction between 1,3-dialkyl-5-chloropyrazoles and aroyl chlorides; (b) 5-chloro-1,3-disubstituted 4-lithiopyrazoles can be prepared and used to synthesize these ketones directly or indirectly; and (c) 1,3-dialkyl-2-pyrazolin-5-ones can be synthesized in high yield by the reaction of alkylhydrazines with the methyl ester of an alkylacetylenecarboxylic acid.

Experimental Section[15]

The aroyl chlorides were commercially available or were prepared from the commercially available aromatic carboxylic acids using thionyl chloride and distilled before use. The arylcarbonitriles were commercially available as were the arylcarboxaldehydes with the following exceptions: (a) 2-chloro-3-methoxybenzaldehyde, mp 56–57°, was prepared by a modification of the method of Hodgson and Beard;[16,17] and (b) 3-thiophenecarboxaldehyde, bp 86–88° (20 mm), was prepared as described by Gronowitz.[18] 1,3-Dimethyl-2-pyrazolin-5-one was prepared from ethyl acetoacetate as described by Knorr,[11] mp 117–118° (lit. mp 117°). 1-Ethyl-3-methyl-2-pyrazolin-5-one was prepared by the method of Büchi, Ursprung, and Lauener,[10] mp 108–109° (lit. 109°). 1-Cyclohexyl-3-methyl-2-pyrazolin-5-one was prepared by hydrogenation of 3-methyl-1-phenyl-2-pyrazolin-5-one as described by Schuster and Krzikalla,[19] mp 149–151° (lit. mp 139°). 5-Chloro-1,3-dimethylpyrazole, bp 156–157° (lit. bp 157°), 5-chloro-1-ethyl-3-methylpyrazole, bp 166–167° (lit. bp 167°), and 4-bromo-5-chloro-1,3-dimethylpyrazole, mp 35–36°, bp 85–87° (10 mm) (lit. mp 35–36°), were prepared as described by von Auwers and Niemeyer.[1] Because of the importance of this type of intermediate to our synthetic purposes, a brief description of the preparation of this compound has been included in the Experimental Section. 4-Bromo-5-chloro-1-methyl-3-phenylpyrazole, mp 65–66°, bp 95–97° (0.2 mm) (lit. mp 65°), and 4-bromo-5-chloro-3-methyl-1-phenylpyrazole, mp 56–57°, bp 93–95° (0.2 mm) (lit. mp 56°), were prepared as described by Michaelis with Dorn[20] and Pasternach,[21] respectively. The α-acetylenic acids and their methyl esters were prepared as described by Zoss and Hennion.[22] Methylhydrazine was commercially available (Olin). *n*-Propylhydrazine, bp 118–120° (lit. bp 119°),[23] was prepared by alkylation and continuous extraction with diethyl ether.

Typical Preparation of 1,3-Dialkyl-4-aroyl-5-chloropyrazoles Using Friedel-Crafts Conditions. Method A. 5-Chloro-1,3-dimethylpyrazol-4-yl Phenyl Ketone (8).—5-Chloro-1,3-dimethylpyrazole,[1] 39 g (0.3 mol), was added slowly to a suspension of 40 g (0.3 mol) of anhydrous aluminum chloride in 200 ml of *s*-tetrachloroethane. Benzoyl chloride, 46 g (0.33 mol), was added in one portion and the mixture was stirred and refluxed 18 hr. The reaction mixture was poured into 200 ml of ice–water and 50 ml of concentrated hydrochloric acid. The organic layer was separated and stirred with 200 ml of 4 *N* sodium hydroxide for 1 hr. The organic layer was separated, dried ($MgSO_4$), and distilled *in vacuo* to yield **8**: 57 g (79%); bp 128–130° (0.2 mm); mp 49–52°; nmr ($CDCl_3$) 7.2–7.84 (5 H, aromatic CH), 3.77 (3 H, singlet, 1-CH_3), 2.26 (3 H, singlet, 3-CH_3); ir 1655 cm^{-1} (ketone C=O).

Typical Preparation of 1,3-Dialkyl-5-chloro-4-lithiopyrazoles. 5-Chloro-1,3-dimethyl-4-lithiopyrazole.—4-Bromo-5-chloro-1,3-dimethylpyrazole[1] (**52**), 21 g (0.1 mol), was dissolved in 400 ml of anhydrous diethyl ether under N_2. The solution was maintained between 20 and 25° by cooling and a solution of commercial *n*-butyllithium, 60 ml (0.1 mol), was added rapidly with stirring. The lithio reagent was present as a white precipitate and could be used in any typical aryllithium reaction. No attempt was made to isolate these compounds.

Typical Preparation of 1,3-Dialkyl-4-aroyl-5-chloropyrazoles Using the Lithio Reagent. Method B. Addition to an Aroyl Chloride. 5-Chloro-1,3-dimethylpyrazol-4-yl o-Methoxyphenyl Ketone (18).—5-Chloro-1,3-dimethyl-4-lithiopyrazole (0.1 mol), prepared as in the example, was poured into a −70° solution of 34 g (0.2 mol) of *o*-anisoyl chloride with stirring. The flask in which the lithio reagent was prepared was washed into the second solution with two 100-ml portions of anhydrous diethyl ether. The reaction mixture was allowed to warm to room temperature and 200 ml of methanol was added, followed by 500 ml of 0.5 *N* sodium hydroxide. The mixture was stirred overnight to complete the esterification of the excess aroyl chloride. The organic layer was separated, washed with water, dried ($MgSO_4$), concentrated, and distilled *in vacuo* to yield **18**: 16.5 g (62%); bp 131–133° (0.15 mm); mp 76–78; nmr ($CDCl_3$) δ TMS 6.8–7.5 (4 H, aromatic CH), 3.76 (6 H, singlet, 1-CH_3 and *o*-CH_3O), 2.3 (3 H, singlet, 3-CH_3); ir (KBr) 1628 cm^{-1} (ketone C=O). The analysis is in Table I.

Method B′. Addition to an Aryl Anhydride. 5-Chloro-1,3-dimethylpyrazol-4-yl *o*-Tolyl Ketone (20).—5-Chloro-1,3-dimethyl-4-lithiopyrazole, prepared from **52**, 60 g (0.287 mol), was added to a −70° suspension–solution of *o*-toluic anhydride, 127 g (0.5 mol) in 1 l. of anhydrous diethyl ether. The reaction mixture was stirred 1 hr and refluxed 1 hr, and 150 ml of methanol was added. The mixture was refluxed 1 hr, 500 ml of 2 *N* sodium hydroxide was added, and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated, and the residue distilled *in vacuo* to yield **20**: 44 g (70%); bp 105–107° (0.15 mm); nmr ($CDCl_3$) δ TMS 7.1–7.3 (4 H, aromatic CH), 3.7 (3 H, singlet, 1-CH_3), 2.3 (3 H, singlet, 3-CH_3), 2.2 (3 H, singlet, *o*-CH_3); ir (thin film) 1635 cm^{-1} (ketone C=O). The analysis is in Table I.

Method C. Addition to an Arylcarbonitrile and Hydrolysis of the Imine. 5-Chloro-1,3-dimethylpyrazol-4-yl *p*-Methoxyphenyl Ketone (19).—5-Chloro-1,3-dimethyl-4-lithiopyrazole, prepared from **52**, 58 g (0.28 mol), in 500 ml of anhydrous diethyl ether was treated with a diethyl ether solution of 40 g (0.3 mol) of *p*-anisonitrile. The reaction mixture was stirred and refluxed overnight, cooled, and treated with 300 ml of a saturated solution of ammonium chloride. The mixture was diluted with ethyl acetate, and the organic layer was separated and washed with water. The organic layer was extracted with 350 ml of 3 *N* hydrochloric acid. The acid extract was swiftly made basic with concentrated ammonium hydroxide and extracted with benzene. The benzene solution was dried ($MgSO_4$) and concentrated *in vacuo* to yield 5-chloro-1,3-dimethylpyrazol-4-yl *p*-methoxyphenyl ketone imine **59**: 63 g (85%); mp 94–96° (from diethyl ether–petroleum ether); ir (KBr) 1600 cm^{-1} (C=N).

Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.94. Found: C, 59.47; N, 5.49; N, 15.96.

The imine **59** was hydrolyzed to **19** in 90% yield by heating 30 min on the steam bath in 4 *N* hydrochloride acid. The mixture was allowed to cool and the **19** filtered: mp 128–130° (from 95% ethanol); ir (KBr) 1630 cm^{-1} (ketone C=O). The analysis is in Table I.

Method D. Addition to an Arylcarboxaldehyde Followed by Oxidation Using Jones Reagent.[24] 5-Chloro-1,3-dimethylpyrazol-

(15) Melting points (uncorrected) were taken in open capillary tubes in a Thomas-Hoover melting point apparatus. Ir spectra were determined on a Beckman IR-9 instrument and nmr spectra with a Varian A-60 spectrophotometer at ambient temperature (Me_4Si). We are indebted to Mr. C. E. Childs and associate for microanalyses, Mr. W. Pearlman for the catalytic hydrogenations and pressure reactions and to Dr. J. M. Vandenbelt and associates for spectral data.

(16) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 147 (1926).

(17) The chlorination of *m*-hydroxybenzaldehyde was performed between 0 and −30° using tetrahydrofuran as the solvent. The yield and the by-products were the same as those reported by Hodgson and Beard; however, much larger amounts can be chlorinated in a shorter time.

(18) S. Gronowitz, *Ark. Kemi.*, **8**, 441 (1955); *Chem. Abstr.*, **51**, 1935 (1957).

(19) C. Schuster and H. Krzikalla, *ibid.*, **33**, 180 (1939); U. S. Patent 2,132,193 (1938).

(20) A. Michaelis and H. Dorn, *Justus Liebigs Ann. Chem.*, **352**, 163 (1907).

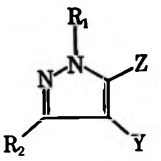
(21) A. Michaelis and R. Pasternach, *Ber.*, **32**, 2398 (1899).

(22) A. O. Zoss and G. F. Hennion, *J. Amer. Chem. Soc.*, **63**, 1151 (1941).

(23) R. Stolle and R. Bernath, *J. Prakt. Chem.*, **70**, 280 (1904).

(24) L. F. Fieser and M. Fieser in "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 142.

TABLE II



Compd no.	Registry no.	R_1	R_2	Z	Y	Yield, %	Mp (recrystn solvent[d]) or bp (mm),[b] °C
1	29938-63-4	CH_3	C_6H_5	Cl	H	80	82–83 (28)
2	29938-64-5	CH_3	C_3H_7	Cl	H	88	78–79 (10)
3	29938-65-6	CH_3	i-C_3H_7	Cl	H	81	72–74 (10)
4	29938-66-7	CH_3	C_4H_9	Cl	H	85	90–92 (10)
5	29938-67-8	C_3H_7	CH_3	Cl	H	71	83–84 (22)
6	29938-68-9	C_3H_7	C_2H_5	Cl	H	82	104–105 (30)
7	29938-69-0	C_6H_{11}	CH_3	Cl	H	62	109–111 (10)
52	29939-06-8	CH_3	CH_3	Cl	Br	95	35–36[c,d]
53	30093-84-6	C_2H_5	CH_3	Cl	Br	90	93–94 (10)
54	29939-07-9	C_3H_7	CH_3	Cl	Br	93	93–95 (6)
55	29939-08-0	C_6H_{11}	CH_3	Cl	Br	96	166–168 (24)
56	30093-85-7	CH_3	C_3H_7	Cl	Br	90	105–107 (17)
57	29939-09-1	CH_3	i-C_3H_7	Cl	Br	92	98–100 (16)
58	29939-10-4	CH_3	C_4H_9	Cl	Br	95	118–120 (16)
60	29939-12-6	CH_3	CH_3	Cl	C_6H_5CHOH	95	96–98 (P)
61	29939-13-7	CH_3	CH_3	Cl	2-C_4H_3SCHOH	97	101–103 (J)
62	29939-14-8	CH_3	CH_3	Cl	2-(5-BrC_4H_2S)CHOH	88	118–120 (J)
63	29939-15-9	CH_3	CH_3	Cl	3-C_4H_3SCHOH	95	158–160 (0.2)
64	29939-16-0	CH_3	CH_3	Cl	2-Cl-3-$CH_3OC_6H_3CHOH$	90	148–150 (H)
65	30093-86-8	CH_3	C_3H_7	Cl	2-C_4H_3SCHOH	90	125–127 (0.1)
66	29939-17-1	C_6H_5	CH_3	Cl	2-C_4H_3SCHOH	93	100–102 (J)
67	29939-18-2	CH_3	C_6H_5	Cl	2-C_4H_3SCHOH	97	122–124 (J)
68	29939-19-3	CH_3	C_4H_3	Cl	2-$CH_3OC_6H_4CHOH$	85	136–138 (J)
69	29939-20-6	CH_3	CH_3	Cl	$CH_3C{=}O$[a]	75	54–55 (J)
70	27006-82-2	CH_3	CH_3	Cl	CO_2H[e]	85	195–197 (P)
71	29939-22-8	CH_3	C_2H_5	OH	H	92	101–103 (J)
72	29939-23-9	CH_3	C_3H_7	OH	H	93	109–111 (J)
73	29939-24-0	CH_3	i-C_3H_7	OH	H	92	113–115 (J)
74	29939-25-1	CH_3	C_4H_9	OH	H	95	102–104 (N)
75	29939-26-2	C_3H_7	CH_3	OH	H	96	107–109 (O)[f]
76	29939-27-3	C_3H_7	C_2H_5	OH	H	75	96–97 (H)

[a] This compound was prepared by method B′ using acetic anhydride. [b] Satisfactory analytical values (±0.4% for C, H, and N) were reported for compounds 55–70; values within these limits for C and H were reported for the remaining compounds in the table (not analyzed for N). Exceptions: compound 52 was old and the melting point checked the literature; see *c*. [c] Seet ext, ref 1. [d] See footnote c in Table I for recrystallization solvents, P = methanol. [e] This compound was prepared by adding the lithio reagent to chunks of Dry Ice in anhydrous ether and acidification of the lithio salt. [f] See text, ref 10; these workers had mp 115°, and isolated the product in 22.8% yield.

4-yl 2-Thienyl Ketone (26).—5-Chloro-1,3-dimethyl-4-lithiopyrazole, prepared from 52, 209.5 g (1.0 mol), was stirred and cooled to 10° and 124 g (1.1 mol) of 2-thiophenecarboxaldehyde was added. The reaction mixture was stirred 15 min and 1 l. water was added. The layers were separated and the water layer was extracted with two portions of diethyl ether. The organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was triturated with petroleum ether to yield 5-chloro-1,3-dimethyl-α-2-thienylpyrazole-4-methanol (61): 235 g (97%); mp 101–103°; nmr ($CDCl_3$) δ TMS 6.7–7.5 (3 H, aromatic CH), 5.9–6.15 (1 H, broad singlet, CHO), 3.7 (4 H, singlet with a broad base, 1-CH_3 and OH, 1 H removed by D_2O wash), 2.11 (3 H, singlet, 3-CH_3). The analysis is in Table II.

The carbinol, 194 g (0.8 mol), 61 was dissolved in 2 l. of reagent acetone and cooled with stirring to 10°. Jones reagent, 205 ml (0.8 equiv), was added rapidly with stirring and cooling. The temperature rose to 45° during the addition. The liquid was filtered through Celite and concentrated. The inorganic sludge was treated with excess saturated sodium bicarbonate solution and extracted with diethyl ether. The concentrate was dissolved in diethyl ether and treated with excess sodium bicarbonate solution. The organic layers were combined, dried ($MgSO_4$), concentrated, and distilled *in vacuo* to yield 26: 168 g (88%); bp 120–121° (0.15 mm); mp 97–99°; nmr ($CDCl_3$) δ TMS 7.45–7.7 (2 H, multiplet, aromatic CH), 6.95–7.18 (1 H, multiplet, aromatic CH), 3.8 (3 H, singlet, 1-CH_3), 2.33 (3 H, singlet, 3-CH_3); ir (KBr) 1628 cm^{-1} (ketone C=O). The analysis is in Table I.

Typical Bromination of 1,3-Dialkyl-5-chloropyrazoles. 4-Bromo-5-chloro-1,3-dimethylpyrazole (52).—5-Chloro-1,3-dimethylpyrazole,[1] 390 g (3.0 mol), was dissolved in 1.5 l. of glacial acetic acid and 496 g (3.1 mol) of bromine was added rapidly with stirring. The reaction mixture was concentrated and treated with diethyl ether and excess ice cold 2 *N* sodium hydroxide. The organic layer was dried ($MgSO_4$) and concentrated using a Vigreux column and distilled *in vacuo* to yield 52: 597 g (95%); bp 95–96° (15 mm); mp 35–36° (lit. mp 35–36°); nmr ($CDCl_3$) δ TMS 3.8 (3 H, singlet, 1-CH_3), 2.3 (3 H, singlet, 3-CH_3). This was patterned after the synthesis of von Auwers and Niemeyer.[1]

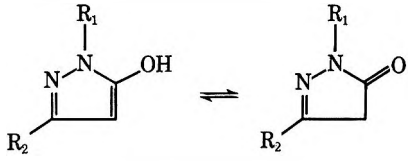
Typical Preparation of 1,3-Dialkyl-2-pyrazolin-5-one. 3-Methyl-1-propyl-2-pyrazolin-5-one (75).—A solution of 81 g (1.1 mol) of propylhydrazine in 1 l. of methanol was cooled to 0° and 98 g (1.0 mol) of methyl tetrolate was added dropwise with stirring. The mixture was stirred at 0° for 4 hr and then refluxed 1 hr and concentrated to dryness. The residue was recrystallized from toluene–petroleum ether to yield 75: 135 g (96%); mp 107–109° (lit. 115°);[10] nmr ($CDCl_3$) δ TMS 10.2–10.6 (0.5 H), 5.0–5.25 (0.25 H), 3.4–4.0 (2 H, broad ill-defined triplet, 1-CH_2), 3.1–3.4 (1.25 H, broad singlet, $CH_2C{=}O$), 2.13 (3 H, singlet, 3-CH_3),

1.4–2.1 (2 H, multiplet, CH_2), 0.85–1.15 (3 H, triplet, CH_3).[25] The analysis is in Table II.

Typical Preparation of 1,3-Dialkyl-5-chloropyrazoles. 5-Chloro-3-methyl-1-propylpyrazole (5).—75, 100 g (0.714 mol), was dissolved in 453 g (2.95 mol) of phosphoryl chloride and the mixture was refluxed 24 hr. The reaction mixture was concentrated *in vacuo* at 60° (water bath temperature) and the residue was poured into water. The resulting oil–water mixture was made strongly basic with concentrated ammonium hydroxide with cooling and extracted with diethyl ether. The extracts were dried ($MgSO_4$) and distilled through a Vigreux column, finally under vacuum to yield 5: 81 g (71%); bp 83–84° (22 mm); nmr ($CDCl_3$) δ TMS 5.82 (1 H, 4-H), 3.8–4.15 (2 H, triplet, 1-CH_2), 2.18 (3 H, singlet, 3-CH_3), 1.6–2.1 (2 H, multiplet, CH_2), 0.75–1.15 (3 H, triplet, CH_3). The analysis is in Table II.

Registry No.—59, 29939-11-5; 4,4′-(oxydi-2-thenylidene)bis[5-chloro-1-cyclohexyl-3-methylpyrazole],[26] 29939-28-4.

(25) The absorption between 10.2–10.6 and 5.0–5.25 was observed in all of the 1,3-dialkyl-2-pyrazolin-5-ones prepared in this study and was independent of the synthetic route used. It is the result of the equilibrium with the 1,3-dialkylpyrazol-5-ol tautomer in solution.



Thus the absorption between 3.1 and 3.4 due to the hydrogens at position 4 in the 1,3-dialkyl-2-pyrazolin-5-one is diminished proportionally. This was demonstrated by taking the same spectrum in DMSO-d_6. In this solvent the equilibrium is shifted almost exclusively to the 1,3-dialkylpyrazol-5-ol tautomer. The absorption between 10.2 and 10.6 accounts for 0.9 protons and is assigned to the 5-OH as salt-like. the absorption at 5.15 is a singlet accounting for 0.9 protons and is due to the hydrogen at position 4, and the absorption at 3.1–3.4 accounts for 0.2 protons. Equilibration with deuterium oxide in both solvent systems results in rapid removal of the absorption at all three of the given areas.

(26) See Table I, footnote *e*.

Reductions with Organosilicon Hydrides. III. Reduction of Acyl Fluorides to Esters

JOEL D. CITRON

Contribution No. 246 from the Research Laboratory, Elastomer Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received January 8, 1971

The previous paper[1] in this series dealt with the palladium-catalyzed reaction of silicon hydrides with acyl chlorides (eq 1). Since it is known, in contrast to the

$$R_3SiH + RCOCl \xrightarrow{Pd} R_3SiCl + RCHO \quad (1)$$

other halogens, that carbon–fluorine bonds of fluorocarbons are not cleaved readily by silicon hydrides in the presence of palladium catalysts,[2] it was of interest to discover if this was also true of acyl fluorides.

A mixture of pentanoyl fluoride, triethylsilane, and 5% Pd/C showed no sign of reaction, and this was confirmed by infrared spectrum (the chloride would have reacted vigorously under these conditions). However, it was found that the reaction with the fluoride proceeded thermally to yield pentyl pentanoate (eq 2),

$$2n\text{-}C_4H_9COF + 2Et_3SiH \longrightarrow n\text{-}C_4H_9CO_2C_5H_{11}\text{-}n + 2Et_3SiF \quad (2)$$

with no trace of pentanal in the product mixture (a test with 2,4-dinitrophenylhydrazine solution was negative). Table I summarizes the results of this and other similar reactions. The reduction of terephthaloyl fluoride yielded a polymer, whose pmr and infrared spectra indicated that it was a polyester of terephthalic acid, *p*-hydroxymethylbenzoic acid, and *p*-bis(hydroxymethyl)benzene. Highly hindered esters can also be prepared, as exemplified by the high yield of 2,2-dimethylpropyl 2,2-dimethylpropionate obtained. However, a silicon dihydride, diphenylsilane, yielded only a complex mixture of carbonyl compounds.

The reaction products could be altered by the addition of other compounds, such as aldehydes. Reduction of pentanoyl fluoride in the presence of equimolar hexanal led to the formation of hexyl pentanoate. As judged from chromatography, no pentyl pentanoate was formed. As noted in Table I, benzonitrile seemed to have no effect upon the reaction. The aldehydes had another effect on the reaction, that of increasing the rate. This was especially true of crotonaldehyde, but only a mixture of carbonyl compounds was isolated from this reaction (a referee has pointed out that this very rapid reaction may not necessarily be the reduction to the ester).

These data are strikingly similar to those obtained in the analogous reductions of tin hydrides.[3] In those reductions of acyl fluorides, esters are also the only products.[4] Based on the mechanism developed for tin hydrides,[3] the steps involved in the present reaction are probably as shown in eq 3–6. The unpaired species

$$R_3Si\cdot + RCOF \longrightarrow RCO\cdot + R_3SiF \quad (3)$$

$$RCO\cdot + R_3SiH \longrightarrow RCHO + R_3Si\cdot \quad (4)$$

$$RCO\cdot + RCHO \longrightarrow RC(=O)\text{—}O\text{—}\dot{C}HR \quad (5)$$

$$RC(=O)\text{—}O\text{—}\dot{C}HR + R_3SiH \longrightarrow RCO_2CH_2R + R_3Si\cdot \quad (6)$$

(radicals) represented in eq 3–6 may or may not actually exist (they may only be transition states) but they are useful in visualizing the mechanism. There are two other experiments which tend to substantiate this pathway. After 19 hr at 75°, equimolar amounts of Et_3SiH and pentanoyl fluoride with 0.9 mol % of α,α′-azobisisobutyronitrile contained 19% of the original silicon hydride; a control reaction without the azonitrile initiator contained 43% of Et_3SiH. Thus, as expected, a radical source increased the reaction rate. Another alternate mechanism, addition of the silicon hydride across aldehydic carbonyl, followed by reaction of the resulting alkoxysilane with the acyl fluoride[5] (eq 7), is much less likely because the first step does not

$$R'CHO + R_3SiH \longrightarrow R'CH_2OSiR_3 \xrightarrow{R''COF} R''CO_2CH_2R' + R_3SiF \quad (7)$$

(1) For part II, see J. D. Citron, *J. Org. Chem.*, **34**, 1977 (1969).
(2) J. D. Citron, J. E. Lyons, and L. H. Sommer, *ibid.*, **34**, 638 (1969).
(3) E. J. Walsh, Jr., and H. G. Kuivila, *J. Amer. Chem. Soc.*, **88**, 576 (1966).
(4) E. J. Walsh, Jr., *et al.*, *J. Org. Chem.*, **34**, 1156 (1969).
(5) J. D. Citron, *J. Organometal. Chem.*, in press.

TABLE I
REDUCTIONS OF ACYCL FLUORIDES BY SILICON HYDRIDES

Silicon hydride (mmol)	Acyl fluoride (mmol)	Other additives (mmol)	Time, hr (temp, °C)	Acyl fluoride derivative, %	Silicon product, %
Et_3SiH (94)	n-C_4H_9COF (95)		24 (115)	n-$C_4H_9CO_2C_5H_{11}$-n, 71	Et_3SiF, 89
$(PhCH_2)_3SiH$ (83)	n-C_4H_9COF (87)		67 (125)	n-$C_4H_9CO_2C_5H_{11}$-n, 47	$(PhCH_2)_3SiF$, 95
Et_3SiH (140)	p-$C_6H_4(COF)_2$ (70)		6 (280)	Polymer,[a] 63	Et_3SiF, 65
Et_3SiH (160)	$(CH_3)_3CCOF$ (160)		8 (160)	$(CH_3)_3CCO_2CH_2C(CH_3)_3$, 74	Et_3SiF, 85
Ph_2SiH_2 (52)	n-C_4H_9COF (100)		10 (220)	Unidentified carbonyl compds	Ph_2SiF_2, 61
Et_3SiH (12)	n-C_4H_9COF (12)	n-$C_5H_{11}CHO$ (12)	27 (115)	n-$C_4H_9CO_2C_6H_{13}$-n[b]	Et_3SiF[b]
Et_3SiH (62)	n-C_4H_9COF (62)	C_6H_5CHO (62)	1 (125)	n-$C_4H_9CO_2CH_2C_6H_5$, 59	Et_3SiF, 87
Et_3SiH (16)	n-C_4H_9COF (16)	C_6H_5CN (15)	96 (125)	n-$C_4H_9CO_2C_5H_{11}$-n[c]	Et_3SiF[c]

[a] See text. [b] Identified by glpc and infrared spectrum. [c] By infrared spectrum; there was no evidence of the nitrile reacting.

occur under the reaction conditions, even in the presence of trace amounts of HF. Finally, if the mechanism of eq 3–6 is correct, the fact that no aldehyde is isolated, and that all added aldehyde reacts, indicates that reaction 5 is much faster than reaction 4.

Experimental Section

All of the silanes used were purchased from the Peninsular ChemResearch Corporation. Acyl fluorides were prepared from the corresponding chlorides by reaction with HF and had previously reported physical constants.[6] The physical constants of all products were identical with those in the literature, and the infrared spectra were in accord with their structures. Some typical procedures are given below.

Reaction of Pentanoyl Fluoride with Triethylsilane.—Into a 1.25-in.-i.d. Teflon tube equipped with a magnetic stirrer and under nitrogen was added 9.9 g of pentanoyl fluoride and 15.0 ml of triethylsilane. The solution was stirred and heated at 110–115° for 24 hr. After cooling, the material was distilled on a platinum spinning-band column to yield 12.8 g of Et_3SiF, bp 107–108.5°, and 5.8 g of pentyl pentanoate, bp 200–204.5°, $n^{23}D$ 1.4155.

Reaction of Terephthaloyl Fluoride with Triethylsilane.—An 80-ml bomb was loaded with 12 g of terephthaloyl fluoride and 22.7 ml of triethylsilane, evacuated, and then heated at 280° for 6 hr. The total recovery of a mixture of solid and liquid was 24 g. The material was subjected to a vacuum, and the volatile fraction was distilled to yield 12.4 g of Et_3SiF, bp 108–110.5°.

The solid was placed in a sublimator at 100° and 0.1 mm for 40 hr. The residue, 6.0 g, was, as indicated by pmr and infrared spectra, a polyester of terephthalic acid, 1,4-bis(hydroxymethyl)-benzene and p-hydroxymethylbenzoic acid.

Anal. Calcd for $(C_8H_6O_2)_n$: C, 71.7; H, 4.5. Found: C, 71.3; H, 4.2.

Reaction of Pentanoyl Fluoride with Triethylsilane in the Presence of 2-Butenal.—Into a 50-ml round-bottom flask under nitrogen were charged 9.7 g of pentanoyl fluoride, 14.8 ml of triethylsilane, and 7.7 ml of 2-butenal. The liquid was heated slowly and stirred. When the oil bath reached *ca.* 70° a violent reaction took place; the mixture refluxed rapidly enough to fill the condenser tube with a solid column of liquid. After the reaction subsided, the flask was heated at 70–80° for an additional 10 min and then the contents were transferred to a spinning-band column and distilled. The distillate consisted of 12.7 g of Et_3SiF, bp 107–111°, and several fractions (9.7-g total) of a mixture of carbonyl compounds. Infrared and pmr spectra indicated these were mixtures of ester and a small amount of carboxylic acid. Some of the ester appeared to be one or more of the butenyl pentanoates.

Registry No.—n-$C_4H_9CO_2C_5H_{11}$-n, 2173-56-0; $(CH_3)_3CCO_2CH_2C(CH_3)_3$, 5340-26-1; n-$C_4H_9CO_2C_6H_{13}$-n, 1117-59-5; n-$C_4H_9CO_2CH_2C_6H_5$, 10361-39-4; Et_3SiF, 358-43-0; $(PhCH_2)_3SiF$, 429-76-5; Ph_2SiF_2, 312-40-3; polyester of terephthalic acid, 1,4-bis(hydroxymethyl)-benzene, and p-hydroxymethyl benzoic acid, 30135-79-6.

Acknowledgment.—The author wishes to thank Messrs. Lawrence Whyte, William Whisler, and Robert Hamilton for technical assistance.

(6) G. Olah and J. Kuhn, *Org. Syn.*, **45**, 3 (1965).

The Catalytic Dehydrator for Rapid Ester Synthesis

GEORGE F. VESLEY AND VIRGIL I. STENBERG*

Department of Chemistry, University of North Dakota, Grand Forks, North Dakota 58201

Received November 17, 1970

We wish to report a potentially important modification in the use of ion exchange resins (acid polymers) as catalysts, *i.e.*, the combination of an acid polymer with a drying agent, the catalytic dehydrator, for the purpose of promoting acid-catalyzed, equilibrium reactions which have water as one of the products.

The advantages of the catalytic dehydrator over conventional esterification techniques are (1) the reaction can be done at room temperature or lower, a factor which may prove valuable for heat sensitive compounds; (2) the reaction apparatus is simple; (3) theoretically the catalytic dehydrator can be reused;[1] (4) it can be made quantitative in many cases; (5) it is a one-step reaction from the acid and the alcohol; and (6) the reaction work-up is simple since both of the components of the catalytic dehydrator are insoluble in the reaction media.

The catalytic dehydrator was used in two ways, first, in a column with the acid and alcohol flowing through it and, second, as a component in a stirred mixture of the alcohol and acid. The latter proved more valuable for this study because the exposure time could be more carefully controlled although both were successful. The data in Table I were obtained by the second procedure.

The two reactions studied in detail were chosen on the basis of their equilibrium points and adaptability to glpc analysis. As a control, the extent of esterification at a given time using p-toluenesulfonic acid as the catalyst was given in entries 1–4 and 12 on Table I. Although rate studies using the acid polymer were not undertaken, it was quite apparent from the data of Table I that the esterification rate of 1-butanol was much slower than that of methanol which was in ac-

(1) N. G. Polyanskii, *Russ. Chem. Rev.*, **39**, 244 (1970).

TABLE I
YIELD DATA FOR ESTERIFICATIONS

Run	Alcohol	Solvent	Reaction ratio, acid:alcohol (v/v)	Time	Acid polymer: dehydrator (g/g)	D_{total}	Acid polymer	Yield, ±5%
1	Methanol		1:10	10 min	*a*			67
2	Methanol		1:10	14 hr	*a*			82
3	Methanol	Ether, 10 ml	2:0.6	10 min	*a*			21
4	Methanol	Ether, 10 ml	2:0.6	17 hr	*a*			59
5	Methanol		1:10	10 min	10:0	16.1	R204	87
6	Methanol		1:10	10 min	3:7	6.3	R204	94
7	Methanol		1:10	10 min	3:0	4.7	R231	32
8	Methanol		1:10	20 min	3:7	6.3	R204	93
9	Methanol	Ether, 10 ml	1:2	20 min	3:7	6.3	R231	52
10	Methanol		10:0.6	120 min	3:7	7.5	R204	73
11	Methanol	Ether, 10 ml	2:0.6	20 min	3:7	7.5	R231	33
12	1-Butanol		1:10	60 min	*a*			58
13	1-Butanol		1:10	60 min	3:7	6.3	R231	84
14	1-Butanol		1:10	60 min	3:0	4.7	R231	26
15	1-Butanol		1:10	10 min	3:7	6.3	R204	22
16	1-Butanol		1:10	160 min	3:0	4.7	R231	58
17	1-Butanol		1:10	17 hr	3:7	6.3	R231	100
18	1-Butanol		1:10	190 min	3:0	4.7	R231	68
19	1-Butanol		1:10	14 hr	3:0	4.7	R231	100
20	1-Butanol		1:10	60 min	3:7[b]		R231	52
21	1-Butanol		1:10	90 min	3:7[b]		R231	65
22	1-Butanol		1:10	17 hr	3:7[b]		R231	93
23	2-Propanol		1:10	17 hr	3:7	6.3	R231	91
24	2-Propanol		1:10	17 hr	3:7[b]		R231	73

[a] No catalytic dehydrator used in these runs. The reactions were catalyzed by *p*-toluenesulfonic acid. [b] Anhydrous silica gel used as the drying agent.

cordance with the results of Karpov and Brystrova[2] using the acid polymer alone. As a consequence, the 1-butanol reaction provided the better test of the capabilities of the catalytic dehydrator.

Calcium sulfate was selected as the drying agent. Although it was shown not to dry polar media to the same extent as the others,[3] it had a more desirable feature of being able to dry solutions more rapidly than others tested. Anhydrous silica was also tried but found to be slower than $CaSO_4$.

An obvious problem with commercially available acid polymers was that they contain 40–50% water by weight as supplied which first had to be removed if the drying agent was to affect the esterification equilibrium. This was done by air drying the acid polymer in a 100–110° oven for 24 hr.

The total capacity of both the acid polymer and $CaSO_4$ for absorbing water under practical conditions was determined in order to evaluate the total drying capacity of the dehydrator in relation to the water produced (D). The predried acid polymer was capable of increasing its weight by 50% when exposed to wet ether for 30 min followed by a 15-min vacuum filtration and air drying for 24 hr. Anhydrous $CaSO_4$ gained 6.3% in weight when exposed to the wet ether treatment.

A 10-g quantity of catalytic dehydrator was chosen arbitrarily and a 3:7 ratio of acid polymer:$CaSO_4$ was found to be an optimum balance of catalytic and drying activity. Presumably, the excess drying capacity required for short reaction times was not necessary for reactions whose equilibria lie close to the products, but it was advisable for others.

Since the dried acid polymer had a drying capacity of its own, its effect on the equilibrium alone was determined. By comparing reaction 1 with that of 5 in Table I, it was obvious that the reaction was shifted by 20% toward products, *i.e.*, from 67 to 87%, due to the effect of the dry acid polymer alone. Presumably the methyl acetate equilibrium could be shifted to completion if enough acid polymer were added or the reaction time increased, *cf.* run 5 with 7. However, the acid polymer was a slow drying agent. If the amount of acid polymer was kept constant, then the effect of $CaSO_4$ could be measured. By doing this, the 10-min reaction yield of methyl acetate was reduced by 62%, *cf.* run 6 with 7, and the 1-butyl acetate yield by 58%, *cf.* 13 with 14. This difference was a dramatic demonstration of the rapid drying action of $CaSO_4$. The effect of ether as a solvent was to retard the reaction rate, *cf.* run 8 with 9. The reaction rate was slower when the acid was in excess than when the alcohol was in excess, *cf.* run 8 with 10, as was found with acid polymer alone.[4] The reaction mixtures tended to turn yellow if the optimum reaction time were exceeded; however, the yields were not significantly changed by this discoloration.

The slower esterification reaction employing 1-butanol was made to go to the extent of 84% in 1 hr and quantitatively overnight. Significantly, the reaction was quantitative using the acid polymer alone with long reaction times; however, the reaction rate was faster in the presence of the drying agent, *cf.* 13 with 14. A practical yield of 65–75% using conventional techniques has been reported for this reaction.[5]

(2) Cited in ref 1.

(3) B. D. Pearson and J. E. Ollerenshaw, *Chem. Ind. (London)*, **9**, 370 (1966).

(4) Cited in ref 1.

(5) R. Adams, J. R. Johnson, and C. F. Wilcox, Jr., "Laboratory Experiments in Organic Chemistry," 6th ed, Macmillan, New York, N. Y., 1970, p 223.

The effect of branching on secondary alcohols such as 2-propanol was to retard the reaction. However, quite respectable yields were obtained on longer exposure times, *cf.* run 23 and 24.

There was an apparent discrepancy between the control run 1 with a 67% yield and run 7 with a 32% yield of water. We presume this was due to lack of attainment of equilibrium in the latter run. The yields as cited in Table I were determined with the use of an internal standard and must not be considered to be recovered yields. To obtain high recovery yields, the catalytic dehydrator washing procedure was of utmost importance.[6]

Experimental Section

The acid polymers used were sulfonated polystyrene copolymers with total exchange capacities on the dry basis of 4.5 mequiv/g (Rexyn 101 (H) R-231) and 4.8 mequiv/g (Rexyn 101 (H)-R-204) sold by Fisher Scientific Co., Fair Lawn, N. J. Anhydrous $CaSO_4$, mesh size 40–80, was used. The acid polymer was dried in a 100° oven prior to use and the $CaSO_4$ dried at 180°. The glpc analyses were performed on a flame ionization Varian Model 1200-2 instrument equipped with a 6 ft × $^1/_8$ in. 10% QF-1 column. Noteworthy were the facts that $CaSO_4 \cdot 2H_2O$ loses 1.5 mol of water at 128° and the remainder of the water at 163°.

General Procedure.—The acetic acid, acid polymer, $CaSO_4$, internal standard, and alcohol were magnetically stirred in an erlenmeyer flask. At the designated time, the mixture was filtered and washed with a solvent. Benzene was used as the internal standard for all runs and the washing liquids were ether or bromobenzene for the methyl acetate runs, and ether or dioxane for 2-propyl acetate and 1-butyl acetate runs. The results reported in Table I were averages of several runs. There were no detectable differences noted on switching from one acid polymer to the other. All products were isolated and compared to authentic samples.

Registry No.—Methanol, 67-56-1; 1-butanol, 71-36-3; 2-propanol, 67-63-0.

Acknowledgment.—The authors are grateful to D. A. Kubik for helpful discussions and the drying agent data used in this paper. One of us (G. F. V.) acknowledges the partial support of a Faculty Research Grant from the University of North Dakota.

(6) V. I. Stenberg, G. F. Vesley, and D. A. Kubik, *J. Org. Chem.*, **36**, 2550 (1971).

The Catalytic Dehydrator for Rapid Acetal and Ketal Synthesis

VIRGIL I. STENBERG,* GEORGE F. VESLEY, AND DONALD KUBIK

Department of Chemistry, The University of North Dakota, Grand Forks, North Dakota 58201

Received November 17, 1970

The catalytic dehydrator,[1] composed of an acid polymer and a drying agent, has been employed for the synthesis of 1-butanol–ethylene glycol acetal, 2-propyl-1,3-dioxolane (I), and cyclohexanone–ethylene glycol ketal, 1,4-dioxaspiro[4.5]decane (II). The dehydrator accomplishes the synthesis by removal of the water *via* the drying agent and the predried acid polymer, whereas the catalysis is accomplished by the strong acid polymer, a principle which conceivably can be applied to the corresponding base-catalyzed reactions as well.

Acid polymers alone have been employed for the synthesis of ketals.[1-7] The ketal II has been prepared in a 57% yield as the refluxing temperature using an acid polymer and a Barrett-type water separator.[2] With the same procedure I was prepared in a 92% yield.[2] As a comparison, an 85% yield of II was obtained using *p*-toluenesulfonic acid together with azeotropic distillation.[8]

A number of drying agents were tested for the present application. The order of decreasing effectiveness of those used with the synthesis of II is $CaSO_4$ > $CaCl_2$ > silica gel > molecular sieve 5A. Since $CaSO_4$ was found to be the most efficient dehydrator of the series, it was selected for the more comprehensive study.

Our efforts were directed toward using minimum practical quantities of both the acid polymer and the drying agent for the butanal reaction. In doing so, it was necessary to run a compromise balance between the minimum acid polymer necessary to obtain an adequate reaction rate and enough drying agent to put the equilibrium at or near completion without putting in an excess of either.

The recovered yields reported in Table I were determined by glpc analysis. The internal standard was added subsequent to filtration and washing of the catalytic dehydrator. Since some of the I or II was retained by the catalytic dehydrator with simple filtration, the choice of solvent used to wash the catalytic dehydrator was extremely important. Unreproducible, low yields were obtained using ether as the washing solvent, whereas dioxane gave reproducible results, *cf.* runs 1 with 2 and 3 with 4.

The yields of both I and II could be made quantitative considering the experimental error. The task for the catalytic dehydrator was only a moderate one, however, since both reactions studied had equilibrium points near 60%, *cf.* runs 5 and 10 of Table I. D_{total}, defined as the total drying capacity of the dehydrator in relation to the water produced, only need be near 1 for near-quantitative formation of I and II.

Longer reaction times caused more erratic results although there seemed to be more product formed and less butanal present, *cf.* run 6 with 2. Suspecting retention of product in the inner regions of the solid catalytic dehydrator particles, I was placed in contact with various drying agents and the concentration monitored *vs.* time. It is evident from the data illustrated in Table II that the drying agents, $CaSO_4$, $CaCl_2$, and silica gel,

(1) G. F. Vesley and V. I. Stenberg, *J. Org. Chem.*, **36**, 2548 (1971).

(2) M. J. Astle, J. A. Zaslowsky, and P. G. Lafyatis, *Ind. Eng. Chem.*, **46**, 787 (1954).

(3) P. Mastagli, Z. Zafiriadis, and G. Lagrange, *C. R. Acad. Sci.*, **237**, 187 (1953); *Chem. Abstr.*, **48**, 11385e (1954).

(4) Olin Mathieson Chemical Corp., British Patent, 739,022 (1955); *Chem. Abstr.*, **50**, 15592e (1956).

(5) T. R. E. Kressman, *Ind. Chem.*, **36**, 3 (1960); *Chem. Abstr.*, **54**, 7004e (1960).

(6) Farbenfabriken Bayer A.-G., German Patent, 882,091 (1953); *Chem. Abstr.*, **52**, 11121a (1958).

(7) Celanese Corp. of America, U. S. Patent, 2,840,615 (1958); *Chem. Abstr.*, **52**, 17109g (1958).

(8) M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Amer. Chem. Soc.*, **70**, 2827 (1948).

TABLE I
YIELD DATA AND REACTION TIMES FOR THE ACETAL AND KETAL REACTIONS

Run	Compd	Acid polymer, g	Drying agent, g	Carbonyl reactant, mmol	Glycol, mmol	Time, min	D_{toto}[a]	D_{CaSO_4}[b]	Yield, %
1	Butanal	0.10	1.50	11.3	5.39	30	0.7	0.4	50–65[c]
2	Butanal	0.10	1.50	11.3	5.39	30	0.7	0.4	85 ± 2
3	Butanal	0.20	1.50	11.3	5.39	30	0.9	0.4	61–82[c]
4	Butanal	0.20	1.50	11.3	5.39	30	0.9	0.4	99 ± 2
5	Butanal	*d*		11.3	5.39	2880			60 ± 2
6	Butanal	0.10	1.50	11.3	5.39	180	0.7	0.4	83–96
7	Butanal	0.10	0.00	11.3	5.39	30	0.3	0.0	77 ± 2
8	Butanal	0.20	0.00	11.3	5.39	30	0.5	0.0	93 ± 2
9	Butanal	0.10	0.00	11.3	5.39	180	0.3	0.0	88 ± 2
10	Cyclohexanone	*d*		9.7	5.39	30			57 ± 2
11	Cyclohexanone	0.10	1.50	9.7	5.39	30	0.8	0.5	91 ± 2
12	Cyclohexanone	1.02	0.00	9.7	5.39	30	2.9	0.0	78 ± 5
13	Cyclohexanone	1.02	0.97	9.7	5.39	30	3.3	0.4	97 ± 5
14	Cyclohexanone	1.01	1.77	9.7	5.39	30	3.7	0.6	92 ± 5
15	Cyclohexanone	0.50	1.73	9.7	5.39	30	3.5	0.6	94 ± 5

[a] Ratio of the drying capacity of the catalytic dehydrator to the water produced. [b] Ratio of the drying capacity of $CaSO_4$ to the water produced. [c] These samples had the catalytic dehydrator washed with ether rather than dioxane. [d] Catalyzed by *p*-toluenesulfonic acid.

TABLE II
RECOVERY OF 2-PROPYL-1,3-DIOXOLANE (I)

Drying agent	Time, hr	Recovery, %
$CaSO_4$	0.5	99
	3	90
$CaCl_2$	3	80
Silica gel, 6–16 mesh	1[a]	71
	3[a]	70
	6[a]	66

[a] The drying agent was not washed in these cases. In all other runs, the drying agent was washed with dioxane.

all cause the end product to "disappear" with time. This was demonstrated to be an adsorption–inner diffusion process within the drying agent particles rather than a destructive chemical reaction because the missing starting material could be recovered from the drying agent by appropriate filtering and washing procedures. To further demonstrate this, a preparative scale reaction to make II was done using the proportions of run 11. A 92% recovered yield was attained despite the 6-hr reaction time. This was only possible when the washing portion of the work-up procedure was optimum.

Both $CaSO_4$ and the dried acid polymer effectively accomplished the yield enhancement in contrast to the ester studies where it was found that the $CaSO_4$ was more efficient than the acid polymer.[1] The addition of $CaSO_4$ for the formation of II increased the yield 19%, *cf.* run 12 with 13. For the preparation of I, $CaSO_4$ enhanced the yield by 8%, *cf.* run 2 with 7, and 6%, *cf.* run 4 with 8, depending upon the amount of acid polymer present. Noteworthy is the comparison of run 8 with that of 7. Doubling the amount of the acid polymer increased the yield by 16% which effectively demonstrates the good drying ability of the acid polymer.[1] It is significant that small amounts of the acid polymer induced high conversions.

The 30-min reaction time was determined to be a minimum for quantitative conversions with these amounts of the catalytic dehydrator. At this time, the absorption–inner diffusion processes are also at a minimum.

Experimental Section

The acid polymers used were sulfonated polystyrene copolymers with total exchange capacities on the dry basis of 4.5 mequiv/g (Rexyn 101 (H) R-231) and 4.8 mequiv/g (Rexyn 101 (H) R-204) sold by Fisher Scientific Co., Fair Lawn, N. J. Finely ground, anhydrous $CaSO_4$ was used. The acid polymer was dried in a 100° oven prior to use and the $CaSO_4$ dried at 200°. The glpc analyses were performed on a flame ionization Beckman GC-5 equipped with a 20 ft × 1/8 in. 20% Carbowax 20M (Chromosorb W) column.

General Procedure for Ketal Formation.—The carbonyl compound was stirred at room temperature with ethylene glycol and the catalytic dehydrator. To terminate the reaction, it was filtered, and the solid washed with a solvent. For the structure proofs, the products were isolated by distillation and identified by comparison of physical properties to literature values[2,9] and nmr analysis. For obtaining the results in Table I, an internal standard was added to the filtrate and the filtrate analyzed by glpc. The internal standards were inert materials of noninterfering retention times. The acid polymer used was Rexyn 101CH, R-204, a sulfonated polystyrene copolymer, and the drying agent was anhydrous $CaSO_4$. Each item of data reported in Table I is the average of several runs.

Preparative Scale Ketalization of Cyclohexanone.—Reagent cyclohexanone, 30 ml (28.4 g, 0.290 mol), 90 ml (100.4 g, 1.620 mol) of ethylene glycol, 3.0 g of cation exchange resin, and 46.5 g (0.392 mol) of anhydrous calcium sulfate were added to a dry 500-ml erlenmeyer flask. The mixture was stirred for 6 hr. Diethyl ether (75 ml) was then added and the mixture was allowed to stir for an additional 10 min. Next the mixture was filtered with suction and the filtered material washed alternately with 50-ml portions of water and diethyl ether until most of the ketal odor disappears from the filtered catalytic dehydrator. Sodium chloride (30 g/100 ml of wash water) was added to the filtrate, the layers were separated, and the organic layer was dried over anhydrous potassium carbonate. The dry organic layer was distilled through a 15-in. Vigreux column. The column was washed with ether and the washing liquid distilled in a semimicro Vigreux column. The two appropriate fractions were combined to give 37–38 g (90–92%) of 1,4-dioxaspiro[4.5]decane, a colorless liquid: bp 65–67° (10 mm); $n^{25}D$ 1.4572 [lit.[9] bp 65–67° (13 mm); $n^{25}D$ 1.4575–1.4565].

Registry No.—I, 3390-13-4; II, 177-10-6.

(9) R. A. Daignault and E. L. Eliel, *Org. Syn.*, **47**, 37 (1967).

Deamination of 2-*exo*-Hydroxy-3-*exo*-aminobornane. An Endo–Endo Hydride Shift to a Secondary Carbonium Ion[1]

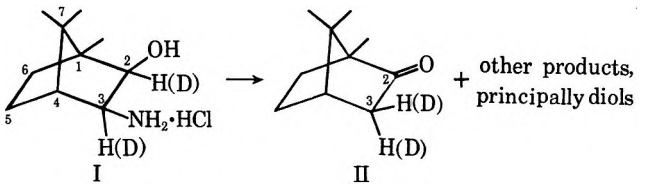
PELHAM WILDER, JR.,* AND WEN-CHENG HSIEH

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received January 18, 1971

Vicinal 2,3-hydride migrations in the norbornyl series have been reported to proceed *via* an exo–exo pathway.[2,3] Only recently the first vicinal 2,3 endo–endo hydride migration in the bornyl series was observed in this laboratory.[4] We would like now to report what appears to be the first case of an endo–endo hydride shift to a secondary carbonium ion.

The reaction of the hydrochloride (I) of 2-*exo*-hydroxy-3-*exo*-aminobornane with nitrous acid according to the method of Wildman and Saunders[5] afforded products containing camphor (II) (20%), diols (48%), and



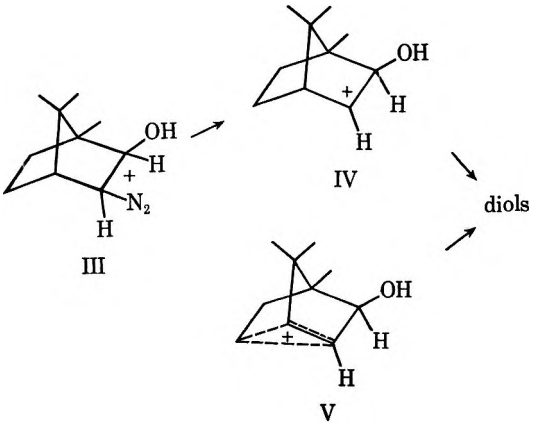
I II

a mixture of unknowns. The diols did not appear to be homogeneous. The unseparated diol mixture was oxidized by the CrO_3–pyridine complex to the respective ketones which showed carbonyl absorptions at 1779[6] and 1742 cm^{-1}. The camphor produced by deamination was shown to be identical with a commercial sample, including its mass spectral fragmentation pattern.[7] A mixture melting point of 2,4-dinitrophenylhydrazones showed no depression.

The hydrochloride I was prepared from 3-oximino camphor[8] by reduction with lithium aluminum hydride. The exo–cis structure of the salt was established by its nmr spectrum. Two sharp doublets, centered at 3.83 (J = 7.5 cps) and 3.33 ppm (J = 7.5 cps), are assigned respectively to the endo protons at C_3 and C_2.

The endo–endo 2,3 hydride shift was confirmed by subjecting 2-*exo*-hydroxy-3-*exo*-aminobornane-2,3-d_2 hydrochloride to the same rearrangement conditions. The nmr trace of the deuterated camphor was identical with the protonated form except for signals for 3-exo and 3-endo protons centered at 2.39 and 1.79 ppm, respectively. A comparison of the mass spectral data with those of the protonated camphor confirmed that the deuterated camphor contained more than 95% of the deuterium at the 3 position.[7] *We believe that these observations represent the first case of an endo–endo hydride migration to a secondary carbonium ion.*[9]

In the deamination of I the diazonium ion III gives directly the "hot" classical ion[9,10] IV from which camphor



is produced *via* an endo–endo hydride shift. The diazonium ion may also yield the bridged ion V by assisted ionization. Since the yield of camphor is 20%, it can be concluded that at least this percentage of classical ion IV is formed This value is close to that reported by Hückel and Nerdel in the deamination of 2-*endo*-aminobornane.[11] Both ions IV and V may yield diols (48%).

Finally, the possibility of a concerted mechanism should be considered. Decomposition of the diazonium ion III to camphor by a concerted 2,3-endo hydride shift seems unlikely since (a) the leaving group and migrating group are at an angle of 120°, and (b) the rates of Wagner–Meerwein rearrangements and of 6,2-hydride shifts are fast compared to a 3,2-hydride shift.[11,12]

Our results are inconsistent with a bridged carbonium ion intermediate which is reported to prevent endo–endo migrations.[3] These results can, however, be interpreted in terms of open, classical intermediates.

Experimental Section[13]

3-Oximinocamphor.—A mixture of 33.2 g (0.20 mol) of camphorquinone and 13.9 g (0.20 mol) of hydroxylamine hydrochloride was dissolved in 250 ml of methanol. To this solution, 21.6 g (0.22 mol) of potassium acetate was added. The stirred mix-

(1) (a) Taken from a dissertation submitted by W.-C. Hsieh to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree, 1970. (b) The support of this research by a grant (CA-4298) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, is acknowledged with gratitude.

(2) D. C. Kleinfelter and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **83**, 2329 (1961); C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *ibid.*, **86**, 4913 (1964); B. M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966); D. C. Kleinfelter and T. E. Dye, *ibid.*, **88**, 3174 (1966).

(3) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2561 (1967), and references therein.

(4) A. W. Bushell and P. Wilder, Jr., *ibid.*, **89**, 5721 (1967).

(5) W. C. Wildman and D. R. Saunders, *ibid.*, **76**, 946 (1954).

(6) The carbonyl absorption at 1779 cm^{-1} is characteristic of 7-norbornanones.

(7) D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, **31**, 115 (1966).

(8) L. Claisen and O. Manasse, *Justus Liebigs Ann. Chem.*, **274**, 71 (1863); A. Hassner, W. Wentworth, and I. Pomerantz, *J. Org. Chem.*, **28**, 304 (1963).

(9) J. Berson, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience, New York, N. Y., Chapter 3, 1963.

(10) A. Streitwieser, *J. Org. Chem.* **22**, 861 (1957); A. Streitwieser and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **79**, 2893 (1957).

(11) W. Hückel and F. Nerdel, *Justus Liebigs Ann. Chem.*, **528**, 57 (1937).

(12) M. Saunders, P. v. R. Schleyer, and G. A. Olah, *J. Amer. Chem. Soc.*, **86**, 5680 (1964).

(13) Melting points and boiling points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn., or M-H-W Laboratories, Garden City, Mich. Analytical glpc analyses were performed on a Varian Aerograph Series 1200 instrument; preparative glpc analyses were performed on an Aerograph Model A-700 autoprep. Nmr spectra were recorded on a Varian T-60 spectrometer. Mass spectra were recorded on a Bendix time-of-flight spectrometer.

ture was heated under reflux for 3 hr. Most of the methanol was removed (about 200 ml) by distillation and 150 ml of ethyl acetate was added. Potassium chloride was removed (about 15 g) by filtration and was washed several times with ethyl acetate. The combined ethyl acetate solutions were neutralized with saturated $NaHCO_3$ solution and were dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure yielded the pale yellow ketoxime. A single recrystallization from ligroin afforded 28.3 g (78%) of 3-oximinocamphor, mp 120–123° (reported[14] 131–133°). The product was used without further purification.

2-*exo*-Hydroxy-3-*exo*-aminobornane.—In a 2-l. three-necked flask, equipped with a condenser, a mechanical stirrer, and a dropping funnel, were placed 400 ml of anhydrous ethyl ether (dried over sodium wire) and 21.4 g (0.56 mol) of $LiAlH_4$. After the mixture had been stirred for 15 min, 33.9 g (0.19 mol) of 3-oximinocamphor in 400 ml of anhydrous ethyl ether was added from a dropping funnel at a rate such as to maintain reflux. After being heated under reflux overnight, the mixture was cooled to room temperature and excess $LiAlH_4$ was then destroyed by addition of wet ether, followed by cold water. A white curdy mass of aluminum hydroxide was removed by filtration and was washed several times with ether. The combined ether solutions were dried over anhydrous magnesium sulfate. When the solvent was removed, the residue was distilled under reduced pressure. The product which distilled at 65.1–65.8° (0.5 mm) solidified and was recrystallized from cold heptane. The yield was 23.6 g (75%), mp 213–214°.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70 96; H, 11.32; N, 8.28. Found: C, 71.12; H, 11.47; N, 8.29.

A benzenesulfonate derivative was prepared, mp 147–149°.

Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.13; H, 7.50; N, 10.34. Found: C, 62.33; H, 7.60; N, 10.65.

2-*exo*-Hydroxy-3-*exo*-aminobornane Hydrochloride (I).—Dry hydrogen chloride gas was bubbled through a vigorously stirred solution of 30 g of 2-hydroxy-3-aminobornane in 1 l. of dry ethyl ether. When the ether solution was acidic to litmus paper, addition of hydrogen chloride gas was halted and the white precipitate was collected. The yield was 33 g (90%). Further recrystallization from ether and methanol mixture afforded 27 g (74%) of hydrochloride salt, dec >175°.

Anal. Calcd for $C_{10}H_{20}NOCl$: C, 58.38; H, 9.79; N, 6.80; Cl, 17.23. Found: C, 58.15; H, 9.70; N, 6.93; Cl, 17.42.

When the hydrochloride salt was treated with 20% NaOH, free amine was collected as white crystals, mp 213–214°, which had the same nmr and ir as the amino alcohol from which the salt had been prepared.

2-*exo*-Hydroxy-3-*exo*-aminobornane-2,3-*d*.—The procedure described above for the preparation of the amino alcohol was followed except for the use of $LiAlD_4$. The deuterated hydrochloride salt (3.9 g) was isolated from 4.5 g of 3-oximinocamphor. The nmr spectrum of the deuterated salt in D_2O was identical with the protonated form except for the absence of signals at 3.33 and 3.83 ppm. When subjected to sublimation at 40° (0.5 mm), deuterated amino alcohol with mp 211–213° was obtained. The mass spectrum of the deuterated amino alcohol confirmed two deuterium atoms in the molecule.

Deamination of 2-*exo*-Hydroxy-3-*exo*-aminobornane Hydrochloride (I) in Water.—The hydrochloride salt (4.2 g) in 42 ml of H_2O was stirred and cooled in an ice–water bath. A solution of 3.1 g of $NaNO_2$ in 21 ml of H_2O was added. Eight drops of concentrated H_2SO_4 was added to induce the deamination reaction. The mixture was stirred for 4 hr and was stored overnight in a refrigerator. The mixture was poured into water and then was extracted with ethyl ether. Camphor was isolated by preparative gc using a 10-ft 20% Carbowax 20M column at 150°, mp 177–178° (reported[14] 178.8°). A 2,4-dinitrophenylhydrazone derivative was prepared, mp 167.5–168° (reported[15] 164°).

Deamination of 2-*exo*-Hydroxy-3-*exo*-aminobornane-2,3-d_2 Hydrochloride.—The procedure was the same as that described above. The nmr spectrum of deuterated camphor was identical with protonated camphor except for the signals for 3-exo and 3-endo protons which were absent. The mass spectrum showed two deuterium atoms in the molecule.

Registry No.—I, 25050-53-7; I benzenesulfonate, 30248-03-4; I HCl, 26126-95-4; II, 76-22-2.

(14) A. Hassener, W. Wentworth, and I. Pomerantz, *J. Org. Chem.*, **28**, 304 (1963).

(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1962.

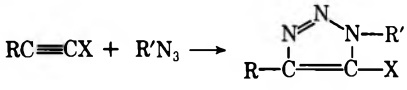
Synthesis of 1-*N*-Glycosyl-1,2,3-triazoles from Glycosyl Azides and Substituted Acetylenes

ROBERT E. HARMON,* ROBERT A. EARL, AND S. K. GUPTA

Department of Chemistry, Western Michigan University, Kalamazoo, Michigan 49001

Received December 22, 1970

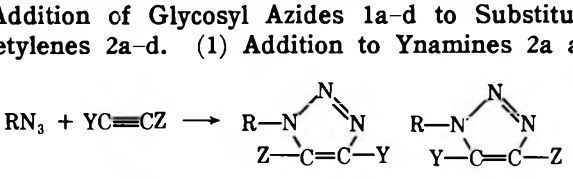
The additions of simple alkyl and aryl azides to various substituted acetylenes are known to produce the corresponding triazoles[1-4] (eq 1). As an extension



(1)

of this work, we investigated the addition of several fully acetylated β-D-glycosyl azides to acetylenes substituted by *N*,*N*-dialkylamino, ethoxy, and ethylthio groups. This study has led to some interesting observations. In particular, the additions of hepta-*O*-acetyl-β-D-maltosyl and hepta-*O*-acetyl-β-D-cellobiosyl azides to ethoxyacetylene were quite significant because each of them yielded both the possible isomeric triazoles. Previously reported additions of azides to ethoxyacetylene afforded only one of the two triazoles.

Addition of Glycosyl Azides 1a–d to Substituted Acetylenes 2a–d. (1) Addition to Ynamines 2a and



1a–d **2a–d** **3a–k** **4a–c**

1a, R = D-glucosyl
b, R = D-galactosyl
c, R = maltosyl
d, R = cellobiosyl

2a, Y = CH_3; Z = $N(Et)_2$
b, Y = Ph; Z = $N(Me)_2$
c, Y = OEt; Z = H
d, Y = SEt; Z = Ph

3a, Y = CH_3; Z = $N(Et)_2$; R = D-glucosyl
b, Y = CH_3; Z = $N(Et)_2$; R = D-galactosyl
c, Y = CH_3; Z = $N(Et)_2$; R = maltosyl
d, Y = CH_3; Z = $N(Et)_2$; R = cellobiosyl
e, Y = Ph; Z = $N(Me)_2$; R = D-glucosyl
f, Y = Ph; Z = $N(Me)_2$; R = D-galactosyl
g, Y = Ph; Z = $N(Me)_2$; R = maltosyl
h, Y = H; Z = OEt; R = D-glucosyl
i, Y = H; Z = OEt; R = D-galactosyl
j, Y = H; Z = OEt; R = cellobiosyl
k, Y = H; Z = OEt; R = maltosyl

4a, Y = H; Z = OEt; R = cellobiosyl
b, Y = H; Z = OEt; R = maltosyl
c, Y = Ph; Z = SEt; R = cellobiosyl

D-glucosyl = 2,3,4,6-tetra-*O*-acetylglucopyranosyl

D-galactosyl = 2,3,4,6-tetra-*O*-acetylgalactopyranosyl

maltosyl = hepta-*O*-acetylmaltosyl

cellobiosyl = hepta-*O*-acetylcellobiosyl

(1) R. Fuks, R. Buijle, and H. G. Viehe, *Angew. Chem.*, **78**, 594 (1966).

(2) R. Huisgen, R. Knorr, L. Mobius, and G. Szeimies, *Chem. Ber.*, **98**, 623 (1965).

(3) M. T. Garcia-Lopez, G. Garcia-Munoz, J. Iglesias, and R. Madronero, *J. Heterocycl. Chem.*, **6**, 639 (1969).

(4) F. Micheel and G. Baum, *Chem. Ber.*, **90**, 1595 (1957).

TABLE I

NMR DATA OF COMPOUNDS 3a–k AND 4a–c

Compd no.	Name	Nmr data, τ
3a	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl)-4-methyl-5-*N*,*N*-diethylamino-*v*-triazole	3.9–4.7 (m, 4, ring H), 5.8 (m, 3, OCH_2 and ring H), 6.9 (q, 4, $N(CH_2)_2$), 7.6 (s, 3, CCH_3), 7.9 (s, 3, $OCOCH_3$), 8.0 (s, 3, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 9.0 (t, 6, $N(CH_2CH_3)_2$)
3b	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactosyl)-4-methyl-5-*N*,*N*-diethylamino-*v*-triazole	3.74–4.9 (m, 5, ring H), 5.8 (s, 2, OCH_2), 6.9 (q, 4, $N(CH_2)_2$), 7.68 (s, 3, CCH_3), 7.78 (s, 3, $OCOCH_3$), 9.01 (t, 6, $N(CH_2CH_3)_2$)
3c	1-(Hepta-*O*-acetyl-β-D-maltosyl)-4-methyl-5-*N*,*N*-diethylamino-*v*-triazole	4.0–5.2 (m, 8, ring H), 5.7–5.8 (m, 6, OCH_2 and 2 ring H), 6.9 (q, 4, $N(CH_2)_2$), 7.7 (s, 3, CCH_3), 7.9–8.0 (m, 18, $OCOCH_3$), 8.3 (s, 3, $OCOCH_3$), 9.0 (t, 6, $N(CH_2CH_3)_2$)
3d	1-(Hepta-*O*-acetyl-β-D-cellobiosyl)-4-methyl-5-*N*,*N*-diethylamino-*v*-triazole	3.8–6.2 (m, 14, OCH_2 and ring H), 6.9 (q, 4, $N(CH_2)$, 7.7 (s, 3, CCH_3), 7.9–8.0 (m, 18, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 9.0 (t, 6, $N(CH_2CH_3)_2$
3e	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl)-4-phenyl-5-*N*,*N*-dimethylamino-*v*-triazole	2.45 (m, 5, Ar H), 3.6–4.9 (m, 4, ring H), 5.7 (m, 3, OCH_2 and 1 ring H), 7.2 (s, 6, $N(CH_3)_2$), 7.9 (s, 9, $OCOCH_3$), 8.1 (s, 3, $OCOCH_3$)
3f	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactosyl)-4-phenyl-5-*N*,*N*-dimethylamino-*v*-triazole	2.5 (m, 5, Ar H), 3.9–6.0 (m, 4, ring H), 5.8 (s, 3, OCH_2 and ring H), 7.2 (s, 6, $N(CH_3)_2$), 7.8 (s, 3, $OCOCH_3$), 7.9 (s, 6, $OCOCH_3$), 8.1 (s, 3, $OCOCH_3$)
3g	1-(Hepta-*O*-acetyl-β-D-maltosyl)-4-phenyl-5-*N*,*N*-dimethylamino-*v*-triazole	2.5 (m, 5, Ar H), 3.9–6.0 (m, 14, OCH_2 and ring H), 7.2 (s, 6, $N(CH_3)_2$), 7.9–8.0 (m, 18, $OCOCH_3$), 8.1 (s, 3, $OCOCH_3$)
3h	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl)-5-ethoxy-*v*-triazole	3.0 (s, 1, C=CH), 4.0–5.0 (m, 5, ring H), 5.9 (m, 4, OCH_2), 7.9 (s, 6, $OCOCH_3$), 8.0 (s, 3, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 8.5 (t, 3, OCH_2CH_3)
3i	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactosyl)-5-ethoxy-*v*-triazole	2.9 (s, 1, C=CH), 4.2–5.0 (m, 5, ring H), 5.7 (m, 4, OCH_2), 7.8–8.1 (m, 12, $OCOCH_3$), 8.6 (t, 3, OCH_2CH_3)
3j	1-(Hepta-*O*-acetyl-β-D-cellobiosyl)-5-ethoxy-*v*-triazole	2.9 (s, 1, C=CH), 4.0–6.1 (m, 16, OCH_2 and ring H), 7.8–8.1 (m, 18, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 8.5 (t, 3, OCH_2CH_3)
3k	1-(Hepta-*O*-acetyl-β-D-maltosyl)-5-ethoxy-*v*-triazole	3.0 (s, 1, C=CH), 4.2–6.1 (m, 16, OCH_2 and ring H), 7.9–8.0 (m, 18, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 8.5 (t, 3, OCH_2CH_3)
4a	1-(Hepta-*O*-acetyl-β-D cellobiosyl)-4-ethoxy-*v*-triazole	2.9 (s, 1, C=CH), 4.2–6.2 (m, 18, $OCOCH_3$), 8.1 (s, 3, $OCOCH_3$), 8.6 (t, 3, OCH_2CH_3)
4b	1-(Hepta-*O*-acetyl-β-D-maltosyl)-4-ethoxy-*v*-triazole	2.9 (s, 1, C=CH), 4.2–6.1 (m, 16, OCH_2 and ring H), 7.9–8.1 (m, 18, $OCOCH_3$), 8.1 (s, 3, $OCOCH_3$)
4c	1-(Hepta-*O*-acetyl-β-D-cellobiosyl-5-phenyl-4-ethylthio-*v*-triazole	2.5 (s, 5, Ar H), 4.2–6.1 (m, 14, OCH_2 and ring H), 7.2 (q, 2, SCH_2), 7.8 (m, 18, $OCOCH_3$), 8.2 (s, 3, $OCOCH_3$), 8.5 (t, 3, OCH_2CH_3)

2b.—The glycosyl azides **1a–d** were found to react readily with *N*,*N*-diethylaminoprop-1-yne (**2a**). The resulting adducts **3a**, **3c**, and **3d** were obtained by simple recrystallization, whereas the adduct **3b** could be isolated only as a colorless gum after column chromatography over silica gel. The addition of azides **1a–d** to *N*,*N*-dimethylaminophenylacetylene (**2b**)[5] required longer periods of refluxing (5–10 hr) and the product isolation involved column chromatography over silica gel. Only one of the adducts, **3e**, could be obtained crystalline, the rest (**3f**, **3g**) were identified as 1-*N*-glycosyl-1,2,3-triazoles by nmr and ir spectroscopy. The nmr data are included in Table I. The nmr spectra of compounds **3a–d** showed the expected signals for pyranose ring hydrogens as well as hydrogens of $OCOCH_3$, CCH_3, and $N(CH_2CH_3)_2$ groups. The nmr data also support the structures assigned to the triazoles **3e–g**, because in each case the phenyl hydrogens

(5) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *J. Org. Chem.*, **35**, 1936 (1970).

TABLE II

PROPERTIES OF COMPOUNDS 3a–k AND 4a–c[a]

Compd no.	Mp, °C	Recrystn solvent	Yield, %	$[\alpha]^{25}D$,[b] deg
3a	162–162.5	C_6H_6, petroleum ether	97	−18.5 (*c* 1.5)
3b	Glass		82	−5.6 (*c* 1.5)
3c	138–139.5	C_6H_6, petroleum ether	83	33.2 (*c* 1.0)
3d	196–196.5	>=O, Et_2O	79	−28.4 (*c* 1.0)
3e	124.5–126.5	C_6H_6, petroleum ether	55	−29.3 (*c* 1.1)
3f	Glass		55	−10.6 (*c* 0.9)
3g	Glass		60	30.1 (*c* 1.5)
3h	151–152	>—OH	26	−16.8 (*c* 1.5)
3i	132.5–133.5	>=O, Et_2O, petroleum ether	16	−2.0 (*c* 1.5)
3j	169–170.5	>—OH	22	−22.5 (*c* 1.5)
3k	165.5–166	>=O, Et_2O, petroleum ether	18.5	47.8 (*c* 1.5)
4a	205.5–206.5	$CHCl_3$–Et_2O	11	−23.6 (*c* 1.5)
4b	173–173.5	CH_3OH	16	51.4 (*c* 1.5)
4c	175.5–177	>—OH, $CHCl_3$, Et_2O	18	−26.5 (*c* 1.5)

[a] C, H, and N analyses were within 0.3% of theoretical values. [b] All the rotations were measured using chloroform as solvent.

appeared as a broad multiplet centered around τ 2.50. This is in agreement with the observations of Garcia-Lopez, *et al.*[3] According to them, in the nmr spectrum the phenyl hydrogens of a 1-glycosyl-4-phenyl-*v*-triazole (like **3e–g**) appear as a broad multiplet, whereas in a 1-glycosyl-5-phenyl-*v*-triazole the phenyl hydrogens appear as a singlet.

(2) Addition to Ethoxyacetylene (2c).—The addition of glycosyl azides **1a–d** to ethoxyacetylene (**2c**) required much more severe conditions than the corresponding additions to ynamines. The reactions yielded complex mixtures and isolation of the product from them required extensive column chromatography over silica gel using a fraction collector. The resulting triazoles **3h–k** and **4a,b** could only be isolated in low yields (<35%). The addition of azides **1a** and **1b** led to the isolation of only one of the two possible isomeric triazoles in each case (structures **3h** and **3i**). On the other hand, all the possible triazoles (**3j**, **4a**, **3k**, and **4b**) were isolated from the addition of hepta-*O*-acetyl β-D-cellobiosyl azide (**1c**) and hepta-*O*-acetyl-β-D-maltosyl azide (**1d**). The nmr spectra (Table I) of each set of these isomeric triazoles were very similar but consistent with the structures. This is the first time that both the possible isomeric triazoles have been isolated from the addition of azides to ethoxyacetylene. All the previously reported examples[6–8] led to the isolation of only one (1-substituted 5-ethoxy-*v*-triazole) of the two isomeric triazoles.

(3) Addition to 1-Ethylthio-2-phenylacetylene (2d).—The reactions of the glycosyl azides **1a–d** with 1-ethylthio-2-phenylacetylene (**2d**) were slow. At temperatures below 110° no reaction seemed to take place except for the slow decomposition of the reactants. A crystalline triazole **4c** was obtained in low (18%) yield when a THF solution of **2d** and hepta-*O*-acetyl-β-D-cellobiosyl azide (**1d**) was heated in a sealed tube at 130–140° for 5 days. Even in this case, the reaction mixture turned black and required column chromatography over silica gel before any product could be isolated. The other additions of **1a–c** to **2d** did not lead to any isolable product. In the nmr spectrum (Table I) of **4c** the phenyl hydrogens appeared as a singlet at τ 2.52, suggesting, thereby, the correct structure of the adduct as depicted. The nmr spectrum of the isomeric triazole structure would have shown a broad multiplet for the phenyl hydrogens.[3] These results are also consistent with the observations of Groen and Arens,[9] who demonstrated that the 1,3-dipolar addition of diazomethane to **1d** takes place in a manner opposite to the 1,3-dipolar additions to ynamines (like **1a**, **1b**) or acetylenic ethers (like **1c**).

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. The nmr spectra were run using a Varian A-60 spectrometer with tetramethylsilane as internal standard and $CDCl_3$ as solvent. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel G. Spots on these plates were detected by a sulfuric acid spray followed by baking at 110° for 5–10 min. Dry column chromatography was carried out on glass columns (23 cm × 4.5 cm) packed with silica gel (200–325 mesh). An Instrument Specialist Co. fraction collector Model 272 was used for dry column chromatography.

Preparation of Glycosyl Azides.—The per-*O*-acetyl-β-D-glycosyl azides **1a–d** were prepared by heating the corresponding per-*O*-acetyl-α-D-glycosyl halides with sodium azide in dimethylformamide (DMF) by a procedure similar to that used by Yamamoto, *et al.*,[10] and Carrington, *et al.*[11] The general procedure is described below.

A slurry of per-*O*-acetyl-α-D-glycosyl halide (35.7 mmol) and sodium azide (77 mmol) in dry DMF (100 ml) was heated on a steam bath for 1.5 hr. On pouring the mixture over crushed ice (about 1 l.), the per-*O*-acetyl glycosyl azide precipitated out.

(6) P. Grunanger, P. Finzi, and C. Scotti, *Chem. Ber.*, **98**, 623 (1965).

(7) P. Grunanger, P. Finzi, and E. Fabbri, *Gazz. Chim. Ital.*, **90**, 413 (1969); *Chem. Abstr.*, **55**, 11397 (1961).

(8) P. Finzi, C. Scotti, and A. Quilico, *Atti. Accad. Naz. Lincei., Cl. Sci. Fis., Mat. Nat., Rend.*, **41**, 204 (1966); *Chem. Abstr.*, **67**, 54080 (1967).

(9) S. H. Groen and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 879 (1961).

(10) A. Yamamoto, C. Miyashita, and H. Tsukamoto, *Chem. Pharm. Bull.*, **13**, 1036 (1965); *Chem. Abstr.*, **64**, 8281*f* (1966).

(11) R. Carrington, G. Shaw, and D. V. Wilson, *J. Chem. Soc.*, 6864 (1965).

Filtration, drying, and crystallization afforded the colorless crystals. A comparison of the observed melting points with the corresponding literature values is given below.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (1a), mp 125.5–127.5° (lit.[12] mp 129°).

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl azide (1b), mp 95–96° (lit.[13] mp 96°).

Hepta-*O*-acetyl-β-D-maltosyl azide (1c), mp 94–96° (lit.[14] mp 91°).

Hepta-*O*-acetyl-β-D-cellobiosyl azide (1d), mp 180–181° (lit.[6] mp 182–182.5°).

Preparation of 1-Ethylthio-2-phenylacetylene (2d).—The compound 2d was prepared by treating phenylbromoacetylene[15] with sodium hydride and ethyl mercaptan in dry DMF according to the general procedure of Brandsma, *et al.*[16] The product was characterized: bp 92–96° (1.5 mm); refractive index, $n^{25}D$ 1.6075 (lit.[16] $n^{25}D$ 1.6133); and nmr τ 2.73 (m, 5, Ar H), 7.33 (q, 2, SCH_2), 8.68 (t, 3, SCH_2CH_3).

Addition of Glycosyl Azides 1a–d to Ynamines 2a–b.—A solution of the glycosyl azide (4.6 mmol) and ynamine (7 mmol) in dry THF (10 ml) was heated under reflux. When tlc of the reaction mixture showed the disappearance of the spot due to the azide, the solvent and the excess ynamine were removed by evaporation under reduced pressure. The triazoles 2a, 3c, and 3d were obtained by simple crystallization of the residue. On the other hand, triazoles 3b, 3f, and 3g were obtained by dry column chromatography over silica gel using a fraction collector. A mixture of chloroform and acetone (9:1) was used for elution of the products from the column. The properties are recorded in Table II. The ir spectra were also consistent with the structures proposed.

Addition of 1a–d to Ethoxyacetylene (2c).—A solution of the glycosyl azide (4.6 mmol) and ethoxyacetylene (7 mmol) in dry THF (10 ml) was heated in a sealed tube at 60–70° for 12 days. After that the solvent and excess ethoxyacetylene were removed by evaporation *in vacuo*. Dry column chromatography of the resulting black residue, as described above, afforded the corresponding triazole (Table II).

Addition of 1d to 1-Ethylthio-2-phenylacetylene (2d).—A solution of 1d (4.6 mmol) and 2d (7 mmol) in THF (10 ml) was heated in a sealed tube at 130–140° for 5 days. Column chromatography, as described above, of the resulting black gum afforded the crystalline triazole 4c in low yield (Table II). The reactions of 2d with the azides 1a–c failed to give any isolable products.

Registry No.—3a, 29751-37-9; 3b, 29751-38-0; 3c, 29751-39-1; 3d, 29751-40-4; 3e, 29751-41-5; 3f, 29751-42-6; 3g, 29751-43-7; 3h, 29751-44-8; 3i, 29751-45-9; 3j, 29751-46-0; 3k, 29751-47-1; 4a, 29751-48-2; 4b, 29751-49-3; 4c, 29751-50-6.

Acknowledgment.—This work was supported by Grant CA-6140 from the National Institutes of Health. The authors are grateful to Dr. Carmen V. Zenarosa for supplying a generous sample of *N,N*-dimethylaminophenylacetylene.

(12) A. Bertho, *Chem. Ber.*, **63**, 836 (1930).
(13) A. Bertho and J. Maier, *Justus Liebigs Ann. Chem.*, **498**, 50 (1932).
(14) A. Bertho, *ibid.*, **562**, 229 (1949).
(15) S. Miller, G. Ziegler, and R. Wieleseck, *Org. Syn.*, **45**, 86 (1965).
(16) L. Brandsma, H. E. Wijers, and C. Jonker, *Recl. Trav. Chim. Pays-Bas*, **83**, 208 (1964).

2′,3′-Carbonates of 8-Hydroxypurine Nucleosides

K. K. OGILVIE* AND L. SLOTIN

Department of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada

Received December 18, 1970

The synthesis of modified nucleosides has recently attracted a great deal of attention. Much of this effort has been directed toward nucleosides possessing an oxygen,[1–4] a sulfur,[4–6] or a nitrogen[7–8] bridge between the purine or pyrimidine ring and the sugar ring, in addition to the *N*-glycoside bond. Very successful syntheses of pyrimidine 2,2′-*O*-anhydronucleosides, particularly 2,2′-*O*-anhydrouridines[2] have been developed. However, published methods for obtaining purine 8,2′-*O*-anhydronucleosides are much less efficient[4,9,10] involving many steps and very low yields.

It has been shown[11] that uridine 2′,3′-carbonate can be converted in high yield to *O*²,2′-anhydrouridine by heating in dimethylformamide (DMF) in the presence of a base catalyst such as sodium bicarbonate. It occurred to us that the 2′,3′-carbonates of 8-hydroxyadenosine (1a) and 8-hydroxyguanosine (1b) might closely resemble uridine 2′,3′-carbonate and might therefore be easily converted to the corresponding 8,2′-*O*-anhydronucleosides. This report discusses the synthesis of compounds 1a and 1b and attempts to convert them to the anhydronucleosides.

Syntheses of 8-Hydroxypurine Nucleosides.—Syntheses of both 8-hydroxyadenosine and 8-hydroxyguanosine have been reported.[9,12,13] Our approach (Scheme I) to the 8-hydroxynucleosides was similar to that used by Holmes and Robins[12] to obtain 8-hydroxadenosine. The purine nucleoside 2 was first acetylated[14] to 3 and then brominated[15,16] to yield the 8-bromotriacetyl derivative 4. Treatment with sodium acetate in refluxing acetic anhydride yielded, after work-up, the 8-hydroxytetraacetyl derivative 5. Hydrolysis of the acetyl groups gave the 8-hydroxy nucleosides 6.

The scheme worked smoothly for adenosine resulting in an overall yield of 41% for the conversion to 8-hydroxyadenosine. With guanosine the conversion of 4 to 5 was 53%. However, a 28% yield of 8-bromotetraacetylguanosine (7) was obtained and this was converted in 55% yield to 5. Thus a good yield of 5 could be obtained by recycling the recovered 8-bromotetraacetylguanosine.

Conversion of the 8-hydroxypurine nucleosides 6 to their 2′,3′-carbonates was readily accomplished[2] by heating the nucleoside in DMF at 150° for 30 min with diphenyl carbonate in the presence of a catalyst (sodium bicarbonate). For comparison we first subjected guanosine and adenosine to these conditions and obtained guanosine 2′,3′-carbonate (8) and the previously reported[2] adenosine 2′,3′-carbonate (9) in 77 and 75% yields, respectively. 8-Hydroxyadenosine 2′,3′-carbonate (1a) and 8-hydroxyguanosine 2′,3′-car-

(1) J. J. Fox and I. Wempen, *Tetrahedron Lett.*, 643 (1965).
(2) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).
(3) D. Lipkin, C. Cori, and M. Sano, *Tetrahedron Lett.*, 5993 (1968).
(4) M. Ikehara, *Accounts Chem. Res.*, **2**, 47 (1969).
(5) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).
(6) I. Wempen and J. J. Fox, *ibid.*, **34**, 1020 (1969).
(7) I. L. Doerr, R. J. Cushley, and J. J. Fox, *ibid.*, **33**, 1592 (1968).
(8) I. L. Doerr and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 1760 (1967).
(9) M. Ikehara, H. Tada, and M. Kaneko, *Tetrahedron*, **24**, 3489 (1969); *J. Amer. Chem. Soc.*, **88**, 3165 (1966).
(10) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3039 (1967).
(11) K. K. Ogilvie and D. Iwacha, *Can. J. Chem.*, **47**, 495 (1969).
(12) R. E. Holmes and R. K. Robbins, *J. Amer. Chem. Soc.*, **87**, 1772 (1965).
(13) M. Ikehara, H. Tada, and Muneyama, *Chem. Pharm. Bull (Tokyo)*, **13**, 1140 (1965).
(14) M. Ikehara, *ibid.*, **8**, 367 (1968).
(15) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).
(16) J. F. Gerster, B. C. Hinshaw, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **33**, 1070 (1968).

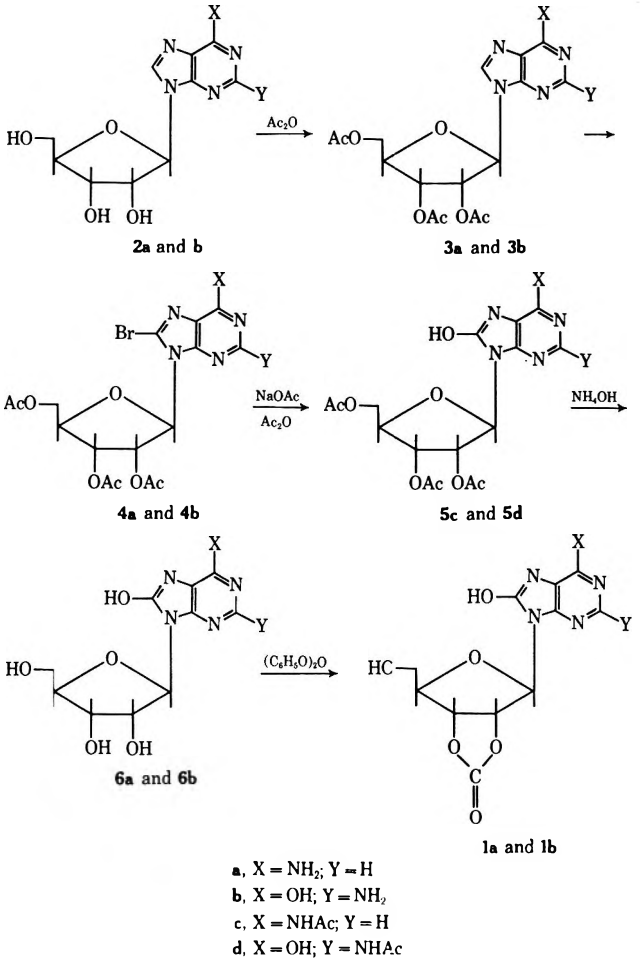
TABLE I

Compd no.	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	Br	Found, % C	H	N	Br
1a	76	151 dec	$C_{11}H_{11}N_5O_6$	42.72	3.59			42.40	3.84		
1b	62	240 dec	$C_{11}H_{11}N_5O_7 \cdot 0.5H_2O$	39.53	3.62	20.95		39.92	3.54	20.08	
5c	80	110–112	$C_{18}H_{21}N_5O_9$	47.89	4.69	15.52		47.43	4.62	15.12	
5d	53	131–134	$C_{18}H_{21}N_5O_{10} \cdot 0.5H_2O$	45.38	4.65	14.70		45.23	4.44	14.62	
6a	94	210 dec	$C_{10}H_{13}N_5O_5$	42.40	4.63	24.73		42.31	4.68	24.64	
6b	83	180 dec	$C_{10}H_{13}N_5O_6 \cdot H_2O$	39.53	3.62	20.95		39.92	3.54	20.08	
7	28	101–104	$C_{18}H_{20}BrN_5O_9$	40.77	3.80	13.21	15.07	40.92	3.82	13.17	14.70
8	77	246 dec	$C_{11}H_{11}N_5O_6 \cdot 0.5H_2O$	41.51	3.80	22.01		42.25	4.31	21.66	

TABLE II

Compd no.	R_f (tlc) THF	EtOH	R_f (paper chromatography) A	B	C	D	Uv spectral data Solvent	λ_{max}, nm (ϵ)
1a	0.87	0.65		0.85	0.83	0.79	95% EtOH	266 (10,300), 257 (10,200)
1b	0.45	0.59		0.75	0.63	0.59	95% EtOH	247.5 (11,400), 295.5 (8,700)
5c	0.88	0.66		0.91	0.89	0.89	95% EtOH	288 (12,300), 219.5 (24,700)
5d	0.70	0.49	0.73				95% EtOH	303 (8,300), 265.5 (15,500)
6a	0.29	0.62	0.44	0.65	0.56	0.65	H_2O	270 (15,800), 260 (13,700) sh
6b		0.48	0.23	0.64	0.63	0.51	H_2O	294 (7,500), 247 (9,000).
7	0.69	0.54	0.78				95% EtOH	286 (13,300), 263 (7,450), 259 (17,380)
8	0.16	0.47		0.75			95% EtOH	273 (8,700), 254.5 (11,100)

SCHEME I



bonate (**1b**) were similarly obtained in 76 and 62% from **6a** and **6b**, respectively.

Several conditions were investigated in attempting to convert **1a** and **1b** to the 8,2′-*O*-anhydronucleosides. These included heating **1** in DMF at 150° for 30 min using sodium bicarbonate, sodium benzoate, or potassium *tert*-butoxide as catalysts. In another attempt potassium *tert*-butoxide in *tert*-butyl alcohol at 80° for 30 min was tried. In all cases only unreacted starting material and the 8-hydroxynucleosides **6** (resulting from hydrolysis of the cyclic carbonate) were obtained. No anhydronucleoside was detected in any of the reactions. It therefore appears that the 8-hydroxy function of purine nucleosides is not completely analogous to the 2-hydroxy function of uridine, at least with respect to interaction with the 2′ position. The incorporation of the 8-bromo- and 8-hydroxynucleosides into oligonucleotides will be reported at a later date.

Experimental Section

Methods and Materials.—Descending paper chromatography was carried out using Whatman 3MM paper. The solvent systems employed were solvent A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2); solvent B, 0.5 *M* ammonium acetate–ethanol (3:7, adjusted to pH 3.5 with acetic acid); solvent C, 5% ammonium bicarbonate in water; solvent D, ethanol–water (7:3). The solvents were prepared on a volume basis. Thin layer chromatography was carried out employing the ascending technique in closed jars which were not coated with absorbent paper. All thin layer chromatography was run on Eastman chromagram sheets 6060, silica gel with fluorescent indicator, on strips 10 cm × 2 cm. Thick layer chromatography was carried out on glass plates (20 cm × 20 cm) coated with a 2-mm-thick layer of silica gel DSF-5 (Mondray Chemicals Ltd.). Nucleosides and their derivatives were detected on paper chromatograms, thin and thick layer sheets, using an ultraviolet source (Mineralite, output ~254 mμ).

Infrared spectra were obtained on a Perkin-Elmer 337 recording instrument using KBr disks for sample preparation. Ultraviolet spectra were obtained on a Perkin-Elmer 450 instrument. Melting points were determined on a Fisher-Johns melting point apparatus and are reported uncorrected. Elemental analyses were performed by Micro-Tech laboratories, Skokie, Ill. Samples submitted to them were prepared by crystallization, lyophilization, or precipitation from tetrahydrofuran with hexane followed by heating in a drying apparatus over P_2O_5.

8-Hydroxy-*N*,2′,3′,5′-tetraacetylpurine Nucleosides (5c and 5d).—The 8-bromo-2′,3′,5′-tri-*O*-acetyl nucleoside[15,16] was refluxed in acetic anhydride for 1.5 hr with a tenfold excess of sodium acetate. The solution was cooled to room temperature, diluted with ethanol, and stored overnight at room temperature. The solvents were removed at reduced pressure and the residue was extracted with chloroform. The chloroform solution was filtered, dried over sodium sulfate, concentrated to a small volume, and applied to thick layer plates. The plates were developed in ether (adenosine) or ethyl acetate (guanosine) and

the product bands were eluted from the silica gel with tetrahydrofuran. In the case of **5d**, a 28% yield of 8-bromo-*N*-2′,3′,5′-tetraacetylguanosine (**7**) was also obtained. Compound **7** could be converted to **5d** in 55% yield using the above procedure. Results and properties are listed in Tables I and II.

8-Hydroxyadenosine (6a) and 8-Hydroxyguanosine (6b).—Compound **5** was dissolved in a mixture of pyridine and ammonium hydroxide (1:3, 20 ml/mmol) and the solution was stirred at room temperature for 3 to 7 days. The solvents were removed at reduced pressure and the product was crystallized from water (Tables I and II).

8-Hydroxypurine 2′,3′-Carbonates (1a and 1b).—Compound **6** (1 mmol), diphenyl carbonate (1.3 mmol), and sodium bicarbonate (6 mg) were heated in dimethylformamide (6 ml) at 150° for 30 min. The products were separated by thick layer chromatography using THF for the adenosine derivative and chloroform–ethanol (7:3) for the guanosine derivative (Tables I and II).

Purine 2′,3′-Carbonates (8 and 9).—Compounds **8** and **9** were prepared from guanosine and adenosine respectively in the same manner as **1** above. The products were isolated by thick layer chromatography using THF. Compound **8** crystallized from ethanol (Tables I and II).

Attempted Synthesis of 8,2′-*O*-Anhydronucleosides.—Several attempts were made to convert **1a** and **1b** to their respective 8,2′-*O*-anhydro derivatives. Both compounds were subjected to each of the following sets of conditions: (A) nucleoside, sodium bicarbonate, and dimethylformamide at 150° for 30 min; (B) nucleoside, sodium benzoate, and dimethylformamide at 150° for 30 min; (C) nucleoside, potassium *tert*-butoxide, and dimethylformamide at 150° for 30 min; (D) nucleoside, potassium *tert*-butoxide, and *tert*-butyl alcohol at 80° for 30 min. In all cases 10 mg of either **1a** or **1b** was used, the volume of solvent was 0.5 ml, and 1 mg of the base catalyst was used. Products were identified by paper chromatography. In all cases only unreacted starting material and **6** were detected. No other nucleoside material was detected in any of these experiments.

Registry No.—**1a**, 29851-53-4; **1b**, 29851-54-5; **5c**, 29851-55-6; **5d**, 29851-56-7; **6a**, 29851-57-8; **6b**, 29851-58-9; **7**, 29851-59-0; **8**, 29842-76-0.

Acknowledgment.—Financial assistance from the National Research Council of Canada and the Faculty of Graduate Studies of the University of Manitoba is gratefully acknowledged.

Synthesis of 19-Hydroxy-19a-methyl-5-ene Steroids *via* the 6β,19-Epoxy Derivatives

YUMI WATANABE AND YUTAKA MIZUHARA*[1]

Chemical Laboratory, School of Medicine, Keio University, Hiyoshi, Yokohama, Japan

MICHIO SHIOTA

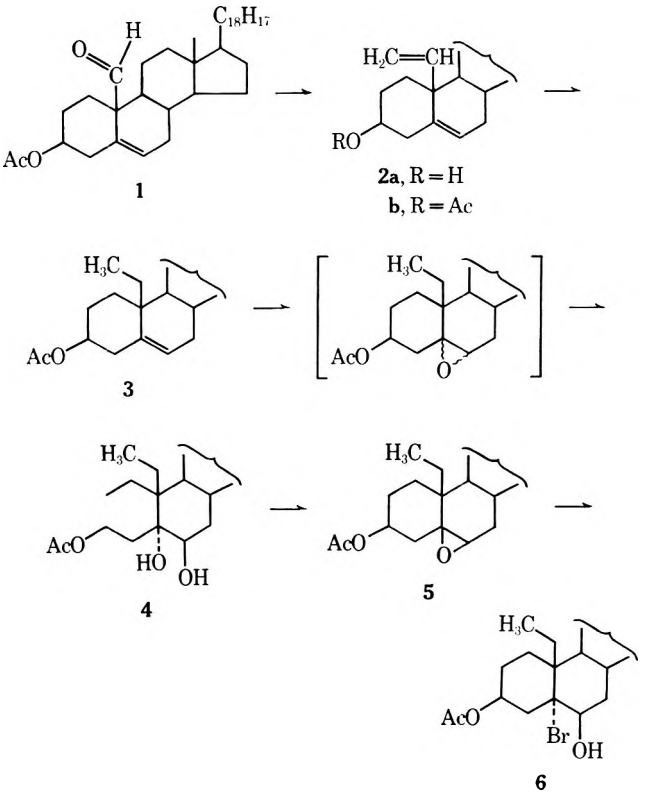
Chemical Laboratory, Ochanomizu University, Oisuka, Tokyo, Japan

Received December 7, 1970

The reaction of methyllithium with steroidal 19-aldehydes has been reported by Caspi to give 19-hydroxy-19a-methyl-5-enes, and it has also been shown that only 19*R* alcohols are formed by this reaction.[2,3] The isomeric 19*S* alcohol was obtained by reduction of the 19a-methyl-19-oxo compound with lithium aluminium hydride.[4] We examined the reaction of lead tetraacetate with 3β-acetoxy-5α-bromo-6β-hydroxy-19a-methylcholestane to determine the stereochemistry of the formation of the ethers, 3β-acetoxy-5α-bromo-6β,19-epoxy-19a-methylcholestanes, and found that the resulting ethers could be reduced to the 19-hydroxy-19a-methyl-5-enes. This paper deals with the stereochemistry of the formation of the 6β,19-epoxides and the synthesis of 19-hydroxy-19a-methylcholest-5-enes from them.

The starting material **6** for the synthesis of the 6β,19-epoxides was prepared by the way summarized in Scheme I The Wittig reaction on 3β-acetoxy-19-oxocholest-5-ene (**1**)[5] with methylene–triphenylphosphorane in ether gave the 19a-methylene derivative **2a** in good yield and its acetate **2b** was partially hydrogenated to the 19a-methyl-5-ene **3** with platinum catalyst in ethanol. The epoxidation of **3** with monoperphthalic acid gave a mixture of 5,6-epoxides, which consisted of 90% of α oxide and 10% of β isomer. The mixture of the epoxides was transformed into the 5α,6β-dihydroxy derivative **4** and then the diol was converted to the 5β,6β-epoxide **5** in the usual way.[6,7] Treatment of **5** with an equimolar amount of hydrobromic acid in acetic acid yielded the compound **6**.

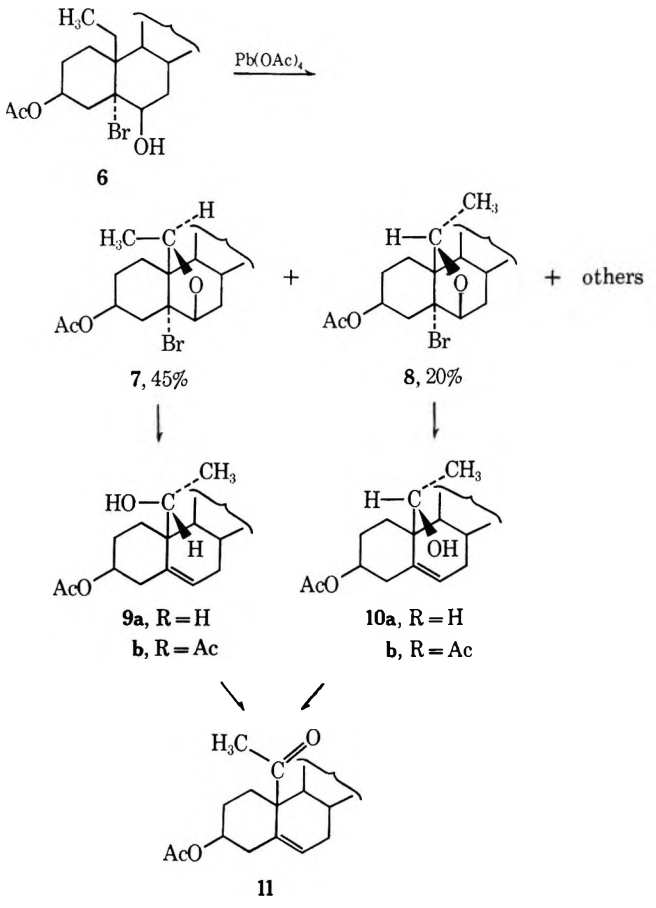
SCHEME I



The 6β-hydroxy-19a-methyl compound **6** was treated with lead tetraacetate in cyclohexane in the presence of iodine, and the two main products, 45% of **7** and 20% of **8**, were obtained by column chromatography. Reduction of **7** and **8** with zinc in acetic acid afforded quantitatively the 19-hydroxy compounds, **9** and **10**, respectively. The results are summarized in Scheme II. The stereochemistry at C-19 of **7** and **8** was assigned in

(1) To whom all correspondences should be addressed.
(2) E. Caspi and J. Wicha, *Chem. Commun.*, 209 (1966).
(3) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 1740 (1968).
(4) J. Wicha and E. Caspi, *ibid.*, 947 (1969).
(5) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).
(6) M. Davis and V. Petrow, *J. Chem. Soc.*, 2536 (1949).
(7) C. W. Shoppee and R. Lake, *ibid.*, 4864 (1960).

SCHEME II



relation to that of the 19-hydroxy compounds **9** and **10**. On reduction, the stereochemistry at C-19 could be maintained, and therefore **7** and **8** have the same configuration at C-19 as that of **9** and **10**, respectively. Oxidation of **9** and **10** gave the same product, the 19a-methyl-19-oxo compound **11**, synthesis of which by a different route was previously reported,[8] and the dehydration of **9** and **10** also gave the same product **2**. The above chemical evidence indicates that the compound **9** is the epimer of **10** at C-19 or that **7** is the epimer of **8**. On the stereochemistry of 19-hydroxy-19a-methyl steroids, Caspi reported that treatment of an aldehyde of the type **1** with methyllithium gave a single product in an almost quantitative yield, and the resulting alcohol had the 19*R* configuration. In our experiments, the aldehyde **1** with methyllithium gave the diol **9a** as the main product, which was therefore concluded to have the 19*R* configuration according to the finding by Caspi. On the other hand, reduction of the 19-oxo compound **11** with lithium aluminium hydride yielded the diol **10a** as the main product. Examination of Dreiding model for the process of reduction suggests that the resulting alcohol **10a** will have 19*S* configuration and this deduction is in agreement with the result reported by Caspi.[4] From the above result, the alcohol **9** has been shown to have the 19*R* configuration while **10** to have the 19*S* stereochemistry.

The above results indicated that the oxidation of **6** with lead tetraacetate gave two isomeric 6β,19-epoxides as the main products and that the ratio of the 19*R* and 19*S* isomers was about 7:3. The formation of ether ring will occur preferably with a conformer, in which the bulky 19a-methyl group will be located at the rear of the molecule, and therefore the oxidation would yield the 19*R* isomer as the major product.

Comparison of infrared spectra of the 19*R* alcohol **9b** and the 19*S* one **10b** showed some differences in absorption bands due to the 19-hydroxy groups. The ir spectrum of **9b** in dilute carbon tetrachloride solution showed a band at 3627 cm^{-1} due to the free hydroxyl group accompanied with a very weak shoulder at 3595 cm^{-1} due to the intramolecular hydrogen-bonded hydroxyl group, while that of the 19*S* one at 3633 and 3540 cm^{-1}. As reported by Caspi,[3] it was apparent from models that C-2, C-4, C-8, and C-11 axial protons would restrict rotation around the C-10–C-19 bond of the 19-hydroxy-19a-methyl-5-enes. Consequently, in usual circumstances, the 19*R* and 19*S* alcohols will remain in reasonably fixed positions with the hydroxyl group. The difference in the ir spectra of the two isomers indicated that rotation around C-10–C-19 bond would be partially restricted. The 19*R* and 19*S* alcohols will perhaps remain with the hydroxyl group over ring A and B, respectively, and therefore the hydroxyl group of the 19*S* alcohol will be hydrogen bonded with the π electrons of the 5,6 double bond more strongly than that of the 19*R* one.

Experimental Section[9]

3β-Acetoxy-19a-methylenecholest-5-ene (2b).—To an ethereal solution of *n*-butyllithium (containing 0.01 mol, about 30 ml), triphenylmethylphosphonium bromide (3.57 g, 0.01 mol) was added over a 5-min period. A gentle flow of nitrogen was maintained throughout the reaction. The solution was stirred for 4 hr at room temperature. An ethereal solution of 2.1 g (0.005 mol) of 3β-acetoxy-19-oxocholest-5-ene (**1**) was added to the red solution of the phosphorane; the solution became almost colorless and a white precipitate separated. The mixture was heated under reflux overnight under nitrogen. After cooling, the mixture was diluted with ether and the precipitate was removed by filtration. The filtrate was washed with water until neutral, dried, and evaporated. The residue was acetylated with pyridine–acetic anhydride. The product was chromatographed on alumina and eluted with *n*-hexane to afford 1.5 g of **2b**, which was recrystallized from methanol: mp 89.5–90°; $[\alpha]^{27}D$ −95° (c 1.739, $CHCl_3$); ir (KBr) 1750, 1628, 1245, 920 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3-OAc), 4.9–5.7 (10-vinyl), 5.65 (6-H).

Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.81.

3β-Acetoxy-19a-methylcholest-5-ene (3).—A solution of 1.0 g of **2b** in 100 ml of ethanol was hydrogenated with 200 mg of prereduced platinum oxide under atmospheric pressure at room temperature for 2 hr. After the catalyst was removed by filtration, the filtrate was concentrated *in vacuo*. Recrystallization of the residue from methanol gave 800 mg of **3**: mp 104–104.5°; $[\alpha]^{25}D$ −23° (c 1.108, $CHCl_3$); ir (KBr) 1745, 1242 cm^{-1}; nmr ($CDCl_3$) δ 0.91 (19a-CH_3, t, J = 3 cps), 2.03 (3-OAc), 5.6 (6-H).

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.26; H, 11.20.

3β-Acetoxy-5α,6β-dihydroxy-19a-methylcholestane (4).—A solution of 1.0 g of **3** in ether containing an excess amount of monoperphthalic acid was allowed to stand at room temperature overnight. The crude product (1.0 g) in 30 ml of acetone was treated with 1.5 ml of 1.5 *N* perchloric acid at room temperature overnight. The product was recrystallized from ether–*n*-hexane and 780 mg of **4** was obtained: mp 185°; $[\alpha]^{25}D$ −26° (*c* 0.631, $CHCl_3$); ir (KBr) 3540, 1720, 1255, 1045, 1035, 870 cm^{-1}.

Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.58; H, 11.00. Found: C, 75.52; H, 10.83.

(8) Y. Watanabe, Y. Mizuhara, and M. Shiota, *Chem. Commun.*, 984 (1969).

(9) All melting points are uncorrected. Nmr spectra were determined at 60 Mc, using $CDCl_3$ as solvent with tetramethylsilane as internal standard. Optical rotations were obtained in a 0.1-dm cell with a DIP-SL Nippon-Bunko polarimeter.

3β-Acetoxy-5β,6β-epoxy-19a-methylcholestane (5).—A suspension of 1.0 g of the diol 4 and 300 mg of *p*-toluenesulfonic acid in 50 ml of acetic anhydride was heated at 110° for 30 min. After cooling, the mixture was poured onto ice and extracted with ether. The ethereal extract was washed with sodium bicarbonate solution and water until neutral, dried, and evaporated *in vacuo*. The residue in 50 ml of ethanol was heated under reflux with 1.5 g of potassium hydroxide for 30 min, and the resulting epoxide was acetylated with pyridine and acetic anhydride. The crude product was chromatographed on alumina and elution with *n*-hexane–chlorcform afforded 850 mg of the β-oxide 5, which was recrystallized from methanol: mp 68°; $[\alpha]^{25}D$ −9° (*c* 0.439, $CHCl_3$); ir (KBr) 1745, 1239, 1040, 820 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (19a-CH_3, t, *J* = 4 cps), 2.05 (3-OAc), 2.95 (6-H).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.75; H, 11.06.

3β-Acetoxy-5α-bromo-6β-hydroxy-19a-methylcholestane (6).—A solution of 700 mg of 5 in 70 ml of acetic acid and 0.21 ml of 47% hydrobromic acid was allowed to stand at room temperature for 30 min. The solution was diluted with water and then extracted with ether. The ether layer was washed with sodium bicarbonate solution and water, dried, and evaporated *in vacuo* below 30°. The residue was recrystallized from *n*-hexane–ether, and 550 mg of 6 was obtained: mp 134–135° dec; ir (KBr) 3490, 1725, 1260, 1040, 760 cm^{-1}.

Anal. Calcd for $C_{30}H_{51}O_3Br$: C, 66.77; H, 9.53. Found: C, 66.57; H, 9.75.

Oxidation of 6 with Lead Tetraacetate.—A suspension of 2.0 g of lead tetraacetate and 950 mg of calcium carbonate in 40 ml of cyclohexane was stirred and heated to 80°; then 350 mg of 6 and 400 mg of iodine was added. The mixture was irradiated with a 500-W lamp under reflux with vigorous agitation for 45 min. After the solution had become colorless, it was filtered, and the filtrate was washed with a 10% sodium thiosulfate solution and water. After evaporation of the solvent, the residue was chromatographed on alumina, and elution with *n*-hexane–chloroform (40:1) gave 70 mg of 8. Further elution with the same solvent gave 159 mg of 7. The products were recrystallized from methanol.

3β-Acetoxy-5α-bromo-6β,19*R*-epoxy-19a-methylcholestane (7): mp 124–125°; $[\alpha]^{25}D$ −3.0° (*c* 0.330, $CHCl_3$); ir (KBr) 1743, 1235, 1035, 790 cm^{-1}; nmr ($CDCl_3$) δ 1.47 (19a-CH_3, d, *J* = 7.5 cps), 2.05 (3-OAc), 4.1 (6-H). 4.58 (19-H, q, *J* = 7.5 cps), 5.2 (3-H).

Anal. Calcd for $C_{30}H_{49}O_3Br$: C, 67.00; H, 9.19. Found: C, 67.05; H, 9.49.

3β-Acetoxy-5α-bromo-6β,19*S*-epoxy-19a-methylcholestane (8): mp 146°; $[\alpha]^{25}D$ +17° (*c* 0.215, $CHCl_3$); ir (KBr) 1747, 1238, 1040, 920, 790 cm^{-1}; nmr ($CDCl_3$) δ 1.44 (19a-CH_3, d, *J* = 7 cps), 2.02 (3-OAc), 4.05 (6-H), 4.4 (19-H, q, *J* = 7 cps), 5.35 (3-H).

Anal. Calcd for $C_{30}H_{49}O_3Br$: C, 67.00; H, 9.19. Found: C, 66.79; H, 8.89.

3β-Acetoxy-19*R*-hydroxy-19a-methylcholest-5-ene (9b).—A solution of 150 mg of 7 in 5 ml of acetic acid and 0.2 ml of water was treated with 900 mg of zinc dust at 50° under vigorous stirring. The usual work-up gave crude 9b and recrystallization from methanol afforded a pure sample (120 mg): mp 93–94°; $[\alpha]^{25}D$ −30° (*c* 0.266, $CHCl_3$); ir (KBr) 3520, 1745, 1240, 1035, 910 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (19a-CH_3, d, *J* = 7.5 cps), 2.00 (3-OAc), 4.2 (19-H, q, *J* = 7.5 cps), 4.5 (3-H), 5.6 (6-H).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.32; H, 10.85.

3β-Acetoxy-19*S*-hydroxy-19a-methylcholest-5-ene (10b).—Reduction of 60 mg of 8 in the same way followed by recrystallization from methanol gave 40 mg of pure 10b: mp 89°; $[\alpha]^{25}D$ −37° (*c* 0.784, $CHCl_3$); ir (KBr) 3510, 1740, 1245, 1040, 910 cm^{-1}; nmr ($CDCl_3$) δ 1.36 (19a-CH_3, d, *J* = 7 cps), 2.02 (3-OAc), 4.28 (19-H, q, *J* = 7 cps), 4.6 (3-H), 5.6 (6-H).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.24; H, 10.88.

3β-Acetoxy-19a-methyl-19-oxocholest-5-ene (11). Oxidation of 9b and 10b with Chromic Acid.—A solution of 125 mg of 9b in 10 ml of acetone was treated with 0.1 ml of 8 *N* chromic sulfuric acid solution at 0° for 30 min. Treatment in the usual way gave the 19-oxo compound 11, and its ir spectrum was identical with that of an authentic sample synthesized by another route and a mixture melting point was not depressed. Oxidation of 10b in the same way also gave the same 19-oxo compound: mp 127–128°; $[\alpha]^{25}D$ −115° (*c* 0.665, $CHCl_3$); ir (KBr); 1742, 1705, 1240 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3-OAc), 2.18 (10-acetyl), 5.8 (6-H).

Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.25.

Dehydration of 9b and 10b with Phosphorus Oxychloride.—A solution of 20 mg of 9b in 0.5 ml of pyridine was treated with 0.05 ml of phosphorous oxychloride at room temperature overnight. Recrystallization of the crude product (18 mg) gave the pure 19a-methylene compound 2, which was identical with an authentic sample prepared by the Wittig reaction. Dehydration of 10b yielded the same compound 2 as that of 9b.

Registry No.—2b, 24183-24-2; 3, 29751-52-8; 4, 29751-53-9; 5, 29751-54-0; 6, 29751-55-1; 7, 29875-95-4; 8, 29875-96-5; 9b, 29875-97-6; 10b, 29751-56-2; 11, 24177-47-7.

Stereochemistry of the Isolongifolene Ketone Epimers

L. K. LALA

International Flavors and Fragrances Research Laboratories, Union Beach, New Jersey 07735

Received January 7, 1971

Recently Dev[1] has reported that BF_3 etherate treatment of an isolongifolene epoxide[2] gives rise to a ketone to which he has assigned the stereochemistry as depicted in structure II. Epimerization of this ketone gives rise to a new ketone to which structure IV has been assigned. However, Eschinasi and coworkers[3] have assigned the opposite stereochemistry of these two ketones at the C-7 position. Described here is chemical evidence which supports Dev's assignment of the stereochemistry of these two epimeric ketones.

We have previously reported that acid treatment of isolongifolene epoxide I gave, among other products, rearranged alcohol III and ketone II.[4] Subsequent treatment of ketone II with base gave a more stable ketone IV. In order to establish the relative stereochemistry of these ketones at the C-7 position, the following approach was taken.

The lithium aluminum hydride reduction of ketone II gave alcohol V, which was refluxed with lead tetraacetate in benzene to give a cyclic ether VI in 60% yield. In contrast to this behavior, no detectable amount of cyclic ether was obtained by a similar lead tetraacetate treatment of alcohol VII which was obtained by the lithium aluminum hydride reduction of ketone IV (Scheme I).

When the stereochemistry of the hydroxyl group with regard to hydrogen at the C-7 position is cis, Dreiding models reveal that a cyclic ether cannot arise from VII; and, indeed, this was found to be the case. The possibility of the hydroxyl group having the opposite configuration is ruled out as Dreiding models indicate that a cyclic ether could be obtained from a compound with such structure. The assigned cis stereochemistry of the

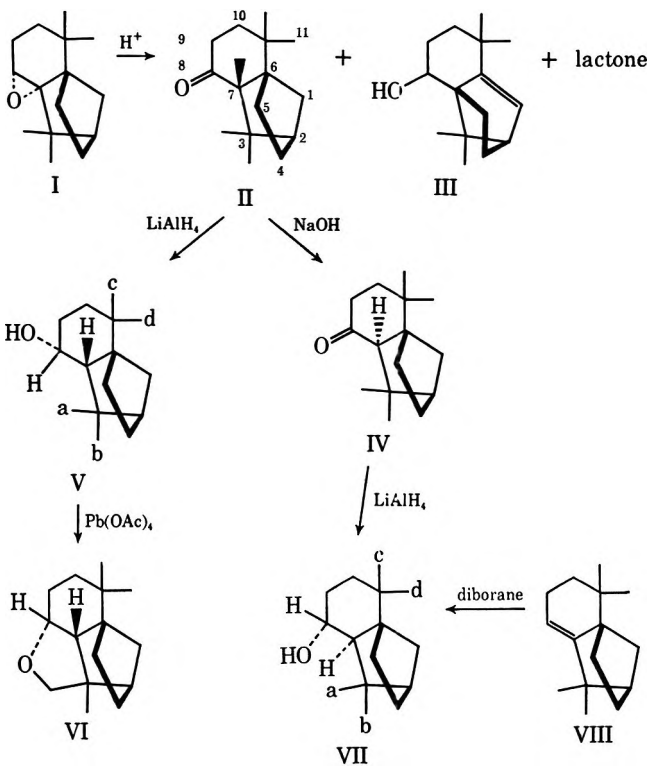
(1) R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron*, **26**, 621 (1970).

(2) R. Prahalad, R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron Lett.*, **8**, 417 (1964).

(3) E. H. Eschinasi, G. W. Shaffer, and A. P. Bartels, *ibid.*, **40**, 3523 (1970).

(4) L. K. Lala and J. B. Hall, *J. Org. Chem.*, **35**, 1172 (1970).

SCHEME I



alcohol VII is further supported by the fact that hydroboration[5] of the isolongifolene VIII gave a compound which was identical in all respects with alcohol VII, mp 124–126° (lit.[5] 122°).

The formation of VII by hydroboration could be attributed to the fact that diborane would preferably attack from the least hindered α side. The stereochemistry of the hydroxyl group at C-8 of alcohols V and VII is further supported by applying the nmr europium complexing technique described by Hinckley[6] and Williams.[7]

We conclude from these results that the more stable epimeric ketone has stereochemistry at C-7, as depicted in structure IV, and the less stable epimer has stereochemistry as shown in structure II. Thus the stereochemistry of the above two ketones and isolongifolene epoxide has been rightly assigned by Dev.[1]

Experimental Section[8]

Isolongifolene Alcohol V.—In a three-necked flask fitted with a condenser, stirrer, and addition funnel were placed 400 ml of dry tetrahydrofuran and 8.2 g (0.215 mol) of lithium aluminum hydride. A solution containing 91 g (0.41 mol) of the isolongifolene ketone II in 100 ml of dry tetrahydrofuran was added dropwise during 45 min to the above mixture. After the addition was over, the mixture was refluxed for 9 hr. The reaction mixture was cooled and 8 ml of water was added slowly followed by 8 ml of 15% sodium hydroxide followed by 24 ml of water. The crude mixture was filtered and the solvent was removed under vacuum. The crude oil was distilled to give a colorless oil: bp 114° (2 mm) (80% yield); infrared (Nujol) λ_{max} 2.94 (OH); nmr ($CDCl_3$) 0.93 $\left(6\text{ H, s, C}<^{CH_3}_{CH_3}\right)$, 1.02 (3 H, s, CCH_3), 1.12 (3 H, s, CCH_3), 1.2–1.73 (12 H, m, CH, CH_2), 4.15 (1 H, broad m, CHOH).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 10.98. Found: C, 81.58; H, 11.71.

Isolongifolene Cyclic Ether VI.—In a three-necked flask fitted with stirrer, thermometer, and reflux condenser were placed 11.0 g (0.025 mol) of lead tetraacetate, 5 g of calcium carbonate, and 185 ml of dry benzene. The mixture was refluxed for 1 hr and then 5.5 g (0.025 mol) of isolongifolene alcohol III was added and the mixture was refluxed for 22 hr. It was then cooled to 25°, 10 ml of ethylene glycol was added, and the mixture was heated to 80° for 1 hr. The mixture was then cooled, the solids were filtered off, and the filtrate was washed twice with 25 ml os 1% sodium hydroxide. The combined aqueous layers were extracted twice with ether and the organic layers were combined and dried over magnesium sulfate. The solvent was removed under vacuum. The crude product was distilled to give colorless liquid: bp 100° (0.2 mm) (60% yield); infrared (film) shows no hydroxyl band at 2.93 μ; nmr ($CDCl_3$) 0.95 (3 H, s, CCH_3), 0.99, 1.00 $\left(6\text{ H, s, C}<^{CH_3}_{CH_3}\right)$, 1.08–1.8 (11 H, m, CH_2, CH), 4.15–3.88 (3 H, m, $HCOCH_2$).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.48; H, 10.95.

Isolongifolene Alcohol VII.—The lithium aluminum hydride reduction of ketone IV, under the similar conditions as described for alcohol V, gave alcohol VII, mp 124–126°, as a major product in 60% yield. It was found to be identical in all respects with the one obtained by the hydroboration of isolongifolene (Table I).

TABLE I

NMR SPECTRAL DATA OF ALCOHOLS V AND VII COMPLEXES WITH $Eu(DPM)_3$[a]

	Alcohol V		Alcohol VII	
	Δ[Eu-$(DPM)_3$]	R, Å	Δ[Eu-$(DPM)_3$]	R, Å
(a) H_3C–C	2.06	2.5	2.27	3.0
(b) H_3C–C–	0.77	4.0	1.60	3.4
(c) H_3C C–	0.77	4.7	1.04	5.1
(d) CH_3 C–	0.60	4.80	0.64	5.4
HC–O–	4.86	1.35	6.06	1.35

[a] Log-log plot of Δ(Eu) *vs.* R (Å) gives best fit for the configurations assigned to the alcohols V and VII.

Registry No.—II, 29641-13-0; IV, 29461-14-1; V, 30469-89-7; VI, 30545-64-3; VII, 30469-90-0.

Acknowledgment.—The author wishes to express his thanks to Dr. W. I. Taylor for his continued interest and encouragement, to Professor G. Stork for his helpful discussions, and to M. Jacobs for the nmr data. The technical assistance of Mr. R. Santangelo is appreciated.

(5) P. Bani Bai, S. Y. Kamat, B. B. Ghatge, K. K. Chakravarti, and S. C. Battacharyya, *Tetrahedron*, **21**, 629 (1965).

(6) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(7) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, **7**, 422 (1970).

(8) All the nmr spectra were run on Varian HA-100 spectrometer. TMS was used as an internal standard. The C and H analyses were run by Schwarzkopf Microanalytical Laboratory, N. Y.

Selenomethionine, a Potential Catalytic Antioxidant in Biological Systems[1,2]

RODERICH WALTER* AND J. ROY

Department of Physiology, The Mount Sinai Medical and Graduate Schools of the City University of New York, New York, New York 10029

Received January 20, 1971

This report describes the first isolation and characterization of products resulting from the oxidation of sel-

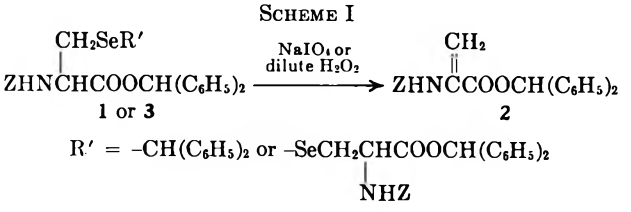
(1) This work was supported by U. S. Public Health Service Grants AM-13567 and AM-10080.

(2) The following abbreviations have been adopted: Z = $C_6H_5CH_2$-OCO; AcOH = acetic acid; MeOH = methanol; EtOAc = ethyl acetate.

enium-containing α-amino acids which possess propionic acid and butyric acid skeletons. Specifically, we investigated the oxidation of selenocysteine, selenocystine, and selenomethionine derivatives by sodium metaperiodate[3] and dilute hydrogen peroxide. Such a study seemed appropriate in view of the conclusion by Caldwell and Tappel[4] that selenocystine is oxidized by hydroperoxides to yield either alanine and metallic selenium or selenocystine diselenoxide, selenocysteine seleninic acid, selenocysteic acid, and alanine and selenate as final products; it was suggested that the conversion of selenocystine to selenocystine diselenoxide is reversible and that selenocystine may express its catalytic antioxidative reactivity in biological systems.

When *N*-carbobenzoxy-*Se*-diphenylmethyl-L-selenocysteine diphenylmethyl ester (1) was treated with a slight molar excess of sodium metaperiodate at ice-bath temperature, only starting material was recovered but not the expected selenoxide of 1. Repetition of the experiment at room temperature likewise did not result in the selenoxide of 1 but rather in the diphenylmethyl ester of *N*-carbobenzoxydehydroalanine (2) (Scheme I). Similar results were obtained when 1 was oxidized

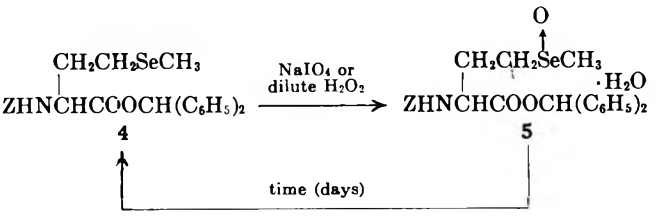
SCHEME I



with an excess of hydrogen peroxide, although the oxidation reaction proceeds even at lower temperature than when sodium metaperiodate was the oxidizing agent. In order to determine whether the diphenylmethyl group alkylating the selenium moiety has any significant influence on dehydroalanine formation, bis(diphenylmethyl) bis(*N*-carbobenzoxy)-L-selenocystinate (3) was oxidized with hydrogen peroxide at room temperature. Again the dehydroalanine derivative 2 was the only product. At this point it was concluded that the selenoxide of the β-selenopropionic acid derivative had been formed but that the electron-withdrawing power of the Se → O moiety is so strong as to evoke an instantaneous β elimination.

To test this contention we next subjected a selenomethionine derivative to a similar oxidation procedure, since a Se → O moiety attached to the γ carbon of an α-amino acid should have a greatly reduced tendency for β elimination. Reaction of *N*-carbobenzoxy-DL-selenomethionine diphenylmethyl ester (4) with either sodium metaperiodate or hydrogen peroxide gave the corresponding selenoxide (5)[5] in practically quantitative yield (Scheme II). Significantly, compound 5 in the dry state or in solution slowly lost the oxygen

SCHEME II



which is attached to the selenium moiety, restoring compound 4. In acetone this deoxidation proceeds particularly smoothly in terms of purity of product. The mechanism of transformations of 5 to 4 is certainly of interest and warrants further study.

In summary, the intrinsic chemical lability of selenocystine and selenocysteine militates against their role as catalytic antioxidants, while selenomethionine has the potential for such a function in biological systems.

Experimental Section[7]

Oxidation of *N*-Carbobenzoxy-*Se*-diphenylmethyl-L-selenocysteine Diphenylmethyl Ester (1). A.—*N*-Carbobenzoxy-*Se*-diphenylmethyl-L-selenocysteine diphenylmethyl ester[8] (200 mg) was dissolved in acetone (10 ml). To the stirred solution, cooled in an ice bath, 30% H_2O_2 (0.5 ml) was added. After 45 min of continued stirring at 4° the reaction mixture was diluted with ice-cold water (50 ml) and extracted with EtOAc. The organic layer was separated, washed with water (three 25-ml portions), dried, and concentrated *in vacuo*. Examination of the resultant oil on tlc with C_6H_6–EtOAc (9:1, v/v) as solvent system revealed two compounds when developed with tolidine/KI following chlorination of the amides.[9] The oil was chromatographed on a silica gel column; the two compounds were eluted with *n*-hexane–C_6H_6 (1:3, v/v) (compound **a**) and C_6H_6 (compound **b**), respectively. Compound **a** was crystallized from a mixture of EtOAc–*n*-hexane, yield 75 mg (61.5%), mp 78.5–79.5°. Ir and nmr revealed the compound **a** as the diphenylmethyl ester of *N*-carbobenzoxydehydroalanine (2): ir 3435 (NH), 1745 (ester), and 1700 cm^{-1} (urethane); nmr τ 2.67 (15, aromatic), 3.05 (1, ester CH), 3.67 (1) and 4.0 (1) (methylene), 4.85 (2) (benzyl CH_2).

Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.4; H, 5.46; N, 3.62. Found: C, 74.7; H, 5.48; N, 3.61.

Compound **b**, crystallized from MeOH (80 mg, 40%), was identified as starting material by melting point, mixture melting point, and ir. If the reaction mixture is kept at room temperature for 15 min in the presence of hydrogen peroxide prior to work-up, the starting material is completely converted to 2.

B.—To another sample of 1 (210 mg) dissolved in ice-cold acetone (10 ml), sodium metaperiodate [78 mg (1.1 *M*) in 3 ml of water] was added. The reaction mixture was stirred in an ice bath for 15 min and then at room temperature for 6 hr. Isolation of products yielded 1 and 2 in approximately equal amounts.

Oxidation of Bis(diphenylmethyl) Bis(*N*-carbobenzoxy)-L-selenocystinate (3).—To a stirred solution of ice-cold acetone

(3) M. Cinquini, S. Colonna, and R. Giovini, *Chem. Ind.* (*London*), 1737 (1969).

(4) K. A. Caldwell and A. L. Tappel, *Biochemistry*, **3**, 1643 (1964); A. L. Tappel, *Fed. Proc.*, **24**, 73 (1965).

(5) The ir of **5** (see Experimental Section) exhibits the characteristic Se → O resonance and in the nmr the methyl group is shifted downfield by 0.52 ppm, as would be expected from the electron-withdrawing character of the Se → O moiety. Elementary analysis of the product would correspond to the structure being a selenone or the monohydrate of a selenoxide. A broad absorption in the ir in the region characteristic for hydroxyl groups is indicative of the selenoxide monohydrate structure of the oxidized product. Aliphatic sulfoxides similarly absorb 1 mol of water.[6]

(6) D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

(7) All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer 457 infrared spectrophotometer in pressed disks of KBr at a concentration of 0.3% for solids and in films between NaCl windows for liquids. Nmr spectra were recorded on a Varian T-60 nmr spectrometer in $CDCl_3$. Amino acids were chromatographed on a Beckman 120C amino acid analyzer using a Beckman Custom Research Resin PA-28 packed in a 56 × 0.9 cm column. The buffer flow rate was set at 68.0 ml/hr, the ninhydrin flow rate at 34 ml/hr; temperature was maintained at 55°. The elementary analyses were carried out by Galbraith Laboratories Knoxville, Tenn. The plates were coated with silica gel.

(8) J. Roy, W. Gordon, I. L. Schwartz, and R. Walter, *J. Org. Chem.*, **35**, 510 (1970).

(9) H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).

(5 ml) containing 50 mg of **3**, 30% H_2O_2 (0.2 ml) was added. Stirring was continued in ice bath for 30 min and then at room temperature for 1 hr. Isolation of product by the usual procedure gave **2** in almost quantitative yield.

***N*-Carbobenzoxy-DL-selenomethionine.**—DL-Selenomethionine (0.5 g) was carbobenzoxylated as described for its sulfur analog.[10] The product crystallized from EtOAc–*n*-hexane: yield 0.5 g (60%); mp 114–116°; nmr τ 0.67 (carboxyl H), 2.66 (aromatic), 4.35–4.75 (amide), 4.88 (benzyl CH_2), 5.25–5.78 (C α H), 7.2–7.98 (C β H_2 and C γ H_2), 8.04 (methyl).

Anal. Calcd for $C_{13}H_{17}NO_4Se$: C, 47.3; H, 5.19; N, 4.24. Found: C, 47.4; H, 5.30; N, 4.25.

***N*-Carbobenzoxy-DL-selenomethionine Diphenylmethyl Ester (4).**—*N*-Carbobenzoxy-DL-selenomethionine (0.66 g) was dissolved in EtOAc (50 ml); to the ice-cold, stirred solution diphenyldiazomethane[11] (0.35 g, 0.9 *M*) was added. Stirring was continued while the reaction mixture was allowed to warm to room temperature. After several hours the solution was washed with 5% $NaHCO_3$ (three 25-ml portions) and water (three 25-ml portions). Following drying over Na_2SO_4, removal of solvent under vacuum gave an oil (0.90 g) which was purified by chromatography on a silica gel column. The product was eluted with C_6H_6–EtOAc (98:2, v/v): yield 0.8 g (91%); nmr τ 2.7 (aromatic), 3.12 (ester CH), 4.4–4.75 (amide), 4.94 (benzyl CH_2), 5.2–5.66 (C α H), 7.35–8.0 (C β H_2 and C γ H_2), 8.17 (methyl).

Anal. Calcd for $C_{26}H_{27}NO_4Se$: C, 62.9; H, 5.48; N, 2.82. Found: C, 62.9; H, 5.60; N, 2.72.

Oxidation of *N*-Carbobenzoxy-DL-selenomethionine Diphenylmethyl Ester. A.—To an ice-cold, stirred solution of acetone (10 ml) containing **4** (265 mg), sodium metaperiodate (143 mg, 1.25 *M*) dissolved in water (5 ml) was added. After stirring at ice-bath temperature for 30 min and at room temperature for 2 hr the aqueous phase was extracted with EtOAc. The organic layer was washed with water saturated with NaCl (three 25-ml portions), dried (Na_2SO_4), and concentrated under vacuum. *N*-Carbobenzoxy-DL-selenomethionine selenoxide diphenylmethyl ester monohydrate (**5**) was obtained as an oil (270 mg, 95% yield), which was examined for purity after chromatography in the solvent systems $CHCl_3$–MeOH (6:1, v/v) and C_6H_6–EtOAc (25:1, v/v) by both uv and Zahn reagent: ir 3500–3100 (broad OH and NH), 810 cm^{-1} (selenoxide);[6,12,13] nmr τ 2.68 (aromatic), 3.1 (ester CH), 4.95 (benzyl CH_2), 5.35–5.75 (C α H), 7.10–8.0 (C β H_2 and C γ H_2), 7.65 (methyl).

Anal. Calcd for $C_{26}H_{29}NO_6Se$: C, 58.9; H, 5.51; N, 2.64. Found: C, 59.1; H, 5.12; N, 2.61.

B.—Another aliquot of **4** was allowed to react with 0.2 ml of 30% hydrogen peroxide. After stirring the mixture in the ice bath for 30 min, the oxide **5** was isolated as product in nearly quantitative yield.

Conversion of the Oxide of *N*-Carbobenzoxy-DL-selenomethionine Diphenylmethyl Ester to *N*-Carbobenzoxy-DL-selenomethionine Diphenylmethyl Ester.—The selenoxide **5** (270 mg) was dissolved in acetone (10 ml) and the solution was stored with exclusion of light at room temperature. Aliquots of the solution were examined by tlc from time to time in solvent systems $CHCl_3$–MeOH (6:1, v/v) and C_6H_6–EtOAc (25:1, v/v). After 7 days the selenoxide had totally disappeared and the reaction mixture contained essentially one compound. The acetone was removed under vacuum and the residue was purified by chromatography on a silica gel column. Elution with C_6H_6–EtOAc (99:1, v/v) yielded 175 mg (69%) of *N*-carbobenzoxy-DL-selenomethionine diphenylmethyl ester **4**, which was identified by superimposable ir, nmr, and also by elementary analysis.

Anal. Calcd for $C_{26}H_{27}NO_4Se$: C, 62.9; H, 5.48; N, 2.82. Found: C, 63.0; H, 5.55; N, 2.74.

A portion of the above compound (5 mg), dissolved in anhydrous AcOH (0.3 ml), was decarbobenzoxylated and deesterified by treatment with 0.3 ml of 4 *N* HBr in AcOH. After 20 min the reaction mixture was evaporated to dryness. The resulting residue was dissolved in 10 ml of citrate buffer (pH 2.2). A 0.25-ml aliquot was analyzed for ninhydrin-active material by amino acid analysis as described.[14] Two ninhydrin-active components were detected, one corresponding to selenomethionine[14] while the other (emerging at 297 ml of buffer after the start of the chromatogram) was identified as selenohomocystine by comparison with authentic DL-selenohomocystine. The fact that selenohomocystine has been identified as one of the ninhydrin-active components leads to the conclusion that selenomethionine (or one of its intermediates) is partially demethylated during the acid treatment and subsequently oxidized to the diselenide.

Registry No.—**2**, 29751-58-4; **4**, 29875-98-7; **5**, 29751-59-5; DL-selenomethionine, 2578-28-1; *N*-carbobenzoxy-DL-selenomethionine, 29751-61-9.

Acknowledgment.—The authors are thankful to Mr. D. H. Schlesinger for performing the amino acid analyses. We are also grateful to Dr. D. F. Petersen, Los Alamos Scientific Laboratory, for kindly supplying us with a sample of DL-selenohomocystine and to Dr. K. D. Gibbons, Rockefeller University, for 220-MHz nmr spectra and discussion.

(10) K. Hofmann, A. Jöhl, A. E. Furlenmeier, and H. Kappeler, *J. Amer. Chem. Soc.*, **79**, 1636 (1957).

(11) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(12) K. A. Jensen and V. Krishnan, *Acta Chem. Scand.*, **21**, 1988 (1967).

(13) R. Steudel, *Z. Naturforsch., B*, **25**, 645 (1970).

(14) R. Walter, D. H. Schlesinger, and I. L. Schwartz, *Anal. Biochem.*, **27**, 231 (1969).

Microbiological Transformation of 2,2,4-Trimethyl-7-*tert*-octyl-6-hydroxychroman

J. R. SCHAEFFER* AND C. T. GOODHUE

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received December 28, 1970

Recent studies on the microbiological transformation of 6-hydroxychromans yielded a mixed culture of soil microorganisms that was able to convert 2,2,4-trimethyl-7-*tert*-octyl-6-hydroxychroman to an *o*-quinone and an *o*-nitrophenol.

We have found that biotransformation of **1** has produced **2** in 3.5% yield and **3** in 5.1% yield (Scheme I). Also a trace amount of product with a molecular weight of 606 was isolated by glc. Attempts to isolate a larger quantity of the compound for structure determination were unsuccessful. A molecular weight of 606 suggests that the compound is a dimer of **1**. Support for this conclusion is found in the reported oxidative dimerization of the 6-hydroxychroman ring of α-tocopherol.[1]

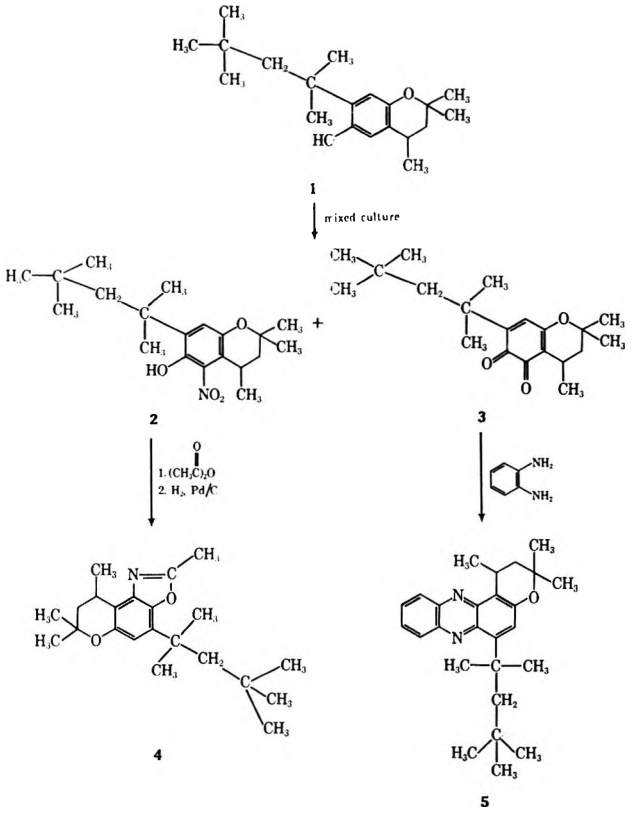
A single aromatic proton was observed in the nmr spectrum of **2** which suggested that either the 5- or 8-position proton had been replaced. Elemental analytical and mass spectral data were in agreement with the molecular formula $C_{20}H_{31}NO_4$. Confirmation of the presence of a nitro group was obtained by nitrosation of **1** followed by a nitric acid oxidation of the nitroso group.[2] That the nitro group is in the 5 position was shown by reductive cyclization of the acetate of **2** to benzoxazole **4**. The physical properties of the nitrochromanol obtained by chemical synthesis are identical with those of the fermentation product.

The nmr spectrum of **3** has a single vinylic proton and no hydroxyl group absorption, which suggests disruption of the aromatic character of the benzene ring in **1**. A molecular formula, $C_{20}H_{30}O_3$, is consistent with the

(1) W. A. Skinner and P. Alaupovic, *J. Org. Chem.*, **28**, 2854 (1963).

(2) C. F. Koelsch, *J. Amer. Chem. Soc.*, **66**, 2019 (1944).

SCHEME I



elemental analytical and mass spectral data. Oxidation of the 6-hydroxychroman ring of α-tocopherol to a quinone has been reported.[3] Nitric acid oxidation of **1** yielded a quinone with physical properties identical with fermentation product **3**. Confirmation of an *o*-quinone structure was obtained by synthesis of phenazine **5** from **3**.

It was not possible to isolate pure cultures that transformed **1**, because no solid medium containing chromanol that would selectively support growth of the active organisms could be found. Plating of the mixed culture onto nutrient agar (1% glucose, 1% yeast extract) separated about 20 different colonies, but none of these organisms was able to transform the chromanol. Consequently, we were forced to maintain the active mixed culture by serial transfer in a liquid medium.

Even though the transformation reactions are rather slow, control experiments indicated that no significant reactions occur in the absence of the mixed culture. It seems probable that the first reaction involves the hydroxylation of chromanol **1**, since this type of reaction is a common method of aromatic hydrocarbon oxidation in microorganisms.[4]

Experimental Section[5]

Isolation of Culture.—An active mixed culture was obtained by percolating soil with a medium containing 0.5% of chromanol **1**, 1% $(NH_4)_2SO_4$, 1% K_2HPO_4, and mineral salt solution (10 ml/l).[6] The percolator was run for 2 weeks at room temperature. During this time the percolation medium became cloudy and orange-yellow insoluble material appeared. A 5-ml portion of this culture was transferred to an erlenmeyer flask containing 25 ml of the percolation medium plus 0.1% yeast extract. Just prior to inoculation chromanol **1** was added to the sterile medium as a fine powder. This first transfer was incubated at 30° with shaking on a rotary shaker at 400 rpm for 28 days. During this time the culture medium became deep orange and the insoluble material turned red. This active culture was maintained by serial transfer at monthly intervals in the same medium.

Microbiological Production of 2 and 3.—Cultures were grown in 2.8-l. wide-mouthed indented Fernbach flasks that contained 1 l. of percolation medium with 0.5% chromanol **1**, 0.1% yeast extract, and 0.05% Tween 80. Each flask was inoculated with 100 ml of an active culture grown in the same medium until it became deep orange. The Fernbach flask cultures were incubated at 30° on a rotary shaker at 200 rpm for approximately 30 days. Transformation products were obtained by extraction as described below.

Control Fermentations.—These experiments were performed in Fernbach flasks containing 1 l. of percolation medium (without chromanol **1**) for the basic mineral medium. Additions were made as follows: flask A, 500 mg of chromanol **1**; flask B, 500 mg of chromanol **1**; flask C, 500 mg of chromanol **1** and 200 mg of o-quinone **3**; flask D, 200 mg of *o*-quinone **3**. Only flask A was inoculated with 150 ml of an active culture. All flasks were incubated together on a shaker in the usual manner for 11 days. The contents of each flask then was analyzed by thin layer chromatography of chloroform extracts.[7] Flask A contained compounds **1**, **2**, and **3** and a trace of an unknown. Flask B contained only **1** and traces of the unknown (R_f value 0.73 in system described in footnote 7). Flask C contained **1** and **3** and traces of the unknown. Flask D contained only **3**.

Isolation of Products from 2,2,4-Trimethyl-7-*tert*-octyl-6-hydroxychroman (1) Fermentation.—The fermentation broth (2.4 l.) was extracted with chloroform. The chloroform-extracted broth was then continuously extracted with ether for 48 hr. The chloroform extract was dried and concentrated to an oil and then it was chromatographed on 300 g of silica. Elution was carried out with hexane–chloroform (95:5, then 85:15). Rechromatography of the three main eluate fractions, each on 60 g of silica, eluting with hexane–chloroform (95:5), furnished 0.34 g of product. Chromatography of the ether extract in the manner described above yielded an additional 0.14 g of product. The total yield of pure **2** was 0.48 g (3.5%): mp 81–82°; mass spectrum *m/e* 349; $\tau_{tms}^{CDCl_3}$ 5.2 (s, 1, OH), 3.0 (s, 1, aromatic).

Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.7; H, 9.0; N, 4.0; mol wt, 349.4. Found: C, 68.9; H, 8.8; N, 3.9; mol wt, 341.

Crude **3** obtained along with pure **2** in the manner described above was further purified by chromatography on silica. Elution was carried out with increasing concentrations of chloroform in hexane.[8] The yield of **3** was 0.63 g (5.1%): mp 92–94°; mass spectrum *m/e* 318; $\tau_{tms}^{CDCl_3}$ 3.5 (s, 1, quinone H).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5; mol wt, 318.4. Found: C, 75.1; H, 9.3; mol wt, 313.

Preparation of 2,2,4-Trimethyl-5-nitro-7-*tert*-octyl-6-hydroxychroman (2).—2,2,4-Trimethyl-7-*tert*-octyl-6-hydroxychroman

(3) P. D. Boyer, *J. Amer. Chem. Soc.*, **73**, 733 (1951).

(4) D. T. Gibson, *Science*, **161**, 1093 (1968).

(5) Melting points are uncorrected. Molecular weights were obtained in acetone by the ebullometric method. All evaporations were carried out under reduced pressure. The drying agent was sodium sulfate. Yeast extract was obtained from Difco Laboratories, silica gel G from Brinkmann Instruments, and all other chemicals were obtained from Eastman Organic Chemicals. The soil percolator was obtained from Belco Glass Co. The nmr spectra were determined with a Varian Model A-60 spectrometer, tetramethylsilane being used as an internal standard. The mass spectra were determined on a 60° sector-type, single-focusing instrument equipped with an all-glass heated inlet system operated at 235°, a modified design of the system described by Caldecourt [V. J. Caldecourt, *Anal. Chem.*, **27**, 1670 (1955)].

(6) The mineral salt solution was prepared by dissolving 0.25 g of $MgSO_4 \cdot 7H_2O$, 0.17 g of $MnSO_4 \cdot 7H_2O$, 0.028 g of $FeSO_4 \cdot 7H_2O$, 0.006 g of NaCl, 0.001 g of $CaCl_2 \cdot 2H_2O$, and 0.006 g of $ZnSO_4 \cdot 7H_2O$ in 1 l. of 0.1 *N* HCl.

(7) Thin layer chromatography of compounds **1**, **2**, and **3** was carried out on Eastman Chromagram silica gel 6061. The developing solvent was hexane–chloroform (95:5); rhodamine G was the indicator. The following R_f values were obtained: **1**, R_f 0.30; **2**, R_f 0.92; **3**, R_f 0.11.

(8) A purple band was observed on the column during purification of **3**. Silica was extruded from the column. The band was cut out and eluted with chloroform. Examination of a peak at 322° on an F & M Model 810 gas chromatograph (Se-30, He flow 30 ml/min program 100–360° at 15°/min) by mass spectrometry indicated a mass of 606 amu.

(1) (10.0 g, 0.033 mol) was dissolved in 250 ml of methanol. The solution was cooled to 5° and 70 ml of glacial acetic acid was added. Sodium nitrite (20 g, 0.29 mol) dissolved in 200 ml of water was added to the stirred solution in several portions over a period of 5 min, the temperature of the reaction mixture being maintained below 10° during the addition. The reaction mixture was stirred for 15 min and then poured onto ice. The product was extracted into ligroin. The extract was evaporated to a red oil and then dissolved in 350 ml of methanol. To the stirred solution, 20 ml of concentrated nitric acid was added in five equal portions. After the reaction mixture had been stirred for 1 hr, it was poured onto water and extracted with ether. The ether extract was dried and evaporated. The crude product was chromatographed on 170 g of silica. Elution was carried out with hexane–chloroform (95:5, then 90:10). The red solid product weighed 4.5 g (39.4%), mp 82–84°, mmp (with fermentation sample) 82–84°.

Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.7; H, 9.0; N, 4.0; mol wt, 349.4. Found: C, 68.4; H, 9.1; N, 4.0; mol wt, 341.

Preparation of 2,2,4-Trimethyl-7-*tert*-octylchroman-4,6-dione (3).—To a stirred solution containing 10 g (0.033 mol) of **1** in 50 ml of methanol was added 30 ml of nitric acid in six equal portions. The reaction mixture was stirred for 1 hr, poured onto 500 ml of water, and extracted with ether. The ether extract was dried and evaporated to red oil. The oil was chromatographed on 170 g of silica. Elution was carried out with increasing concentrations of chloroform in hexane. The red solid product weighed 8.7 g (83%), mp 92–94°, mmp (with fermentation product) 92–94°.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5; mol wt, 318.4. Found: C, 75.7; H, 9.5; mol wt, 312.

8,9-Dihydro-2,7,7,9-tetramethyl-4-*tert*-octyl-7*H*-pyrano[3,2-*e*]benzoxazole (4).—Compound **2** (0.46 g, 0.0013 mol) was dissolved in 9 ml of a 1:1 mixture of acetic anhydride and pyridine. The reaction mixture was stirred 2.5 hr at 55° and then poured onto ice water. The diluted reaction mixture was extracted with ether and the extract dried and evaporated to an oil. The oil was dissolved in 100 ml of ethanol and 0.2 g of 15% palladium on charcoal was added. The mixture was hydrogenated at 500 psi for 4–5 hr (room temperature). After removal of the catalyst and evaporation of the solvent, **4** was isolated on a Varian Aerograph Autoprep gas chromatograph using a $^3/_8$ in. by 20 ft aluminum column of 10% Se-30, 250° column temperature, and 150-ml/min He flow. The product has a 9-min retention time. Compound **4**, an off-white solid, weighed 0.078 g (22%): mp 84–87°; $\tau_{tms}^{CDCl_3}$ 7.4 (s, 3, $CH_3C(O)=N$), 3.4 (s, 1, aromatic).

Anal. Calcd for $C_{22}H_{33}NO_2$: C, 77.1; H, 9.7; N, 4.1; mol wt, 343.5. Found: C, 76.9; H, 9.4; N, 4.4; mol wt, 329.

2,3-Dihydro-1,3,3-trimethyl-6-*tert*-octyl-1*H*-pyrano[3,2-*a*]phenazine (5).—In a mixture of 75 ml of glacial acetic acid and 300 ml of toluene were dissolved 3.0 g (0.0093 mol) of **3** and 2.0 g (0.0186 mol) of *o*-phenylenediamine.[9] During a 26-hr reflux, 2.2 ml of water was collected. The solvent mixture was evaporated to 50 ml. The concentrated solution was dissolved in ether and the resulting solution washed with water. The combined water wash was neutralized with sodium bicarbonate and extracted with ether. The ether extracts were combined, washed with a saturated sodium bicarbonate solution and then with water, dried, and evaporated to an oil. The oil was chromatographed on 75 g of silica. Elution was carried out with increasing concentrations of chloroform in hexane. The yellow solid product weighed 0.37 g (10.2%): mp 48–50°; $\tau_{tms}^{CDCl_3}$ 2.8 (s, 4, C=CHC=C), 2.9 (symmetrical multiplet around 2.1, 4, aromatic).

Anal. Calcd for $C_{26}H_{34}N_2O$: C, 80.0; H, 8.8; N, 7.2; mol wt, 390.6. Found: C, 80.0; H, 8.5; N, 7.2; mol wt, 375.

Registry No.—**1**, 18403-59-3; **2**, 30469-74-0; **3**, 30469-75-1; **4**, 30469-76-2; **5**, 30469-77-3.

Acknowledgment.—We wish to thank Drs. M. H. Stern and T. H. Regan for their advice and suggestions, Mr. D. Maier for interpretation of the mass spectra, and Mr. R. E. Stevens, Mr. H. A. Risley, and Mr. R. E. Sceusa for technical assistance.

(9) V. L. Frampton, W. A. Skinner, Jr., and P. S. Bailey, *J. Amer. Chem. Soc.*, **76**, 282 (1954).

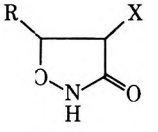
The Conversion of Hydroxamic Acids to *N,O*-Diacylhydroxylamines

EDWARD E. SMISSMAN,* NORMAN A. DAHLE,[1] AND VICTOR D. WARNER[1]

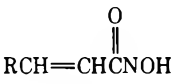
Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

Received November 27, 1970

As an approach to the synthesis of substituted 3-isoxazolidones (**1**), it was predicted that the treatment of α,β-unsaturated hydroxamic acids (**2**) with electrophilic reagents would cause a cyclization to the desired compounds. This reaction would be analogous to the halolactonization reactions of β,γ-unsaturated acids.[2-4]



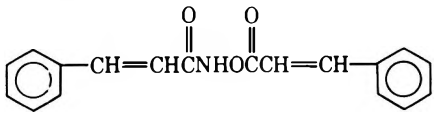
1



2

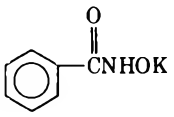
3, R = C_6H_5

Cinnamohydroxamic acid **3** was the initial compound with which this reaction was attempted. A suspension of **3** in sodium bicarbonate was treated with potassium triiodide; however, the product isolated was not the expected 3-isoxazolidone but rather *N,O*-dicinnamoylhydroxylamine (**4**). In order to determine if this is a general reaction of hydroxamic acids, potassium

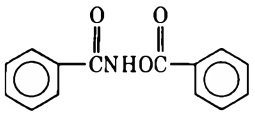


4

benzohydroxamate (**5**) was treated under the same conditions and was found to be converted to *N,O*-dibenzoylhydroxylamine (**6**). When this same reaction

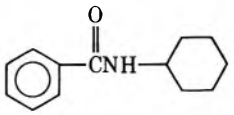


5



6

was repeated in the presence of cyclohexylamine, *N*-cyclohexylbenzamide (**7**) was obtained. Hydroxamic acids are readily converted to the corresponding carboxylic acids and nitrogen or nitrous oxide by such reagents as bromine water and aqueous periodic acids.[5,6] On the basis of these observations and of the products obtained, a plausible mechanistic interpretation of this reaction is as follows.



7

(1) Taken in part from the theses presented by N. A. Dahle, 1965, and V. D. Warner, Sept 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

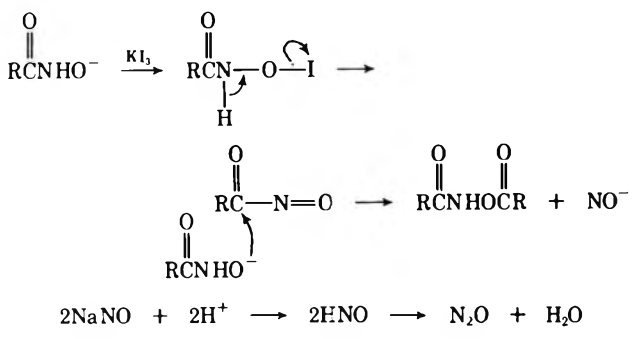
(2) H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

(3) H. Hoyagi, M. Ohno, N. Izumiya, and B. Witkop, *ibid.*, **29**, 1382 (1964).

(4) M. F. Ansell and M. H. Palmer, *Quart. Rev., Chem. Soc.*, **18**, 211 (1964).

(5) I. DePaolini, *Gazz. Chim. Ital.*, **56**, 757 (1926).

(6) J. E. Rowe and A. D. Ward, *Aust. J. Chem.*, **21**, 2761 (1968).



$$2NaNO + 2H^+ \longrightarrow 2HNO \longrightarrow N_2O + H_2O$$

Experimental Section[7]

Cinnamohydroxamic Acid (3).—This compound was prepared in 47% yield by the method of Jones and Mason.[8]

N,O-**Dicinnamoylhydroxylamine (4).**—To a stirred suspension of cinnamohydroxamic acid (**3**) (3.00 g, 0.019 mol) in 100 ml of 0.5 *M* $NaHCO_3$ was added KI (20.0 g, 0.12 mol) and I_2 (10.2 g, 0.04 mol) in 100 ml of H_2O. The reaction mixture was stirred at 25° for 9 hr and extracted with $CHCl_3$ (three 50-ml portions). The combined $CHCl_3$ extracts were washed with 20% $Na_2S_2O_3$ (two 50-ml portions) and dried (Na_2SO_4), and the solvent was removed. The residue was recrystallized (MeOH) to yield 0.93 g (33%) of **4**, mp 161–162°.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.78; H, 5.23; N, 4.78. Found: C, 74.18; H, 5.23; N, 4.78.

An authentic sample of *N,O*-dicinnamoylhydroxylamine was prepared by treating cinnamohydroxamic acid with cinnamoyl chloride[9]. Its spectra were identical with those of **4**.

Dibenzoylhydroxylamine (6).—This compound was prepared by the same method as *N,O*-dicinnamoylhydroxylamine (**4**, 44%) and was found to be identical with an authentic sample prepared by the method of Renfrow and Hauser.[9]

N-**Cyclohexylbenzamide (8).**—To a solution of benzohydroxamic acid (**7**) (2.75 g, 0.020 mol) in 25 ml of pyridine was added I_2 (2.53 g, 0.010 mol) and KI (4.98 g, 0.030 mol) in 10 ml of H_2O. To this reaction mixture was added 5 ml of cyclohexylamine followed by 200 ml of H_2O. After cooling, the insoluble material was removed by filtration and recrystallized (EtOH) to give 0.32 g (7.8%) of **8**, mp 142–147° (lit.[10] 148°), whose spectra were identical with those of an authentic sample.

Registry No.—**4**, 30345-94-9; **8**, 1759-68-8.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants GM-09254 and GM-01341.

(7) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60 and A-60A spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N, analyzer, University of Kansas.

(8) L. W. Jones and J. P. Mason, *J. Amer. Chem. Soc.*, **49**, 2534 (1927).

(9) W. B. Renfrow, Jr., and C. R. Hauser, *ibid.*, **59**, 2308 (1937).

(10) I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1953, p 640.

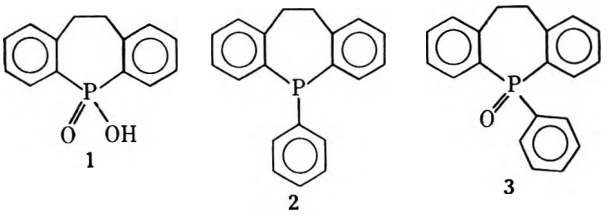
The Preparation and Properties of a Seven-Membered Heterocyclic Phosphinic Acid[1]

J. LAWRENCE SUGGS AND LEON D. FREEDMAN*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607

Received January 27, 1971

Although numerous heterocyclic derivatives of phosphorus have been prepared in recent years,[2] there are still relatively few phosphinic acids in which the phosphorus atom is a member of a ring system. Thus, a recent survey[1] indicates that only 38 such phosphinic acids have been described in the chemical literature; in these compounds the phosphorus atom was a member of a four-, five-, or six-membered ring. The present paper is concerned with the preparation and properties of the seven-membered heterocyclic phosphinic acid **1**.



Since the tertiary phosphine **2** and the phosphine oxide **3** have been previously reported,[3] we used these compounds as precursors to the desired phosphinic acid **1**. The fusion of a tertiary phosphine oxide with sodium hydroxide leads to cleavage of a carbon–phosphorus bond and the formation of the sodium salt of a phosphinic acid (eq 1).[4] When phosphine oxides of the

$$R_3PO + NaOH \longrightarrow R_2PO_2Na + RH \qquad (1)$$

type $R_2R'PO$ are used, the group that is preferentially cleaved is the one that can form the more stable carbanion. This rule is usually followed when the phosphorus atom is a member of a ring system;[5] in two cases,[5a,c] however, a ring carbon–phosphorus bond was cleaved even though this meant formation of the less stable carbanion. We have now found that reaction of the phosphine oxide **3** with fused sodium hydroxide obeyed the general rule and led to a 92% yield of **1**; 7% of the starting material **3** was also isolated from the reaction mixture.

The reaction of tertiary phosphines with lithium (or other alkali metal) results in the formation of a phosphide ion and a carbanion (eq 2).[4b,6] Hydrolysis,

$$R_3P + 2Li \rightarrow R_2PLi + RLi \qquad (2)$$

oxidation, and acidification of the reaction mixture readily gives a phosphinic acid. The direction of cleavage for unsymmetrical phosphines has been shown to be thermodynamically controlled; *i.e.*, it is determined by the stability of the products.[6c,7] When a heterocyclic tertiary phosphine reacts with lithium, cleavage of the ring would result in the formation of a dianion. For a variety of phosphole derivatives, this pathway has proved to be of significantly higher energy than cleavage of the exocyclic carbon–phosphorus bond; in these cases, therefore, no cleavage of the heterocyclic ring was ob-

(1) Abstracted from the M.S. Thesis of J. L. Suggs, North Carolina State University, Raleigh, N. C., 1971.

(2) F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth," Wiley–Interscience, New York, N. Y., 1970, pp 3–354.

(3) F. G. Mann, I. T. Millar, and B. B. Smith, *J. Chem. Soc.*, 1130 (1953).

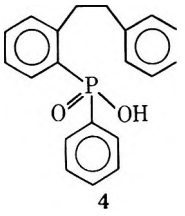
(4) (a) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 64 (1958); (b) A. M. Aguiar, J. Beisler, and A. Mills, *J. Org. Chem.*, **27**, 1001 (1962); (c) E. Zbiral, *Tetrahedron Lett.*, 1649 (1964).

(5) (a) B. R. Ezzell and L. D. Freedman, *J. Org. Chem.*, **34**, 1777 (1969); (b) B. R. Ezzell and L. D. Freedman, *ibid.*, **35**, 241 (1970); (c) B. R. Ezzell, *ibid.*, **35**, 2426 (1970).

(6) (a) D. Wittenberg and H. Gilman, *ibid.*, **23**, 1063 (1958); (b) K. Issleib and H. O. Frohlich, *Z. Naturforsch., B*, **14**, 349 (1959); (c) K. Issleib, *Pure Appl. Chem.*, **9**, 205 (1964); (d) A. D. Britt and E. T. Kaiser, *J. Phys. Chem.*, **69**, 2775 (1965).

(7) B. R. Ezzell, Ph.D. Thesis, North Carolina State University, Raleigh, N. C., 1969.

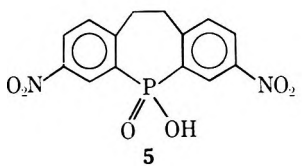
served.[7,8] When the tertiary phosphine **2** was allowed to react with lithium, we obtained from the reaction mixture a 52% yield of the heterocyclic phosphinic acid **1**. A second phosphinic acid, however, was also isolated. Although it was not obtained analytically pure, its mass spectrum strongly suggested that it was compound **4**, formed *via* cleavage of a ring carbon–phos-



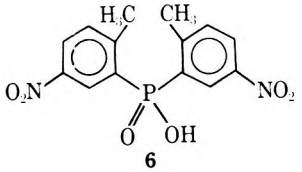
4

phorus bond. This is the first case yet reported in which the reaction of a tertiary phosphine with an alkali metal has led to a mixture of phosphinic acids.

Nitration of the phosphinic acid **1** with 90% nitric acid at room temperature gave an 87% yield of a dinitro derivative. Although the structure of this substance was not proven, it is probably the 3,7-dinitro compound **5**, since the nitration of di-*o*-tolylphosphinic acid under similar conditions was found to give bis(5-nitro-2-tolyl)phosphinic acid (**6**). The structure of **6**



5



6

was established by comparison with an authentic sample.[9]

Ultraviolet Spectra.—Table I gives uv absorption data for the heterocyclic phosphinic acids **1** and **5** and

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compd	λ_{max}, nm	ϵ_{max}
10,11-Dihydro-5-hydroxy-5*H*-dibenzo[*b*,*f*]phosphepin 5-oxide (**1**)	230	10,040
	270	1,616
	277	1,393
Di-*o*-tolylphosphinic acid	223	15,620
	270	2,046
	277	2,012
10,11-Dihydro-5-phenyl-5*H*-dibenzo[*b*,*f*]phosphepin 5-oxide (**3**)	232	21,320
	270	2,152
10,11-Dihydro-3,7-dinitro-5-hydroxy-5*H*-dibenzo[*b*,*f*]phosphepin 5-oxide (**5**)	219	27,240
	278	16,190
Bis(5-nitro-2-tolyl)phosphinic acid (**6**)	219	29,360
	277.5	17,500

[a] The spectra were determined in 95% ethanol with a Cary 14 Model 50 recording spectrophotometer.

for several related organophosphorus compounds. It will be noted that the spectra of **1** and di-*o*-tolylphosphinic acid are very similar. This result suggests that the limited resonance interaction between a phosphinico (PO_2H) group and the aromatic systems attached to it is not appreciably altered by incorporating the phosphorus atom in a heterocyclic ring.[10] The spectrum of the tertiary phosphine oxide **3** also resembles the spectrum of **1**; the intensity of absorption of **3** is somewhat greater, since it contains a third aromatic ring. The spectra of the dinitro derivative **5** and bis(5-nitro-2-tolyl)phosphinic acid (**6**) are virtually identical and help to establish the structure assigned to the former compound.

Experimental Section[11]

10,11-Dihydro-5-phenyl-5*H*-dibenzo[*b*,*f*]phosphepin 5-Oxide (3).—*o*-Bromobenzyl bromide was prepared by the bromination of *o*-bromotoluene and was converted to 2,2′-dibromobibenzyl by the procedure of Letsinger and Skoog.[12] The reaction of this dibromide with *n*-butyllithium and phenylphosphonous dichloride was carried out essentially as described by Mann and coworkers.[3] When the reaction mixture was hydrolyzed and the organic layer was dried and distilled, a pale amber syrup, bp 170–230° at 0.025 Torr, was obtained. This syrup, which presumably consisted mainly of the tertiary phosphine **2**, could not be crystallized. Mann and coworkers[3] had a similar difficulty at this point, but they succeeded in inducing crystallization by seeding the oil with the analogous arsine. We dissolved the oil in acetone and oxidized it with an excess of 3% hydrogen peroxide. When the acetone was allowed to evaporate, a gummy material was obtained which was readily recrystallized from absolute ethanol: yield of **3**, based on 2,2′-dibromobibenzyl, 23%; mp 172–174° (lit.[3] mp 173–174°); nmr ($CDCl_3$) τ 7.02 (m, 4, CH_2CH_2), 2.72 (m, 11, aromatic H), 1.7 (m, 2, aromatic H); mass spectrum *m/e* (rel intensity) 306 (2), 305 (21), 304 (100), 303 (41), 225 (7), 214 (9), 213 (65), 183 (9), 179 (11), 178 (25), 165 (13), 152 (7), 91 (6), 77 (8).

10,11-Dihydro-5-phenyl-5*H*-dibenzo[*b*,*f*]phosphepin (2).—The tertiary phosphine oxide **3** (3.00 g, 9.89 mmol) was dissolved in 75 ml of dry benzene and reduced with trichlorosilane (2.86 g, 19.8 mmol) by the method of Fritzsche and coworkers.[13] After the mixture was refluxed for 2 hr, it was cooled and treated with 50 ml of 40% aqueous sodium hydroxide. The organic layer was then separated, washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a thick orange oil, which crystallized after being washed with a little absolute ethanol. Recrystallization from absolute ethanol gave 1.5 g (53%) of pure **2**: mp 91–93° (lit.[3] mp 94.5–95°); nmr ($CDCl_3$) τ 6.96 (s, 4, CH_2CH_2), 2.83 (m, 13, aromatic H); mass spectrum *m/e* (rel intensity) 290 (3), 289 (18), 288 (85), 287 (9), 274 (15), 273 (77), 210 (23), 209 (29), 208 (10), 207 (50), 197 (30), 196 (35), 183 (55), 179 (35), 178 (100), 177 (12), 176 (15), 170 (12), 166 (14), 165 (67), 157 (10), 152 (33), 151 (10), 139 (10), 133 (33), 115 (23), 109 (23), 108 (23), 107 (41), 91 (33), 89 (23), 78 (53), 77 (53).

10,11-Dihydro-5-hydroxy-5*H*-dibenzo[*b*,*f*]phosphepin 5-Oxide (1). A. From the Fusion of 3 with Sodium Hydroxide.—The phosphine oxide **3** (1.50 g, 4.90 mmol) was thoroughly mixed with finely powdered NaOH (0.40 g, 9.8 mmol) in a 25-ml pear-shaped flask equipped with a condenser. The flask was slowly heated to 250° and maintained between 250 and 260° for 2 hr. During this time 0.35 ml of benzene (identified by ir) distilled. After being cooled, the contents of the flask were dissolved in 100 ml of water, filtered to remove 0.10 g (7%) of phosphine oxide **3**, treated with charcoal, cooled, and acidified to yield 1.1 g (92%) of the phosphinic acid **1**: mp[14] 246–251° after recrystallization

(8) (a) A. D. Britt and E. T. Kaiser, *J. Org. Chem.*, **31**, 112 (1966); (b) E. H. Braye, U. S. Patent 3,338,941 (1967).

(9) L. D. Freedman and G. O. Doak, *J. Org Chem.*, **26**, 2082 (1961).

(10) The ultraviolet spectra of tetracoordinate organophosphorus compounds have been recently reviewed by B. G. Ramsey, "Electronic Transitions in Organometalloids," Academic Press, New York, N. Y., 1969, pp 173–181.

(11) Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Nmr spectra were taken with a Varian HA-100 spectrometer, and tetramethylsilane was used as an internal standard. All solvents used for Grignard or organolithium reagents were distilled over sodium. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(12) R. L. Letsinger and I. H. Skoog, *J. Amer. Chem. Soc.*, **77**, 5176 (1955).

(13) H. Fritzsche, U. Hasserodt, and F. Korte, *Chem. Ber.*, **97**, 1988 (1964).

(14) The broad melting point ranges observed with many arylphosphonic and diarylphosphinic acids are probably due to their rapid decomposition at temperatures above 240°; *cf.* ref 9.

from 95% ethanol; nmr (CF_3CO_2H) τ 6.73 (s, 4, CH_2CH_2), 2.63 (m, 6, aromatic H), 2.0 (m, 2, aromatic H); mass spectrum *m/e* (rel intensity) 488 (<0.1), 246 (2), 245 (15), 244 (100), 243 (37), 229 (10), 226 (21), 225 (22), 209 (3), 208 (3), 183 (3), 179 (20), 178 (45), 165 (15), 152 (11), 91 (9),89 (17), 77 (14).

Anal. Calcd for $C_{14}H_{13}O_2P$: C, 68.85; H, 5.37. Found: C, 69.04; H, 5.54.

B. From the Cleavage of 2 with Lithium.—The tertiary phosphine **2** (0.80 g, 2.78 mmol) was dissolved in 25 ml of dry tetrahydrofuran (THF) and treated with lithium wire (0.06 g, 9 mg-atom) by the procedure of Aguiar and coworkers.[4b] After the mixture was stirred and refluxed for 3 hr, it was cooled, hydrolyzed, and then oxidized with an excess of 3% hydrogen peroxide. The resulting solution was extracted with ether to remove any phosphine oxide formed from unreacted **2**, and the aqueous layer was acidified with hydrochloric acid and cooled. The gummy solid which separated was purified by reprecipitation from aqueous base and then dried, yield 0.70 g. Washing this substance with 10 ml of ether extracted an acidic substance discussed in the paragraph below and left as a residue 0.35 g (52%) of the desired heterocyclic phosphinic acid **1**, mp[14] 249–254° after recrystallization from 95% ethanol. This acid was identical (mixture melting point and mass spectrum) with the sample prepared *via* the fusion of **3** with sodium hydroxide.

The 10-ml ether extract mentioned in the above paragraph was evaporated to dryness, and the oily residue was converted to a solid by reprecipitation from alkaline solution: yield 0.30 g; mp 38–65°; nmr ($CDCl_3$) τ 6.43 (m, 4, CH_2CH_2), 2.55 (m, 14, aromatic H); mass spectrum displayed a base peak at *m/e* 322, which corresponds to the molecular weight of the non-heterocyclic compound **4**.

Anal. Calcd for $C_{20}H_{19}O_2P$: C, 74.52; H, 5.94. Found: C, 72.29; H, 5.79.

10,11-Dihydro-3,7-dinitro-5-hydroxy-5*H*-dibenzo[*b*,*f*]phosphepin 5-Oxide (5).—The heterocyclic phosphinic acid **1** (0.50 g) was nitrated at about 30° with 30 ml of 90% nitric acid (*d* 1.5). The reaction mixture was poured onto 250 g of crushed ice, whereupon 0.60 g (87%) of dinitro compound crystallized from solution: mp[14] 320–330° dec after recrystallization from 95% ethanol.

Anal. Calcd for $C_{14}H_{11}N_2O_6P$: C, 50.31; H, 3.32; N, 8.38. Found: C, 50.12; H, 3.42; N, 8.57.

Di-*o*-tolylphosphinic Acid.[15]—A solution of freshly distilled *o*-chlorotoluene (126.6 g, 1.00 mol) in 250 ml of dry THF was converted to *o*-tolylmagnesium chloride in the usual manner[16] and then treated with di-*n*-butyl phosphonate as in the procedure used by Crofts and coworkers[17] for the preparation of diarylphosphine oxides. After the reaction mixture was hydrolyzed with dilute hydrochloric acid and the THF was removed under reduced pressure, an aqueous solution and a supernatant yellow oil were obtained. On cooling, the oil solidified to give 72.4 g of crude di-*o*-tolylphosphine oxide: mp 94–95° after recrystallization from toluene and drying at 90° *in vacuo;* nmr ($CDCl_3$) τ 7.61 (s, 6, CH_3), 2.75 (m, 6, aromatic H), 2.35 (m, 2, aromatic H).

Anal. Calcd for $C_{14}H_{15}OP$: C, 73.03; H, 6.57. Found: C, 72.73; H, 6.71.

The crude di-*o*-tolylphosphine oxide (from 1.00 mol of *o*-chlorotoluene) was suspended in dilute sodium hydroxide and oxidized with 50 ml of 30% hydrogen peroxide. The resulting alkaline solution was filtered to remove a trace of insoluble material and then acidified with hydrochloric acid to precipitate the phosphinic acid. It was purified by recrystallization from 95% ethanol: yield 47.5 g (58% based on *o*-chlorotoluene); mp 175–177°; nmr ($CDCl_3$) τ 7.77 (s, 6, CH_3), 2.85 (m, 6, aromatic H), 2.20 (m, 2, aromatic H).

(15) This acid was first prepared by A. Michaelis and F. Wegner, *Ber.*, **48**, 316 (1915), but they gave no information about its properties. V. M. Plets, Dissertation, Kazan, 1938 (quoted by G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, p 170) reported that the compound melts at 101° and can be recrystallized from water. It should be noted, however, that a number of workers have questioned the validity of much of Plets's work; *cf.* L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957), and F. A. Cotton, *ibid.*, **55**, 551 (1955). P. Haake, M. J. Frearson, and C. E. Diebert, *J. Org. Chem.*, **34**, 788 (1969), have described the mass spectrum of di-*o*-tolylphosphinic acid but have not reported its synthesis.

(16) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *ibid.*, **22**, 1202 (1957).

(17) P. C. Crofts, I. M. Downie, and K. Williamson, *J. Chem. Soc.*, 1240 (1964).

Anal. Calcd for $C_{14}H_{15}O_2P$: C, 68.29; H, 6.14; mol wt, 246. Found: C, 68.56; H, 6.35; mol wt, 244 (in 95% ethanol with a Thomas isothermal molecular weight apparatus).

Di-*o*-tolylphosphinic acid was also prepared from *o*-bromotoluene. The Grignard reagent was prepared in ether in the conventional manner and converted to di-*o*-tolylphosphine oxide by the procedure described above. Oxidation of the phosphine oxide with hydrogen peroxide gave a 74% yield of phosphinic acid.

Bis(5-nitro-2-tolyl)phosphinic Acid (6).—Di-*o*-tolylphosphinic acid (10.0 g) was nitrated with 100 ml of 90% nitric acid by the procedure described above for the nitration of the heterocyclic phosphinic acid **1**. The yield was 13.0 g (95%), mp[14] 231–241° after recrystallization from 95% ethanol (lit.[9] mp 243–245°). This compound was shown (mixture melting point and ir) to be identical with an authentic sample of **6**.[9]

Anal. Calcd for $C_{14}H_{13}N_2O_6P$: C, 50.01; H, 3.90. Found: C, 49.81; H, 4.08.

Registry No.—**1**, 30309-73-0; **2**, 30309-74-1; **3**, 30309-75-2; **4**, 30309-76-3; **5**, 30309-77-4; **6**, 30309-78-5; di-*o*-tolylphosphinic acid, 18593-19-6; di-*o*-tolylphosphine oxide, 30309-80-9.

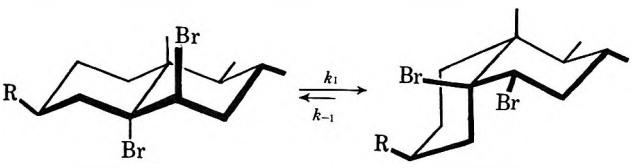
A Novel Catalytic Effect in the Diaxial–Diequatorial Rearrangement of 5,6-Dibromocholesteryl Benzoate[1a]

V. HACH[1b]

MacMillan Bloedel Research Ltd., Vancouver, British Columbia, Canada

Received February 23, 1971

In connection with a specific project in the steroid field, we became interested in the rate of the diaxial–diequatorial rearrangement of 5α,6β-dibromocholesterol and its esters to the corresponding 5β,6α stereoisomers. This rearrangement is typical for 2,3 and 5,6 axially disubstituted steroids. It has been reviewed recently.[2] Although, in general, the reaction reaches an equilibrium, in the case of the 5,6-dibromides the thermodynamically favored 5β,6α isomers constitute not less than 80% of the rearranged product and the reaction can be utilized for preparative purposes. In



1, R = H
3, R = $OCOC_6H_5$

2, R = H
4, R = $OCOC_6H_5$

their detailed studies on 5,6-dibromocholestane, partial structure **1**, Grob and Winstein[3] attempted to discern a rate-influencing species that would be helpful in elucidating the rearrangement mechanism. The lack of a common ion effect and the insensitivity of the rate toward the addition of nucleophiles like CH_3COONa and LiBr were two of the main reasons that led them to

(1) (a) This work was supported, in part, by the National Research Council of Canada. (b) Department of Chemistry, University of British Columbia, Canada.

(2) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 373 ff.

(3) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).

TABLE I

CATALYTIC EFFECT OF $HgBr_2$ ON THE RATE OF REARRANGEMENT OF 5α,6β-DIBROMOCHOLESTERYL BENZOATE TO 5β,6α-DIBROMOCHOLESTERYL BENZOATE IN BENZENE AT 40.30 ± 0.05°

Run	Vol of soln, ml	Dibromide 3		$HgBr_2$			
		g	mol × 10^{-3}	g	mol	mol %	$k_1 - k_{-1}$, sec^{-1}
1	100	1.00	1.53	0.020	5.55×10^{-5}	3.6	3.0×10^{-6}
2	100	1.00	1.53	0.050	1.38×10^{-4}	9.0	4.4×10^{-6}
3	100	1.00	1.53	0.080	2.22×10^{-4}	14.5	7.4×10^{-6}
4	100	1.00	1.53				1.0×10^{-6}

propose for this rearrangement the merged ion-pair cyclic-concerted mechanism. This concept has been recently supported by the extensive work of King, *et al.*[4] Both groups found the rearrangement rate to be solvent dependent and, in broad terms, increasing with solvent polarity. Kwart and Weisfeld[5] found that organic acids and phenols enhanced the rate of rearrangement through general acid catalysis.

In practical terms a reaction time of *ca.* 5 hr is necessary to complete the rearrangement **3** → **4** in benzene at the boiling point.[6] The rearrangement **1** → **2** requires about 10 hr in boiling heptane.[3] We were concerned with reducing this time span without resorting to the use of either organic acids and phenols[5] or polar solvents like ethanol in which substantial solvolysis takes place.[7] Concurring with the opinion of Kirk and Hartshorn[2] that the reaction may be viewed in simple terms as an internal concerted nucleophilic substitution, we were inclined to think that it could be catalyzed by metal salts, particularly Hg^{2+} salts like other nucleophilic reactions are.[8] We indeed found that in benzene solutions the rate of rearrangement of 5α,6β-dibromocholesteryl benzoate (**3**) to the 5β,6α isomer **4** is increased by the addition of $HgBr_2$. Some representative runs are summarized in Table I. The rearrangement was followed polarimetrically and the reaction constants were established graphically from first-order linear plots of the logarithm of concentration of the disappearing 5α,6β-dibromocholesteryl benzoate *vs.* time. In accordance with previous work,[3] the reaction constant is expressed as the sum of two constants corresponding to the forward and retroreaction. Viewing $HgBr_2$ as a Lewis acid permits[9] the present observation to be brought into perspective with previous work, particularly that of Kwart and Weisfeld.[5] Our data give a reasonable agreement with the acid catalysis equation $K = K_0 + K_c[HgBr_2]$ and $K_c \simeq 2.8 \times 10^{-3}\ M^{-1}\ sec^{-1}$. This catalytic constant is then in the same range of magnitude as that found by Kwart, *et al.*, for the strongest acid they studied *viz.* trichloroacetic acid. Due to our limited interest in this area we do not attempt to accommodate our results with any detailed mechanism.

(4) J. F. King and R. G. Pews, *Can. J. Chem.*, **43**, 847 (1965).

(5) H. Kwart and J. B. Weisfeld, *J. Amer. Chem. Soc.*, **78**, 635 (1956).

(6) H. Bretschneider, Z. Földi, F. Galinowski, and G. von Fodor, *Chem. Ber.*, **74**, 1451 (1941).

(7) Exploratory work in this direction was carried out by Mr. J. Hjort. In simple primary and secondary alcohols (MeOH, EtOH, *n*-PrOH, *n*-BuOH, *sec*-PrOH, *sec*-BuOH, and cyclohexanol) complete debromination of selected steroidal 5,6-dibromides took place either at reflux temperature or at 100° in higher boiling alcohols. The reaction was completed in several hours; invariably dibromides with a free 3β-OH group showed the highest rate of debromination. However, in *tert*-BuOH this solvolytic debromination was extremely slow.

(8) (a) C. K. Ingold "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, p 480 ff; (b) C. A. Bunton, "Nucleophilic Substitution," Elsevier, Amsterdam, 1963, p 154 ff.

(9) Thanks are due to Professor J. F. King, University of Western Ontario, for his valuable comments on our results.

Experimental Section

General.—Uncorrected melting points were taken on a Kofler hot stage. Optical rotations were measured in 0.5- or 1-dm tubes using a Carl Zeiss polarimeter whose accuracy was not less than 0.05°.

Materials.—5α,6β-Dibromocholesteryl benzoate (**3**) was prepared according to literature[6,10,11] and recrystallized from C_6H_6–CH_3OH at room temperature, mp 135–137°, $[\alpha]^{24}D$ −39° (*c* 1, C_6H_6) [lit.[10,11] mp 135–136°, $[\alpha]D$ −40° (C_6H_6)]. 5β,6α-Dibromocholesteryl benzoate (**4**) was prepared according to the literature,[6,10] and recrystallized from C_6H_6–CH_3OH, mp 162–164°, $[\alpha]^{24}D$ +100° (*c* 1, C_6H_6) [lit.[6,10] mp 163–164°, $[\alpha]D$ +102° (C_6H_6)]. Reagent grade thiophene-free benzene and mercuric dibromide (Fisher) were used directly.

Kinetic Runs.—These were carried out in volumetric flasks placed in an automatic thermoelectric water bath. Runs were followed for 50–75 hr to 30–60% completion of full rearrangement *i.e.*, to 50–80% attainment of equilibrium by the two isomers. Usually 6–8 samples per run were withdrawn at intervals of several hours and their rotation measured at 25 ± 2°. The measurement, average of eight readings, took about 5 min and we considered this time negligible in relation to the above-mentioned overall reaction time. Excellent agreement was found between runs repeated after several days. The reaction constants were established graphically using common procedures.[12] The solutions from kinetic runs with $HgBr_2$ were kept at 40° until the rearrangement equilibrium was reached and subsequently they were evaporated *in vacuo* at room temperature to dryness. The dark residue was in each case treated with cold methanol and the tan solid which separated was filtered off and recrystallized from benzene–methanol to give pure **4**, identical (melting point, ir, $[\alpha]D$, elemental analysis) with samples of **4** prepared as given above. The yields in these recoveries averaged about 80% thus indicating absence of appreciable side reactions, particularly dehalogenation, during the kinetic runs.

Registry No.—**3**, 6213-04-3; **4**, 5863-62-7.

Acknowledgment.—The technical assistance of Mrs. E. C. Fryberg is appreciated.

(10) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 1066 (1950).

(11) S. P. J. Maas, M. J. D. VanDam, J. G. De Heus, and D. Mulder, *Bull. Soc. Chem. Belg.*, **72**, 239 (1963).

(12) R. Livingston in "Techniques of Organic Chemistry," Vol. VIII, 2nd ed, part 2, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, pp 126, 127. The usual "best fit" lines were drawn. In most runs the scattering of values plotted was negligible.

Selective Degradation of Guaiol. The Synthesis of 7-Epiguaiol

JAMES A. MARSHALL* AND RONALD A. RUDEN[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received February 3, 1971

In connection with a current project dealing with the total synthesis of the hydroazulenic sesquiterpene alco-

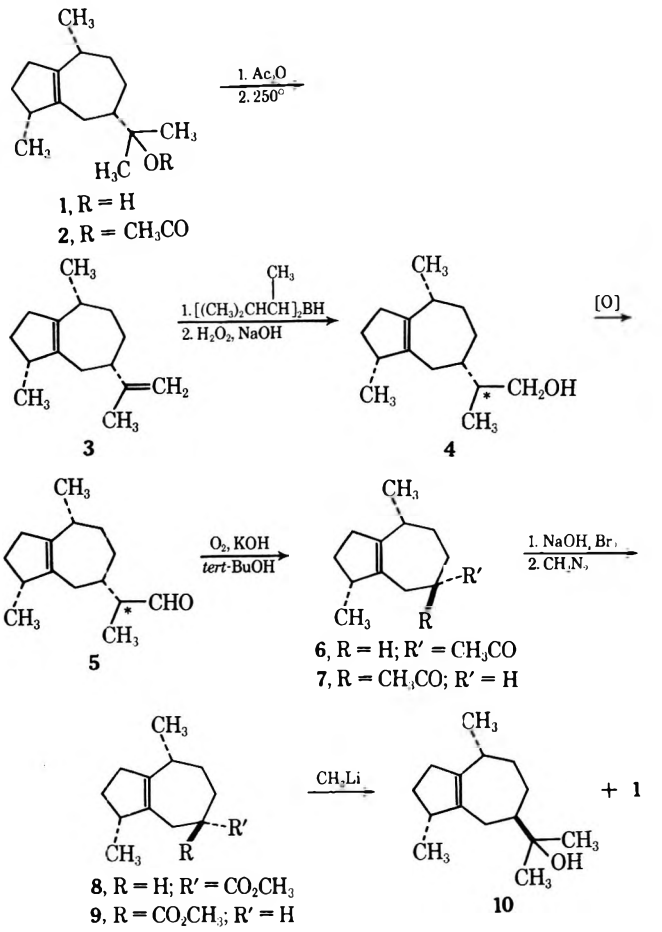
(1) Predoctoral Fellow of the National Institutes of Health, Division of General Medical Sciences.

hol guaiol (1),[2] it became necessary to gain some information regarding the relative configurational stabilities of epimerizable guaiane derivatives such as the ketones **6** and **7** and the related esters **8** and **9**. We also hoped to work out an effective means for separating these epimers in the event that our synthetic route would lead to the racemic counterparts of such mixtures. These goals have been achieved and the details are described herein.

Pyrolysis of guaiyl acetate (2) at 250° as described by Slagel[3] afforded a mixture of dienes composed principally of α-guaiene (**3**).[4] Selective hydroboration of this mixture proceeded smoothly with disiamylborane[5] and, after oxidation with alkaline hydrogen peroxide, alcohol **4** was secured in high yield. This alcohol is undoubtedly a roughly 1:1 mixture of diasterioisomers at the methine center attached to C-7 (asterisk in structure **4**). Oxidation either with Collins bispyridine chromic oxide reagent[6] or the Moffat DMSO–DCC reagent[7] afforded the aldehyde **5**, likewise a diastereomeric mixture. Aldehyde **5** underwent oxidative cleavage upon stirring under an oxygen atmosphere in alkaline *tert*-butyl alcohol[8] to give the ketones **6** and **7** as a nearly 1:1 mixture. These ketones failed to separate on the gas chromatogram under a variety of conditions and the analysis therefore had to be carried out on the alcohols guaiol (1) and 7-epiguaiol (**10**) secured *via* treatment with ethereal methyllithium. These two alcohols showed two distinct peaks in the gas chromatogram.[9] Additional base treatment did not alter the composition of the 1:1 mixture of ketones **6** and **7**, a reasonable finding in view of the conditions employed in their formation from aldehyde **5**.[10] Treatment of this mixture with ethereal methyllithium afforded a comparable mixture of guaiol (1) and 7-epiguaiol (**10**) from which an appreciable amount of the guaiol epimer could be removed *via* low temperature crystallization from hexane. The epiguaiol-enriched mother liquor was subjected to preparative gas chromatography in order to obtain a pure sample of this substance (Scheme I).

Hypobromite oxidation of the 1:1 mixture of ketones **6** and **7** followed by esterification of the resulting acidic material with ethereal diazomethane afforded a mixture of methyl esters **8** and **9** in 30% yield whose composition was surprisingly found to be 85:15 by gas chromatography. An appreciable residue, presumably products arising from double bond bromination of **7** (possibly *via* a bromolactone intermediate), remained upon distillation of the aforementioned ester. Equilibration in refluxing methanolic sodium methoxide led to a 50:50 mixture of these esters.[10] Each of the pure esters **8** and **9** could be obtained through preparative gas chromatography of the equilibrium mixture thus establishing a possible relay point in our projected guaiol synthesis.

SCHEME I



Experimental Section[11]

Hydroboration–Oxidation of α-Guaiene. Alcohol 4.—A stirred solution of 408 mg of α-guaiene[4] in 15 ml of tetrahydrofuran at 0° was treated dropwise with 7.0 ml of 1 *M* disiamylborane.[5] After 1.5 hr water (3.5 ml), 3 *N* aqueous NaOH (28 ml), and 30% hydrogen peroxide (23.4 ml) were added dropwise and the mixture was stirred at room temperature for 1 hr. The product was isolated with ether and distilled affording 397 mg (88%) of alcohol **4**: bp 130° (bath temperature) (0.1 mm); λ_{max}^{film} 3.02, 6.98, and 9.72 μm; $\delta_{TMS}^{CDCl_3}$ 3.58 (CH_2O a pair of doublets, J = 6 Hz), 1.38 (OH), 1.00 (CH_3 doublet, J = 7 Hz), 0.96 (CH_3 doublet, J = 7 Hz), and 0.90 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.05; H, 11.7.

Oxidation of Alcohol 4. Aldehyde 5. A. Collins Reagent.[6]—A solution of 873 mg of alcohol **4** comparable to that described above in 200 ml of methylene chloride was treated portionwise with 8.7 g of bispyridine chromium oxide. After 10 min of intermittent swirling the black solution was diluted with 500 ml of ether and washed with ice-cold 5% NaOH until the washes were nearly colorless. The organic phase was washed with 10% HCl, saturated sodium bicarbonate, and saturated brine and dried over anhydrous magnesium sulfate. Distillation afforded 524 mg (61%) of aldehyde **5**: bp 120° (bath temperature) (0.3 mm); λ_{max}^{film} 3.72, 5.80, 6.90, 7.20, and 7.34 μm; $\delta_{TMS}^{CCl_4}$ 9.56

(2) *Cf.* H. Minato, *Tetrahedron Lett.*, 280 (1961).

(3) R. Slagel, Ph.D. Thesis, University of Illinois, 1962, p 49.

(4) A sample of this material was generously provided by G. Shaffer, Givaudan Corp.

(5) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 33 (1963).

(6) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(7) K. E. Pitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

(8) *Cf.* W. Sucrow, *Ber.*, **100**, 259 (1967); V. Van Rheenen, *Tetrahedron Lett.*, 985 (1969).

(9) Ordinary Carbowax columns effected the dehydration of these alcohols, evidently the result of acidic sites since this behavior was not observed with KOH–Carbowax columns.

(10) In the analogous ester mixture prepared in connection with the synthesis of bulnesol, a 71:29 ratio of epimers was secured: J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969).

(11) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132). Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(CHO, J = 1 Hz), 1.02 (CH_3 doublet, J = 7 Hz), 1.00 (CH_3 doublet, J = 7 Hz), and 0.97 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.7; H, 11.15.

B. Moffatt Reagent.[7]—A solution of 598 mg of alcohol **4**, 285 mg of pyridinium trifluoroacetate, and 1.44 g of dicyclohexylcarbodiimide in 4.6 ml of benzene and 4.6 ml of dimethyl sulfoxide was stirred at room temperature for 12 hr. Ethyl acetate (25 ml) followed by 1 g of oxalic acid in 8 ml of methanol was added and after 0.5 hr of stirring the product was isolated with hexane and distilled affording 608 mg of aldehyde **5** contaminated with a small amount of dicyclohexylurea.

Oxidation of Aldehyde 5. Ketones 6 and 7.—A mixture of 465 mg of aldehyde **5** and 200 mg of powdered KOH in 20 ml of *tert*-BuOH was vigorously stirred under an oxygen atmosphere for 0.5 hr.[8] The product was isolated with hexane and distilled affording 213 mg (48%) of a nearly 1:1 mixture of ketones **6** and **7**:[12,13] bp 107° (bath temperature) (0.1 mm); λ_{max}^{film} 5.88, 8.61 μm; $\delta_{TMS}^{CCl_4}$ 2.06 (CH_3CO), 2.05 (CH_3CO), 1.17–0.84 ppm (CH_3 doublets). Replicate C and H analyses on a purified sample of this mixture showed successively decreasing carbon percentages indicative of rapid oxygen uptake.

Oxidation of Ketones 6 and 7. Esters 8 and 9.—A solution of NaOBr was prepared from 1.36 g of NaOH in 11.8 ml of water, 1.41 g of bromine, and 7.7 ml of dioxane. This cold (0°) solution was added with stirring to 510 mg of ketone mixture **6** and **7** in 35.5 ml of dioxane and 10.5 ml of water at 0°. After 3 hr a solution of 0.56 g of sodium sulfite in 5.6 ml of water was added. The solution was poured into 15 ml of 10% NaOH and washed with ether. The aqueous phase was acidified with dilute sulfuric acid and the product was isolated with ether affording the crude acid which was directly esterified with ethereal diazomethane to give 157 mg (29%) of an 85:15 mixture[14] of esters **8** and **9**: bp 110° (bath temperature) (0.05 mm); λ_{max}^{film} 5.78, 7.00, and 8.60 μm; $\delta_{TMS}^{CCl_4}$ 3.56 (CH_3O), 1.02 (CH_3 doublet, J = 7 Hz), and 0.97 ppm (CH_3 doublet, J = 7 Hz).

Equilibration in refluxing methanolic sodium methoxide (0.4 M) afforded a 50:50 mixture. The equilibrium mixture of these esters was separated *via* preparative gas chromatography[15] (t_R of **8**:**9** = 1.1).

Ester 8: λ_{max}^{film} 5.78, 6.92, 7.00, 8.59, and 9.75 μm; $\delta_{TMS}^{CCl_4}$ 3.56 (OCH_3), 1.02 (CH_3 doublet, J = 7 Hz), and 0.96 ppm (CH_3 doublet, J = 7 Hz).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.8; H, 10.1.

Ester 9: λ_{max}^{film} 5.77, 6.92, 7.00, 8.62, and 9.63 μm; $\delta_{TMS}^{CCl_4}$ 3.56 (OCH_3), 1.00 (CH_3 doublet, J = 7 Hz), and 0.94 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.4; H, 10.1.

Guaiol (1) and Epiguaiol (10). A. From Ketones 6 and 7.—To a stirred solution of 1.10 g of ketones **6** and **7** (1:1 mixture) in 50 ml of ether was added 10 ml of 1.6 M ethereal methyllithium. After 1 hr, 2 ml of water was carefully added and the product was isolated with ether. Low temperature crystallization from hexane yielded 342 mg of guaiol (**1**): mp 82–85°; λ_{max}^{KBr} 3.00, 7.37, 8.69, 8.70, 10.03, 10.41, 10.80, 10.97, 11.36, and 12.18 μm; $\delta_{TMS}^{CDCl_3}$ 1.18 (CH_3), 0.98 (CH_3 doublet, J = 7.5 Hz), and 0.96 ppm (CH_3 doublet, J = 7 Hz).

From the mother liquor was obtained an enriched sample (75%) of epiguaiol (**10**) which was purified by preparative gas chromatography[16] (t_R of 1:10 = 0.92): λ_{max}^{film} 2.95, 6.85, 7.32, 8.82, 10.79, and 11.14 μm; $\delta_{TMS}^{CDCl_3}$ 1.19 (CH_3), 1.04 (CH_3 doublet, J = 7 Hz), and 1.03 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.9; H, 11.8.

B. From Esters 8 and 9.—A purified sample of ester **8** (10 mg) was treated with ethereal methyllithium (1.0 ml of 1.6 M) as described above affording 9.6 mg (96%) of guaiol (**1**) identified by spectral comparison.

A sample of ester **9** when similarly treated afforded epiguaiol (**10**) identified by spectral comparison with the aforementioned sample.

Registry No.—**1**, 489-86-1; **4** (11R), 30166-94-0; **4** (11S), 30166-99-5; **5** (11R), 30166-95-1; **5** (11S), 30167-00-1; **6**, 30246-75-4; **7**, 30246-76-5; **8**, 30166-96-2; **9**, 30166-97-3; **10**, 30166-98-4.

Acknowledgments.—We are indebted to the National Institutes of Health for their support of this research through a grant (National Cancer Institute, 5 RO1 CA11089) and a predoctoral fellowship (Institute of General Medical Sciences, 5 FO1 GM41100). A generous gift of α-guaiene from G. Shaffer, Givaudan Corp., is also acknowledged.

(12) This ratio was determined by gas chromatographic analysis of the alcohols secured through addition of ethereal methyllithium to this mixture.

(13) A 22 ft × 1/8 in. column of 1% Carbowax 20M on 80–100 mesh CG, AW-DMCS, was used.

(14) A 15 ft × 1/8 in. column of 3% FFAP on Chromosorb G, 70–80 mesh AW-DMCS, was used for this analysis.

(15) A 15 ft × 3/8 in. column of 6% FFAP on 60–80 mesh Chromosorb G-NAW was used.

(16) A 15 ft × 0.25 in. column of 24% 1:4 KOH–Carbowax 20M on 60–80 mesh Chromosorb G was used for the separation.

Inhibition of the Hydrolysis of Bis-2,4-dinitrophenyl Phosphate by a Nonionic Detergent[1]

C. A. BUNTON,*[2] A. KAMEGO, AND L. SEPULVEDA

Department of Chemistry, University of California, Santa Barbara, California 93106, and Faculty of Chemistry and Pharmacy, University of Chile, Santiago, Chile

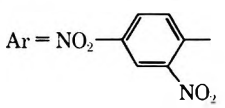
Received March 1, 1971

There are many examples of catalysis or inhibition by micellized detergents, and they generally follow the simple electrostatic rules put forward by Hartley to explain equilibrium effects (for reviews, see ref 3–5). In agreement with these rules, nonionic detergents generally have only small effects upon the rates of ionic reactions.[3–5] However, micellar effects depend very markedly upon hydrophobic interactions, and a few reactions between an ionic reagent and an uncharged substrate are inhibited by nonionic micelles,[6,7] probably because the substrate becomes buried in the interior of the micelle.

We unexpectedly observed that the reaction of hydroxide ion with bis-2,4-dinitrophenyl phosphate monoanion is strongly inhibited by Igepal,[8] and we suggested that despite its negative charge the ionic substrate is

$$(ArO)_2PO_2^- + OH^- \xrightarrow{k_1} ArO^- + ArOPO_3^{2-}$$

$$ArOPO_3^{2-} \xrightarrow{k_2} ArO^- + PO_3^- \longrightarrow HPO_4^{2-}$$



(1) Support of this work by the National Institute of Arthritis and Metabolic Diseases and the University of Chile–University of California Cooperative Program supported by the Ford Foundation is gratefully acknowledged.

(2) To whom inquiries should be addressed.

(3) E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969).

(4) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(5) T. C. Bruice in "The Enzymes," Vol. 2, 3rd ed, Academic Press, New York, N. Y., 1970. p 217.

(6) R. A. Anderson and A. M. Slade, *J. Pharm. Pharmacol.*, **18**, 640 (1966).

(7) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).

(8) G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. Stam, *J. Amer. Chem. Soc.*, **92**, 4072 (1970).

incorporated strongly into the nonionic micelle and protected by it from hydroxide ion. (Igepal is a polyoxyethylene dinonylphenol with 24 ethylene oxide units).

The spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion is unaffected by nonionic micelles of Igepal[9] and in their presence is much faster than the first step of the reaction, the attack of hydroxide ion upon the diaryl phosphate monoanion.

The aim of the present work was to find out whether other nonionic detergents had the same kinetic effect as Igepal and, if possible, to find evidence for incorporation of the substrate into the micelle. The general methods for demonstrating micellar incorporation, *e.g.*, column chromatography[10] or solubility,[11] were unsatisfactory, and we therefore fell back on the observation that mixtures of water and Triton X-114 separated into two phases with an increase in temperature.[12] (Triton X-114 is a polyoxyethylene octylphenol, with 7–8 ethylene oxide units.) Aqueous Igepal does not give this phase separation at a low temperature.

The detergent-rich phase contains 20% by weight of the detergent, whereas the water-rich phase contains only the critical micelle concentration of the detergent (2.5×10^{-4} *M*).[12] When bis-2,4-dinitrophenyl phosphate was dissolved in a 10% (by weight) aqueous solution of Triton X-114 and the temperature was raised to 40°, approximately 90% of the diaryl phosphate was found in the detergent-rich layer, indicating strong interactions between the phosphate monoanion and the detergent.

Triton X-114 retards the attack of hydroxide ion upon bis-2,4-dinitrophenyl phosphate monoanion (Table I). This rate retardation is very similar to that

TABLE I

EFFECT OF TRITON X-114 UPON THE REACTION OF BIS-2,4-DINITROPHENYL PHOSPHATE WITH HYDROXIDE ION[a]

C_D, *M*	10^5K, sec^{-1}
	3.0[b]
0.005	0.54
0.010	0.43
0.025	0.32

[a] At 25.0° in 0.01 *M* NaOH. The concentration of Triton (C_D) is calculated on the assumption that it contains 7 ethylene oxide units. [b] Reference 8.

observed with Igepal,[8] although slightly smaller, probably because of the shorter side chain of Triton. The loss of hydration of the relatively hydrophobic anionic phosphate ester in incorporation into a nonionic micelle is apparently more than offset by the hydrophobic binding of the nonpolar aryl groups with the micelle. Micelles of both Igepal and Triton X-114 appear to contain a considerable amount of water in their interiors[12] which could assist incorporation of the diaryl phosphate monoanion.

(9) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K-U. Yang, *J. Amer. Chem. Soc.*, **90**, 5512 (1968).

(10) D. G. Herries, W. Bishop, and F. M. Richards, *J. Phys. Chem.*, **68**, 1842 (1964); R. B. Dunlap and E. M. Cordes, *J. Amer. Chem. Soc.*, **90**, 4395 (1968); L. R. Romsted and E. M. Cordes, *ibid.*, **90**, 4404 (1968).

(11) C. A. Bunton and L. Robinson, *ibid.*, **90**, 5972 (1968).

(12) L. Sepulveda and F. MacRitchie, *J. Colloid Interface Sci.*, **28**, 19 (1968).

Experimental Section

Kinetics.—The reaction was followed spectrophotometrically using a Cary 11 spectrophotometer with a water-jacketed cell at 25.0°. The preparation of the materials and the kinetic solutions has already been described.[8] Triton X-114 was used without purification, and we are indebted to Rohm and Haas for a sample of it. The first-order rate constants, k_1, for the attack of hydroxide ion upon bis-2,4-dinitrophenyl phosphate monoanion are in reciprocal seconds. Solutions containing less than 5×10^{-3} *M* Triton were turbid and were not used for kinetic experiments. The rate constants were cleanly first order for 3 half-lives, indicating that the second step of the overall reaction, the hydrolysis of 2,4-dinitrophenyl phosphate dianion is much faster than the first step. (Igepal has little effect upon the hydrolysis of the dianion.[9])

Phase Separation.—Bis-2,4-dinitrophenyl phosphate (pyridinium salt, 5 mg) was dissolved in 50 ml of a 10 wt % aqueous solution of Triton X-114, and the mixture heated to 40°. Phase separation occurred,[12] portions (5 ml) of each phase were removed, and the diaryl phosphate was completely hydrolyzed. The concentration of 2,4-dinitrophenol, determined spectrophotometrically as phenoxide ion at 3580 Å in the water-rich phase was 0.28×10^{-4} *M*, and in the detergent-rich phase it was 3.03×10^{-4} *M*.

Registry No.—Bis-2,4-dinitrophenyl phosphate, 18962-97-5; hydroxide ion, 14280-30-9.

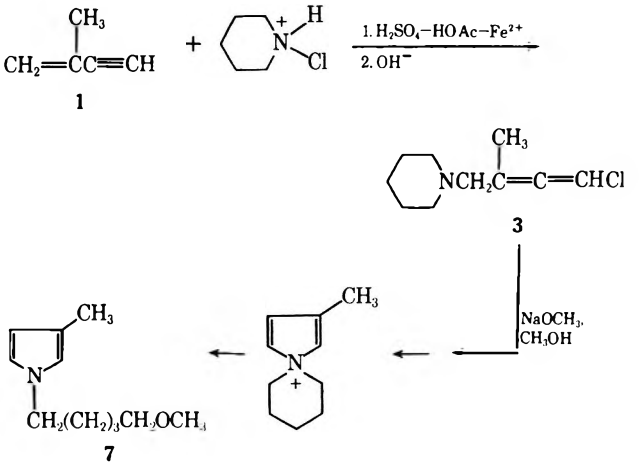
Radical Addition of Protonated *N*-Chloropiperidine to Conjugated Enynes

MARVIN L. POUTSMA* AND PEDRO A. IBARBIA

Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York 10591

Received February 8, 1971

As part of a general survey of radical additions to conjugated enynes,[1] we have briefly examined the addition of *N*-chloropiperidine in acidic solution to 2-methyl-1-buten-3-yne (1), 1-penten-3-yne (2), and



1-buten-3-yne. Additions of *N*-chloramines in acidic media to olefins, allenes, and conjugated dienes have been studied extensively by Neale[2] and are believed to involve aminium cation radicals ($R_2\overset{+}{N}H$) as the chain-carrying species. Although the polar character of the

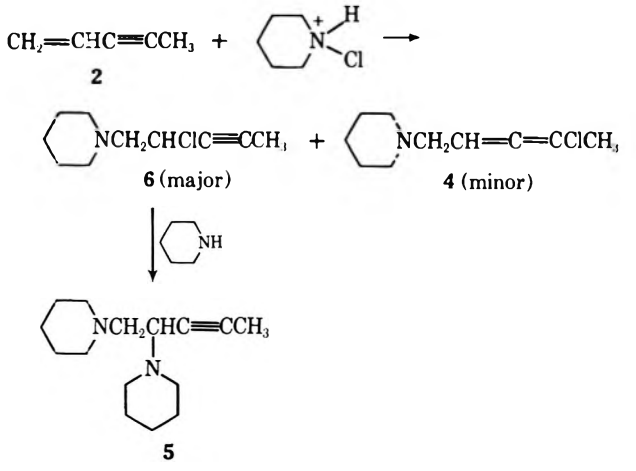
(1) M. L. Poutsma and P. A. Ibarbia, *J. Org. Chem.*, **35**, 4038 (1970).

(2) R. S. Neale, *ibid.*, **32**, 3263 (1967).

reaction medium (4 *M* sulfuric acid in acetic acid), the method of mixing reactants (enyne:$R_2\overset{+}{N}HCl$ < 1 during most of the reaction), and the work-up procedure are such as not to allow us to be absolutely certain that the isolated products are those of kinetic control, the nature of the products is of some synthetic interest.

Reaction of enyne **1** and *N*-chloropiperidine proceeded smoothly with use of a catalytic amount of ferrous ion to give as the only isolable basic product a 1,4 adduct, 1-chloro-3-methyl-4-piperidino-1,2-butadiene (**3**), in 70–75% yield. Similar structures lacking the 3-alkyl group, *i.e*, 1-bromo-4-dialkylamino-1,2-butadienes, have been prepared previously by treatment of the bromination product of vinylacetylene (largely $BrCH_2CH{=}C{=}CHBr$) with secondary amines.[3]

Parallel reaction with enyne **2** gave 60–65% crude basic product whose spectral properties and distillation range indicated a complex mixture. The most and least volatile components were each isolated by distillation in 85–90% purity. Spectral and analytical data allowed their assignment as the 1,4 adduct, 4-chloro-1-piperidino-2,3-pentadiene (**4**) (low yield) and 4,5-bispiperidino-2-pentyne (**5**). Fractions of intermediate boiling point showed spectral evidence for hydroxyl and acetoxy groups in addition to piperidino groups. Therefore, on the hypothesis that the initial product was largely the 1,2 adduct, 4-chloro-5-piperidino-2-pentyne (**6**), which largely solvolyzed during basification and work-up, the reaction was repeated except that excess piperidine was added after reaction but before basification. Under these conditions diamine **5** was indeed isolated in 47% yield along with again a small amount of allene **4**.



Reaction with vinylacetylene gave only 30% crude basic product which largely decomposed on attempted distillation in contrast to the adducts from **1** and **2**. Nmr evidence tentatively suggests that the basic product was >50% the 1,4 adduct, 1-chloro-4-piperidino-1,2-butadiene, but this product could not be purified. Reaction with 2-penten-4-yne also gave only a moderate amount of basic product which was not successfully purified or identified.

In the context of our previous discussion[1] concerning the factors affecting orientation in radical addition to enynes,[4] the conversion of enyne **1** to allene **3** is unusual in that an allenic product is the *major* product from an atom transfer reaction to a propargylic radical.[5] However, since it has not been rigorously demonstrated that the isolated products are those of kinetic control, mechanistic conclusions should be drawn with caution. It is nevertheless true that an added electrostatic factor is operative in the present system which would be expected to favor 1,4 over 1,2 addition; *i.e.*, approach of the positively charged atom transfer agent ($R_2\overset{+}{N}HCl$) at the site farthest removed from the positively charged substituent in the intermediate propargylic radical [$C_5H_{10}\overset{+}{N}HCH_2\dot{C}(CH_3)C{=}CH$] should be favored from coulombic considerations.

Treatment of adduct **3** with sodium methoxide in refluxing methanol led to formation in moderate yield of 1-(5′-methoxypentyl)-3-methylpyrrole (**7**); the assignment as a 1,3-dialkylpyrrole was unambiguous based on the uv and nmr spectral behavior in strong acid compared to nonpolar solvents.[6,7] This initially surprising rearrangement has analogy in the conversion of 1-bromo-4-dialkylamino-1,2-butadienes[3] to pyrroles by treatment with excess amine, a reaction which proceeds *via* an intermediate propargylic amine [$C{\equiv}CC(NR_2)CNR_2$];[8] similarly, acetylenic aminohydrins [$C{\equiv}CC(OH)CNR_2$] can be converted to pyrroles.[9]

Experimental Section

All ir and nmr spectra were taken in carbon tetrachloride unless otherwise specified. Preparation of the enynes has been described.[1] A typical preparation of *N*-chloropiperidine follows.[2] A solution of 17.0 g (0.20 mol) of piperidine in 100 ml of ether was stirred for 1 hr with a suspension of 28.4 g (0.21 mol) of *N*-chlorosuccinimide. The mixture was washed with water and with 2.5 *N* sulfuric acid, dried, and evaporated to leave 19.0 g (0.16 mol) of crude chloramine which was dissolved in a cooled mixture of 75 ml of sulfuric acid and 260 ml of acetic acid for subsequent use.

Addition of *N*-Chloropiperidine to 2-Methyl-1-buten-3-yne (1).—To a stirred solution of the chloramine (0.16 mol) in sulfuric acid–acetic acid was added dropwise 11.2 g (0.17 mol) of enyne **1**. A few crystals of ferrous ammonium sulfate were added after *ca.* 1 g of **1** had been introduced; from that point on, external cooling was needed to maintain a temperature of <30°. After addition of **1** was complete, the mixture was stirred 30 min before it was poured into 600 ml of water and 200 g of ice. Extraction with pentane gave 0.7 g of neutral product. The aqueous solution was carefully neutralized with 12 *M* sodium hydroxide solution. Extraction with ether gave, after drying and evaporation, 21.7 g of crude basic adduct (73%). Distillation through an 18-in. spinning-band column gave 12.7 g of adduct **3**: bp 50–51° (0.1 mm); $n^{22}D$ 1.5093; ir 1960 cm^{-1} (C=C=C); nmr δ 5.92 (m, =CHCl), 2.88 (d, $J \sim 1.7$ Hz, $R_2NCH_2C{=}$), 2.35 (br m, CH_2NCH_2), 1.97 (d, $J \sim 2$ Hz, $CH_3C{=}$), and 1.48 ppm (br m, ring CH_2). Ir and nmr spectral comparison showed that distillation had achieved negligible purification and that the crude adduct was >95% pure. Adduct **3** was analyzed as its crystalline picrate, mp 91–92° (95% ethanol).

(3) M. V. Mavrov, E. S. Voskanyan, and V. P. Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2646 (1967)

(4) If 4,3 ($CH_2{=}CRCCl{=}CRNR_2$) or 4,1 adducts ($ClCH_2CR{=}C{=}CRNR_2$) had formed, they would have been expected to hydrolyze during work-up to α,β-unsaturated aldehydes in analogy to the behavior of the adducts from acetylenes (ref 2). No spectral evidence for aldehydic material in the neutral products was obtained.

(5) R. M. Fantazier and M. L. Poutsma, *J. Amer. Chem. Soc.*, **90**, 5490 (1968).

(6) R. L. Hinman and S. Theodoropulos, *J. Org. Chem.*, **28**, 3052 (1963).

(7) Y. Chiang and E. B. Whipple, *J. Amer. Chem. Soc.*, **85**, 2763 (1963).

(8) E. S. Voskanyan, M. V. Mavrov, and V. F. Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1736 (1968).

(9) F. Y. Perveev and V. M. Demidova, *J. Gen. Chem. USSR*, **34**, 3220 (1964).

Anal. Calcd for $C_{16}H_{19}ClN_4O_7$: C, 46.33; H, 4.62; Cl, 8.58; N, 13.51. Found: C, 46.01; H, 4.82; Cl, 8.73; N, 13.27.

Reaction of Adduct 3 with Sodium Methoxide.—Allene **3** (7.41 g, 40.1 mmol) was added to a solution prepared from 1.80 g (78.3 mg-atoms) of sodium in 60 ml of methanol; the mixture was held at reflux 17 hr. The mixture was flooded with water and extracted with ether. The ether extracts were washed with 0.5 *N* sulfuric acid, dried, and evaporated to leave 2.79 g of crude product. Distillation gave 2.48 g (34%) of **7**: bp 78–79° (0.1 mm); uv (heptane) λ_{max} 222 nm (ϵ 5800);[6] uv (5 *M* H_2SO_4) λ_{max} 266 nm (ϵ 3900);[7,10] nmr δ 6.3 and 5.8 (m, pattern analogous to that of 1-*n*-propyl-3-methyl pyrrole[11]), 3.68 (t, J = 6.5 Hz, NCH_2), 3.27 (t, J = 6.5 Hz, OCH_2), 3.22 (s, OCH_3), 2.03 (s, ring CH_3), and 1.8–1.1 ppm (m, $-(CH_2)_3-$); nmr (H_2SO_4) consistent with protonation at the 2 position[7] δ 8.52 (br s, C^5 H), 6.71 (br s, C^4 H), 4.80 (br s, C^2 H_2), 4.35 (t, $J \sim 7$ Hz, $=\overset{+}{N}CH_2$), 4.05 (s, OCH_3), 4.02 (t, $J \sim 7$ Hz, OCH_2), 2.40 (br s, ring CH_3), and 2.35–1.0 ppm (br m, $-(CH_2)_3-$); mass spectrum (70 eV) *m/e* (rel intensity) 181 (85), 166 (60), 95 (100), and 94 (75).[12]

Addition of *N*-Chloropiperidine to 1-Penten-3-yne (2).—Reaction of 14.6 g (0.122 mol) of the crude chloramine and 8.0 g (0.121 mol) of enyne **2** gave, after the usual work-up, 0.32 g of neutral product and 14.0 g of basic product. Distillation of the latter gave several arbitrary fractions, bp 83–110° (0.5 mm), totalling 9.14 g. The first (0.2 g) had spectral properties consistent with adduct **4**: ir 1965 cm^{-1} (C=C=C); nmr δ 5.4 (m, CH=), 2.98 (d, J = 6.5 Hz, NCH_2), 2.4 (m, CH_2NCH_2), 2.08 (d, J = 2.5 Hz, $=CClCH_3$), and 1.5 ppm (m, $-(CH_2)_3-$); the nmr spectrum suggested ~85% purity. The final fraction (4.0 g) had an nmr spectrum consistent with bisamine **5**: δ 3.35 (m, area 1, NCHC≡), 2.24 (m, area 10, NCH_2), 1.82 (d, J = 2 Hz, area 3, $\equiv CCH_3$), and 1.5 ppm (m, area 12, $-(CH_2)_3-$). The nmr spectra of intermediate fractions showed a singlet at δ 2.00 (ir 1740 cm^{-1}, CH_3CO_2, ?), a cluster of bands at δ 1.8 ($\equiv CCH_3$ in a family of similar compounds, ?), and at least two broad multiplets at δ 3.9 and 4.2 ppm (CHXC≡, ?).

A parallel reaction was carried out with 17.9 g (0.15 mol) of the chloramine and 11.2 g (0.17 mol) of **2**. After reaction was complete, piperidine (12.75 g, 0.15 mol) was added with cooling; work-up gave 0.28 g of neutral product and 25.9 g of basic product. Distillation gave, after removal of piperidine at ~20 mm, (1) 1.7 g, bp 58–59° (0.05 mm), (2) 1.5 g, bp 70–95° (0.05 mm), and (3) 14.5 g, bp 95–102° (0.05 mm), $n^{22}D$ 1.5040. The nmr spectrum of **1** showed it to contain ~60% (6% yield) adduct **4** plus several minor components. Treatment of 0.31 g of **1** with picric acid in ethanol gave, after addition of water, 0.42 g of picrate, mp 129–133°; two crystallizations from ethanol–water gave 0.26 g, mp 139–140°.

Anal. Calcd for $C_{16}H_{19}ClN_4O$·: C, 46.33; H, 4.62; Cl, 8.58; N, 13.51. Found: C, 45.84; H, 4.75; Cl, 9.01; N, 13.39.

The nmr spectrum of **3** showed it to be pure **5**. A very insoluble bispicrate formed in 97% yield and could be crystallized from a large volume of ethanol, mp 200° dec.

Anal. Calcd for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 46.55; H, 5.05; N, 15.75.

Addition of *N*-Chloropiperidine to Vinylacetylene.—Reaction between 13.7 g (0.11 mol) of the crude chloramine and 6.4 g (0.12 mol) of vinylacetylene, introduced as a gas in a stream of nitrogen into the reaction solution topped by a Dry Ice filled condenser, gave 1.2 g of neutral product and 5.8 g of basic product which quickly became deeply colored. Short-path distillation gave only 0.9 g, bp 68–71° (0.3 mm). The nmr spectrum showed the following reasonable bands for 1-chloro-4-piperidino-1,2-butadiene but they accounted for only 65% of the integrated area: δ 6.2–5.4 (m, CH=C=CHCl), 3.05 (d, d, J = 7 and 2 Hz, NCH_2), 2.4 (m, CH_2NCH_2), and 1.5 ppm (m, $-(CH_2)_3-$). The nmr spectrum of the original basic residue suggested that it was at least 50% this same product, but purification could not be achieved.

Registry No.—**3**, 30344-85-5; **3** picrate, 30344-86-6; **4**, 30344-87-7; **4** picrate, 30344-88-8; **5**, 30344-89-9; **5** picrate, 30344-90-2; **7**, 30344-91-3; 1-chloro-4-piperidino-1,2-butadiene, 30344-92-4; *N*-chloropiperidine, 2156-71-0.

(10) The group shifts in ref 7 predict λ_{max} 263 nm for an α-protonated 1,3-dialkylpyrrole.

(11) F. Y. Perveev, V. Y. Statsevich, and L. P. Gavryuchenkova, *J. Org. Chem. USSR*, **2**, 395 (1966).

(12) See A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 805 (1965), for discussion of the analogous *m/e* 81 and 80 in *N*-*n*-alkylpyrroles.

The Conversion of Vicinal Nitro Nitrates to Nitroalkanes with Sodium Borohydride

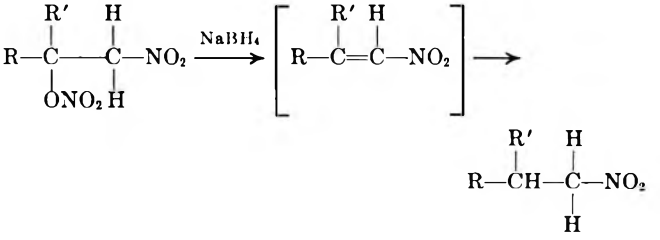
JOHN M. LARKIN* AND KENNETH L. KREUZ

Texaco Research Center, Beacon, New York 12508

Received January 25, 1971

Available literature procedures for the conversion of 1-alkenes to terminal nitroalkanes[1-3] have certain limitations. The operation consists of first converting the olefin to dinitroalkanes, nitro alcohols, nitro nitrites, or mixtures of these compounds, treating the latter with base to form nitro olefins, and then catalytically hydrogenating the nitro olefins to nitroalkanes. The disadvantages are that (a) two separate steps are involved in converting the substituted nitro compounds to nitroalkanes, (b) nitro olefins often dimerize[4] or polymerize,[5] (c) catalytic reductions are sometimes inconvenient on a laboratory scale, and (d) care must be exercised that the nitro paraffins are not further reduced to amines in the last step.

The sodium borohydride reduction of β-nitro nitrates provides a route to nitroalkanes free from these disadvantages. 1-Nitro-2-alkyl nitrates are readily obtained in high yield from 1-alkenes, nitrogen oxides, and oxygen.[6] The sodium borohydride reduction step requires only simple mixing of reactants in ordinary glassware at room temperature. Sodium borohydride has been employed previously in the preparation of nitroalkanes from α-nitro ketones[7] and β-nitro hydroxy and chloro compounds.[8] The reaction presumably proceeds *via* the nitroalkene intermediate resulting from base-induced nitric acid elimination.



Rapid reduction of the nitroalkene intermediate apparently precludes side reactions such as dimerization and polymerization. By contrast, in the reduction of

(1) G. A. Bonetti, J. J. Gavigan, H. O. Hansen, and R. Rosenthal, U. S. Patent 3,240,823 (March 15, 1966).

(2) C. Michalski and G. A. Bonetti, U. S. Patent 3,297,769, (Jan 10, 1967).

(3) W. K. Seifert and L. L. Ferstandig, U. S. Patent 3,035,101 (May 15, 1962); W. K. Seifert, *J. Org. Chem.*, **28**, 265 (1963).

(4) A. I. Meyers and J. C. Sicar, *ibid.*, **32**, 4134 (1967).

(5) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).

(6) (a) D. R. Lachowicz and K. L. Kreuz, U. S. Patent 3,282,983 (Nov 1, 1966). (b) D. R. Lachowicz, J. M. Larkin, and K. L. Kreuz, unpublished results; a less suitable procedure is described in the earlier work of N. Levy, C. W. Scaife, and A. E. Wilder-Smith, *J. Chem. Soc.*, 52 (1948).

(7) A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, **33**, 1733 (1968).

(8) A. Hassner and C. H. Heathcock, *ibid.*, **29**, 1350 (1964).

nitroalkenes with $NaBH_4$, the maintenance of acidic conditions is necessary to prevent dimerization.[4]

By using the sodium borohydride procedure, the nitro nitrates listed in Table I were converted to the

TABLE I
REACTION OF VICINAL NITRO NITRATES (NN) WITH SODIUM BOROHYDRIDE

Nitro nitrate	Product	Reaction time, hr	Mol of $NaBH_4$/mol of NN	Yield, %
1-Nitro-2-octyl nitrate	1-Nitrooctane (1)	19	3.3	94
4-Methyl-1-nitro-2-pentyl nitrate	1-Nitro-4-methylpentane (2)	24	3.2	72
1-Nitro-2,4,4-trimethyl-2-pentyl nitrate	1-Nitro-2,4,4-trimethylpentane (3)	60	3.6	83
3-Nitro-2,4,4-trimethyl-2-pentyl nitrate	No reaction	41	4.3	0
1-Nitro-2-tetradecyl nitrate	1-Nitrotetradecane (4)	25	3.9	58

corresponding saturated nitro compound. The yields given are based on a single run only, and so are probably not optimal.

The nitroalkanes **1**, **2**, and **4** have ir and nmr spectra like those previously recorded[4] (ir absorption at 6.45 and 7.25 μ; nmr triplets at δ 4.35–4.37). 1-Nitro-2,4,4-trimethylpentane (**3**) gives an ABX pattern at δ 4.21 for the protons adjacent to the nitro group and a complex multiplet at δ 2.38 for the tertiary proton.

Only starting material was obtained from the reaction of 3-nitro-2,4,4-trimethyl-2-pentyl nitrate with sodium borohydride. The steric hindrance of the nitro olefin derived from this internal nitro nitrate may be too great to permit its formation.

Experimental Section

The nitro nitrates were prepared as previously described.[6] Ir spectra were recorded on a Perkin–Elmer Model 137 spectrophotometer and nmr spectra were obtained on a Varian Associates Model V-4311 spectrometer operating at 60 Mc.

1-Nitro-2,4,4-trimethylpentane (3). General Procedure.—Sodium borohydride (1.25 g) was slowly added to a solution of 2.00 g of 1-nitro-2,4,4-trimethyl-2-pentyl nitrate in 50 ml of 95% ethanol. The mixture was stirred briefly at room temperature and allowed to stand for 2.5 days. It was diluted with H_2O (100 ml), acidified with 1.2 *N* HCl, and extracted with ether. The extract was washed (NaCl solution), dried ($MgSO_4$), and evaporated. 1-Nitro-2,4,4-trimethylpentane (**3**) (1.20 g, 83%) remained as a pale yellow liquid. The ir spectrum is nearly identical with that of an analytical sample prepared by chromatography on silica gel using mixtures of methylene chloride and hexane as eluents, $n^{20}D$ 1.4317. *Anal.* Calcd for $C_8H_{17}NO_2$: C, 60.3; H, 10.8; N, 8.8. Found: C, 60.2; H, 10.7; N, 8.8.

Nitroalkanes **1**, **2**, and **4**, all colorless liquids, were prepared similarly using the conditions stated in Table I.

Registry No.—**1**, 629-37-8; **2**, 14424-33-0; **3**, 30344-80-0; **4**, 4609-87-4; sodium borohydride, 16940-66-2.

Acknowledgments.—We wish to thank Mr. Lewis P. Larson and Mr. George A. Taylor for recording the nmr spectra and Mr. Paul J. McMahon for technical assistance.

Photolysis of Penta-*O*-acetyl-*aldehydo*-D-glucose[1]

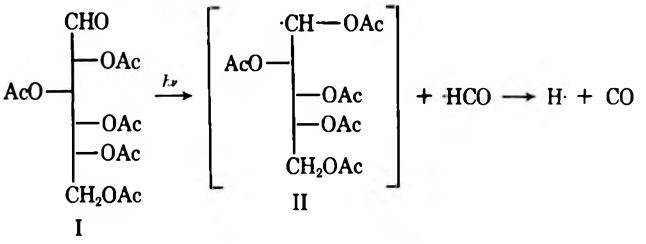
ROY L. WHISTLER* AND KHONG-SENG ONG

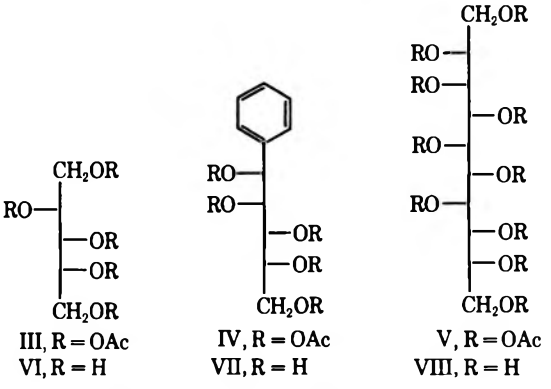
Department of Biochemistry, Purdue University, Lafayette, Indiana 47907

Received February 12, 1971

Although photodecarbonylation of aliphatic aldehydes occurs readily in the vapor phase,[2,3] elimination of carbon monoxide is almost entirely suppressed in solution at 25°. At temperatures above 100°, however, decarbonylation has been observed with quantum efficiency.[4]

It is interesting to observe, therefore, that when a benzene solution of *aldehydo*-D-glucose pentaacetate (I) is irradiated with ultraviolet light at 10–15°, it produces three major crystalline photoproducts, all of which are derived by way of radical II, realized through α-bond cleavage. Compounds III, IV, and V are formed in 16, 2.5, and 1% yield, respectively. At 60° the starting material is consumed in 6 hr as compared to 70 hr at 10–15° and the yields of III, IV, and V increase to 17.5, 6, and 2%, respectively. The small increase in yields might be due to the loss of radical II





through secondary reactions which may also be temperature dependent. The formation of III is, as with aliphatic aldehydes, most prominent and is formed by α-bond fission producing carbon monoxide and a five-carbon radical that combines with a hydrogen atom to produce D-arabinitol pentaacetate, identified by comparison of mixture melting point and ir and nmr spectra with an authentic sample.[5] The nmr spectrum of photoproduct IV gives, in addition to the charac-

(1) This work was presented in part before the 161st Meeting of the American Chemical Society, Los Angeles, Calif., March 1971; Journal Paper No. 4338 of the Purdue Agricultural Experiment Station, Lafayette, Ind. 47907.

(2) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1504 (1935); R. G. W. Norrish and R. P. Wayne, *Proc. Roy. Soc., Ser. A*, **284**, 1 (1965).

(3) P. Ausloos and R. E. Robert, *J. Amer. Chem. Soc.*, **83**, 4897 (1961).

(4) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1544 (1938).

(5) C. S. Hudson, *J. Amer. Chem. Soc.*, **57**, 1753 (1935).

teristic chemical shifts of a glycitol acetate in the τ 4.0–8.5 region, a peak at τ 2.68 attributable to a phenyl group. The proof of configuration of IV, as 1-*C*-phenyl-penta-*O*-acetyl-D-*manno*-pentitol, comes from its deacetylation to the known[6] 1-*C*-phenyl-D-*manno*-pentitol (VII). The configuration at C-2 of the pentitol pentaacetate IV is thus ascertained. Though photochemical amidation[7] and acylation[8] of benzene have been observed, intermolecular alkylation as in the formation of IV is uncommon.

Dimerization of radical II to V generates new asymmetric centers at C-5 and C-6, giving rise to the possible formation of any, if not all, of the three isomeric decaacetates: D-*gluco*-D-*manno*-, D-*manno*-D-*manno*-, and D-*gluco*-L-*gulo*-decitol. The dimer crystallized as a single compound as evidenced by tlc and sharp melting point. To obtain configurational information, decitol VIII, derived from deacetylation of V, was subjected to periodate oxidation. Schwarz[9] has earlier demonstrated that oxidation of hexitols with a limited quantity (0.1 mol equiv) of periodate induces preferential cleavage between vicinal hydroxyls in the *threo* configuration. When the decitol VIII is oxidized with 0.1 mol equiv of periodate at 20°, the only sugars detected on paper chromatography are D-glucose and D-arabinose. The absence of D-mannose in the oxidized products allows tentative assignment to the decitol of the D-*gluco*-L-*gulo* configuration as shown in VIII.

Experimental Section

Irradiations were made with a 450-W 679A-36 mercury lamp without filter under oxygen-free nitrogen. The progress of reactions and purity of products were checked by thin layer chromatography (tlc) on silica gel G[10] coated glass plates (5 × 13 cm) irrigated with benzene–ether (1:2 v/v). Melting points were determined on a Fisher–Johns apparatus and were corrected. Infrared spectra were recorded in Nujol with a Perkin-Elmer Model 337 spectrometer, and nmr spectra were determined in deuteriochloroform solution with TMS as the internal standard using a Varian A-60 spectrometer. Mass spectroscopy was obtained with a Hitachi RMU-6A spectrometer at 200° (75 eV). Optical rotations were measured at 25° in a Perkin-Elmer automatic polarimeter Model 141.

Photolysis of Penta-*O*-acetyl-*aldehydo*-D-glucose.[11]—A solution of the pentaacetate I (15 g) in 1.5 l. of benzene was irradiated for 70 hr (at 10–15°), after which the solution was concentrated to dryness to give a syrup. Investigation of the syrup on tlc showed, besides starting material (R_f 0.18), three main products, corresponding to compounds V, III, and IV with R_f 0.30, 0.59, and 0.70, respectively. There was a considerable amount of tailing. The syrup was applied to a silica gel[12] column (600 g) and eluted with benzene–ether (3:1 v/v). Progress was checked by tlc and the fraction containing starting material I was crystallized from benzene–hexane: yield 2 g.

1-*C*-Phenylpenta-*O*-acetyl-D-*manno*-pentitol (IV) and 1-*C*-Phenyl-D-*manno*-pentitol (VII).—The fraction containing IV was crystallized from ethyl acetate–hexane to give pure IV: mp 92–93°; $[\alpha]^{25}D$ +28.6° (*c* 1.0, chloroform); yield 0.67 g (4.5%); τ ($CDCl_3$) 2.68 (phenyl), 5.80 (H-5), 4.3 (H-1, H-2, H-3, and H-4), 7.90, 7.96, 8.22 (OAc).

Anal. Calcd for $C_{21}H_{26}O_{10}$: C, 57.53; H, 5.97. Found: C, 57.71; H, 5.92.

Compound IV (0.4 g) was deacetylated in absolute methanol (10 ml) with a catalytic amount (0.1 ml) of 0.1 *N* sodium methoxide at 25°. On deionization with Amberlite IR-120 ion-exchange resin, compound VII thus obtained was recrystallized from ethanol–acetone: mp 172–173°; $[\alpha]^{25}D$ −46.8° (*c* 1.0, pyridine) [lit.[6] mp 172.5–173°; $[\alpha]D$ −44.8° (*c* 0.76, pyridine)].

Penta-*O*-acetyl-D-arabinitol (III).—The fraction containing III was crystallized from benzene–hexane: mp 75°; $[\alpha]^{25}D$ +37° (*c* 2.0, chloroform); yield 1.92 g (16%). Nmr and ir spectra and mixture melting point were identical with those of an authentic sample prepared from D-arabinitol. Deacetylation of III in absolute methanol gave D-arabinitol, mp 103–104° (lit.[13] mp 103°).

D-*gluco*-L-*gulo*-Decitol Decaacetate (V). A. From Column Chromatography.—The fraction containing the dimer V was crystallized from methanol: mp 156–157°; $[\alpha]^{25}D$ +55.9° (*c* 2.0, chloroform); yield 0.12 g (1%); ν_{max} 1750 cm^{-1} (OAc); mass spectrum *m/e* 662 (M − HOAc) (calcd *m/e* 722); osmometric mol wt 708.

B. From Fractional Crystallization.—In subsequent reactions where the photolyses were done for longer periods when all the starting material was consumed, the resulting syrup, when taken up in benzene, gave V as crystalline residue, prior to column chromatography.

Anal. Calcd for $C_{30}H_{42}O_{20}$: C, 49.86; H, 5.85. Found: C, 49.58; H, 5.78.

D-*gluco*-L-*gulo*-Decitol (VIII).—Decaacetate V (0.40 g) was deacetylated at 25° in neat methanol (10 ml) with a catalytic amount (0.1 ml) of sodium methoxide (0.1 *N*) to give decitol VIII, crystallized from aqueous ethanol: mp 178–179°; $[\alpha]^{25}D$ −5.2 (*c* 0.70, water); yield 0.152 g; ν_{max} 3500 and 3380 cm^{-1} (OH).

Anal. Calcd for $C_{10}H_{22}O_{10}$: C, 39.74; H, 7.34. Found: C, 40.02; H, 7.44.

Photolysis of Penta-*O*-acetyl-*aldehydo*-D-glucose at Higher Temperature.—Benzene (150 ml) was irradiated while the immersion well was circulated with water; after 3 hr an ambient temperature of 60° had been reached. Pentaacetate I (1.5 g) was then introduced in one addition and irradiation was continued for 6 hr, after which the starting material had been consumed as evidenced by tlc. The syrup, obtained after concentrating the benzene, was chromatographed on silica gel column (90 g). Photoproducts III, IV, and V, after crystallization from the specific solvents as described above, were obtained in the yields of 17.5, 6, and 2% respectively.

Sodium Periodate Oxidation of VIII.—A 0.1 *M* aqueous solution of the decitol (0.1 ml) was mixed with an equal volume of 0.01 *M* sodium periodate at 20°. After 0.5 hr the solution gave a negative starch–KI test for periodate.

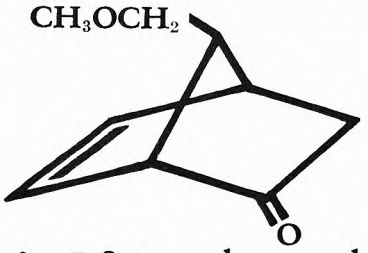
Paper Chromatography of the Oxidized Decitol.—Descending technique and Whatman No. 1 paper were used and developed with ethyl acetate–pyridine–water (8:2:1 v/v). The sugars were detected with *p*-anisidine hydrochloride. Oxidized decitol gave a pink spot and a yellowish brown spot, showing that the components moved at the same rate as D-arabinose and D-glucose, respectively. In addition there was a faint spot with an R_f larger than pentose; no mannose could be detected.

Registry No.—I, 3891-59-6; III, 5401-55-8; IV, 30469-99-9; V, 30545-63-2; VII, 30469-85-3; VIII, 30469-86-4.

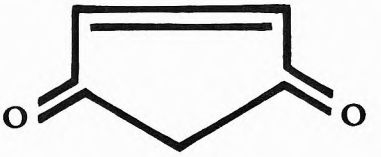
(6) W. A. Bonner, *J. Amer. Chem. Soc.*, **73**, 3126 (1951).
(7) D. Elad, *Tetrahedron Lett.*, 77 (1963).
(8) U. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **4**, 146 (1965).
(9) J. C. P. Schwarz, *J. Chem. Soc.*, 276 (1957).
(10) E. Merck, Darmstadt, Germany. Distributors: Brinkmann Instruments Inc., Westbury, N. Y. 11590.
(11) M. L. Wolfrom, M. Konigsberg, and D. I. Weisblat, *J. Amer. Chem. Soc.*, **61**, 574 (1939).
(12) J. T. Baker Chemical Co., Phillipsburg, N. J.
(13) O. Ruff, *Ber.*, **32**, 554 (1899).

MORE ALDRICH FIRSTS

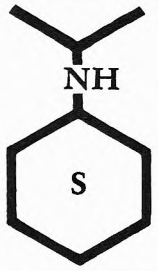
PROSTAGLANDIN INTERMEDIATES



16,200-0 7-Syn-methoxymethyl-2-morbornene-5-one, tech., 90 %
5 g. — $30.



16,168-3
4-Cyclopentene-1,3-dione
1 g. — $6. 5 g. — $20.



ICA

N-Isopropylcyclohexylamine, as its lithium salt (LiICA — readily generated with *n*-butyllithium in THF), reacts rapidly and quantitatively with esters to yield ester enolates. Alkylation of such lithio ester enolates gives the corresponding ∝-alkyl esters, generally in good yield.

M. W. Rathke and A. Lindert, J. Amer. Chem. Soc., *93*, 2318 (1971).

16,197-7 N-Isopropylcyclohexylamine
$12/500g. $48/3kg.

NABS-Cl

4-(4-Nitrophenylazo)-benzoyl chloride

NABS-Cl is an important reagent for the isolation and characterization of many natural products. Its esters and amides are usually crystalline and bright orange, and thus suitable for easy chromatographic purification. Molecular weight of an unknown is easily determined from the UV absorption of the NABS-chromophore.[1]

1. W. H. Nutting, R. A. Jewell and H. Rapoport, J. Org. Chem. *35*, 505 (1970).

15,664-7 NABS-Cl
$5.40/g. $18/5g.

For our latest Catalog, write to—

Aldrich Chemical Company, Inc.

CRAFTSMEN IN CHEMISTRY

940 WEST SAINT PAUL AVENUE · MILWAUKEE, WISCONSIN 53233