Synthesis and Structure Proof of C-2 and C-4 Monofunctional Brexanes and Brendanes

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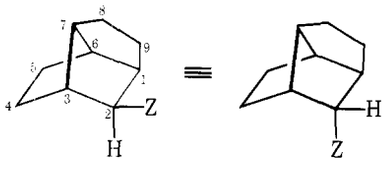
The C_9 skeletons in tricyclo[4.3.0.$0^{3,7}$]nonane ("brexane") and tricyclo[4.2.1.$0^{3,7}$]nonane ("brendane") on the one hand and in tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]nonane ("deltacyclane") on the other are perceived as interesting homologocycles of norbornane and nortricyclane, respectively. For example, brexyl derivatives are chiral and are uniquely structured so that a substituent at C-2 is simultaneously exo to one norbornyl unit and endo to another. Therefore, the ease of ionization of the C-2 substituent can, among other things, reveal the relative importance of "anchimeric assistance" and "steric hindrance to departure" because these two "norbornyl" features oppose each other. This paper describes the preparation and characterization of key monofunctionalized brexanes and brendanes. Brexan-2-one (**10**) was synthesized from a 7-carboxynorbornyl precursor (**6a**) through a sequence that involved lengthening the C-7 chain and ring closure by internal alkylation. Deltacyclane (**21**) was obtained from norbornadiene by four different routes and provides convenient access to brexan-4-one (**24**) and brendan-2-one (**25**) through cleavage of the cyclopropyl ring. We prepared brendan-4-one (**31**) from a known norbornenecarboxylic acid (**28a**) by transformations that involved formation and directed opening of tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]nonan-3-one (**29**). The brexyl and brendyl skeletons were confirmed by cleavage to known bicyclo[3.3.0]octyl systems and were interrelated with deltacyclane by carbene insertion reactions. With KO-*t*-Bu/*t*-BuOH at 185 °C brexan-2-one rearranges to brendan-2-one. This conversion illustrates the potential utility of alkali-induced skeletal changes via homoenolate ions.

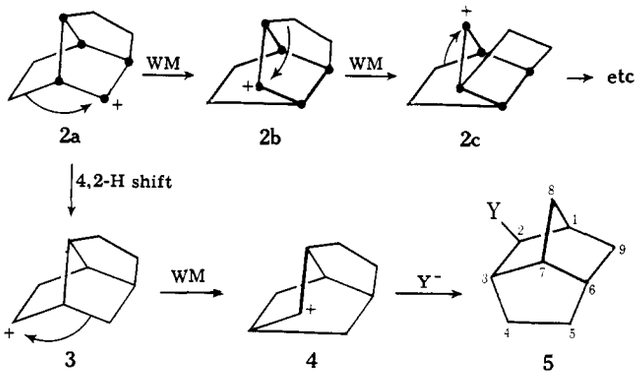
At a time of intense research activity in norbornyl chemistry we pointed out the unique features of the tricyclic C_9 analogue **1**, which we called "brexane", and recommended its study in connection with the "classical–nonclassical" cation controversy.[1] Two norbornyl units can be identified in brexane[2] and these are so arranged that a substituent Z at C-2 is simultaneously exo to one norbornyl unit and endo to the other. Furthermore, interchange of H and Z at C-2 produces neither a diastereomer nor an enantiomer, but a molecule superimposable on the original; i.e., **1a** ≡ **1b**. In norbornyl



1a **1b**

systems, exo derivatives solvolyze faster than do the corresponding endo analogues, but chemists disagree as to whether these differences should be attributed to abnormally high exo rates (due to anchimeric assistance) or to abnormally low endo rates (due to steric interference by an endo hydrogen directly across the ring.[3] The ionization behavior of brex-2-yl systems can uniquely reveal the relative importance of anchimeric assistance and steric interference because both of these factors act on Z simultaneously but oppose each other. Like its norbornyl counterpart, the tricyclic cation **2a** from departure of Z regenerates its mirror image on Wagner–Meerwein rearrangement (e.g., **2a** and **2b** are enantiomers), but has the added novel feature that repetitive rearrangements (e.g., **2a** → **2b** → **2c** → etc., Scheme I) involve consecutive shifts of antiparallel bonds and transfer the positive charge successively to every atom of the core ring, identified in **2a** by heavy dots. In contrast to norbornyl systems, however, 1,2-hydrogen shifts are precluded by the bridgeheads; and 1,3-hydrogen shifts (e.g., from C-4 to C-2 in **2a**) are separately detectable because they produce a new ion (**3**), which can terminate to give brex-4-yl derivatives or which can, by a single Wagner–Meerwein shift (**3** → **4**), give the brendane[4] skeleton **5** (Scheme I). In this paper we describe our syntheses, characterization, and interconversions of monofunctionalized brexanes, brendanes, and related systems. These full details[5] provide

Scheme I



the structural foundation for our own mechanistic work as well as for a variety of studies from other laboratories involving brexyl and brendyl skeletons.[6]

We divide the presentation into these six parts: (I) synthesis of brexan-2-ol; (II) routes to deltacyclane; (III) synthesis of brex-4-yl and brend-2-yl systems; (IV) synthesis and structure proof of brendan-4-one; (V) structural correlations in brexyl and brendyl systems; and (VI) skeletal rearrangements via homoenolate ions. Each part is accompanied by an appropriate formula scheme.

I. Synthesis of Brexan-2-ol. We prepared this C_9 target alcohol as outlined in Scheme II. The known keto acid **6a** was converted to the homologous, keto ester **7** in an overall yield of 43% by an Arndt–Eistert sequence (**6a** → **6b** → **6c** → **7**). The intermediate liquid acid chloride **6b** was not purified, but the crystalline diazomethyl ketone **6c** was fully characterized. Reduction of liquid keto ester **7** with lithium aluminum hydride gave a liquid mixture of epimeric diols (**8**). This diol mixture was selectively monoesterified at the primary alcohol with methanesulfonyl chloride and, without isolation, the monomesylate **8b** was oxidized with Brown's reagent to the liquid keto mesylate **9** and directly cyclized to brexan-2-one (**10**) by the action of NaH in *N*,*N*-dimethylformamide. This liquid ketone incorporated no deuterium in D_2O/K_2CO_3, formed no precipitate with sodium bisulfite, shows a split carbonyl peak in the infrared (1844 w and 1748 s), and gives a crystalline semicarbazone. Reduction with $LiAlH_4$ cleanly converted **10** to brexan-2-ol (**11**), which was readily reoxidized

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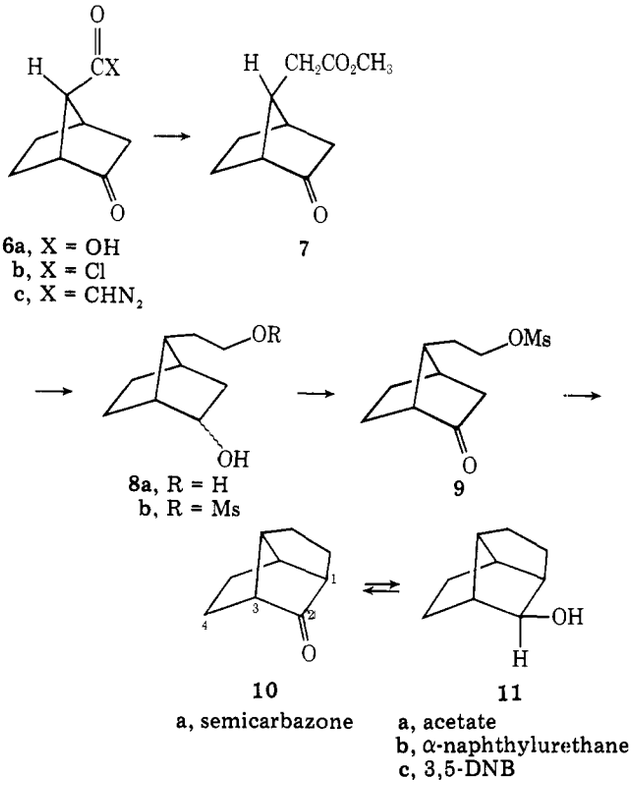
Scheme II. Synthesis of Brexan-2-ol



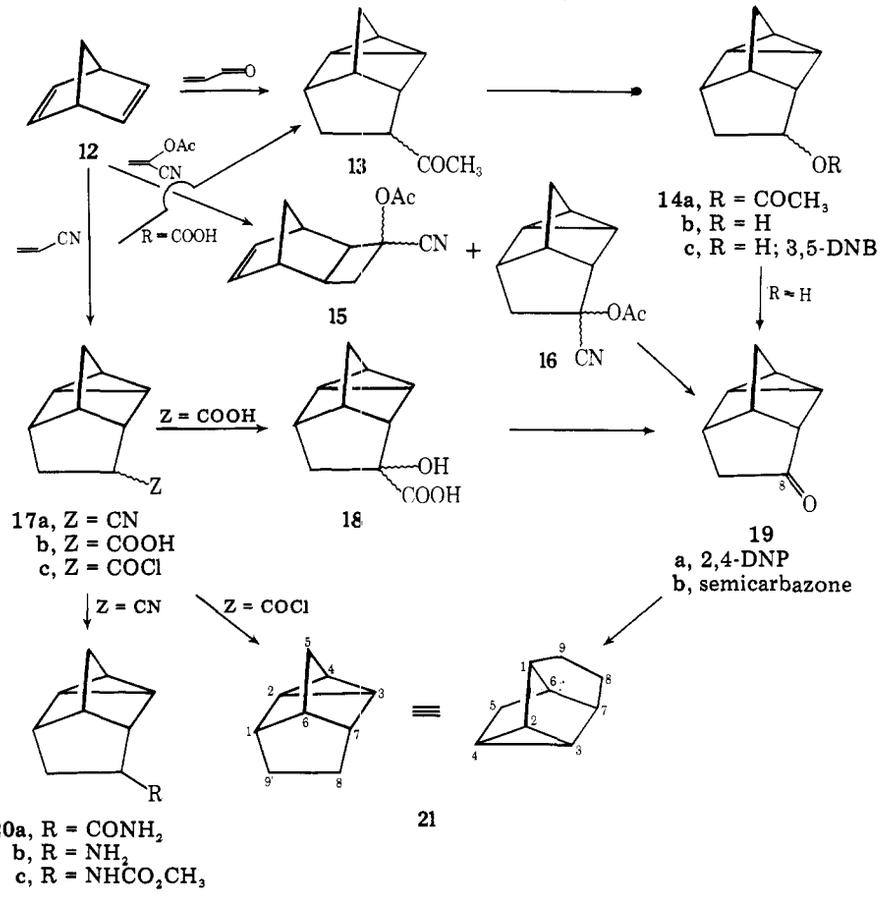
to the ketone. The overall yield in the eight-step sequence **6** → **11** was 6% and was not optimized. Brexan-2-ol (**11**) is crystalline, as are its α-naphthylurethane and 3,5-dinitrobenzoate, but its acetate **11a** (readily obtained with Ac_2O/Py) is liquid. Independent proofs of structure for brexan-2-one are described later in part V.

II. Routes to Deltacyclane.[7] This mesoid hydrocarbon (**21**) was pivotal in our synthetic plans for two reasons. Its tetracyclic skeleton seemed rather directly accessible by homoconjugative Diels–Alder reactions of norbornadiene (e.g., **12** → **17a** had been reported[8]), and electrophilic cleavage of its two types of cyclopropyl bonds could produce functionalized brendanes (e.g., rupture of the 2,3 bond) and/or brexanes (e.g., rupture of the 3,4 ≡ 2,4 bond). Scheme III outlines four routes we explored to deltacyclane, three of which aimed at ketone **19** as the penultimate goal.

Hall first reported the preparation of nitrile **17a**, in 12% yield, by [4 + 2] cycloaddition of norbornadiene (**12**) and acrylonitrile.[8] He converted the nitrile to the tetracyclic ketone **19** by a three-step sequence that involved hydrolysis to the carboxylic acid **17b** (44%), permanganate oxidation to hydroxy acid **18** (17%), and dichromate oxidation to ketone **19** (33%). We obtained this ketone by Hall's route, but in our hands the oxidation steps gave yields that were variable and frequently even lower than those reported.

We also applied Wiberg's[9] general method of decarboxylation to convert acid **17b** to deltacyclane **21**. In this sequence, without purification of intermediates, the acid chloride **17c** was prepared ($SOCl_2$/Py) and converted to the corresponding *tert*-butyl peroxyester by action of *tert*-butyl hydroperoxide. Thermolysis of the peroxyester in *p*-cymene gave deltacyclane (**21**), but its separation from *p*-cymene and from an unknown byproduct proved inefficient. We considered other ways to remove the CN group from **17a** such as conversion to NH_2 followed by reductive deamination.[10] The crystalline carboxamide **20a** was obtained conventionally from nitrile **17a** with H_2O_2. Although Hofmann rearrangement gave **20b** as a colorless liquid, this amine was not further investigated because it readily became colored in air, and its HBr and HCl salts were hygroscopic. Its urethane **20c**, however, was crys-

Scheme III. Routes to Deltacyclane



talline and stable, and served for characterization.

A more practicable synthesis of ketone **19** was developed from methyl ketone **13,** which in turn we prepared either by the action of methyllithium on acid **17b,** or by homoconjugative Diels–Alder addition of methyl vinyl ketone to norbornadiene (**12**). Both paths gave liquid ketone **13** as a mixture of two epimers in which the major component (configuration unassigned) predominates by a factor of ~1.6–2.6:1. Stereoisomerism at C-8 is of little consequence because that center becomes trigonal in ketone **19.** Therefore, the epimeric mixture was carried through the next two stages, viz. Baeyer–Villiger oxidation to acetate **14a** followed by saponification to alcohol **14b.** The oxidation succeeded with trifluoroperoxyacetic or *m*-chloroperoxybenzoic acid. Although deltacyclan-8-ol (**14b**) showed only one peak on gas chromatography, it still may consist of a mixture of epimers. A constant-melting 3,5-dinitrobenzoate (**14c**), however, probably represents a single stereoisomer. Brown's reagent readily oxidized **14b** to liquid ketone **19,** which gives crystalline derivatives **19a** and **19b.**

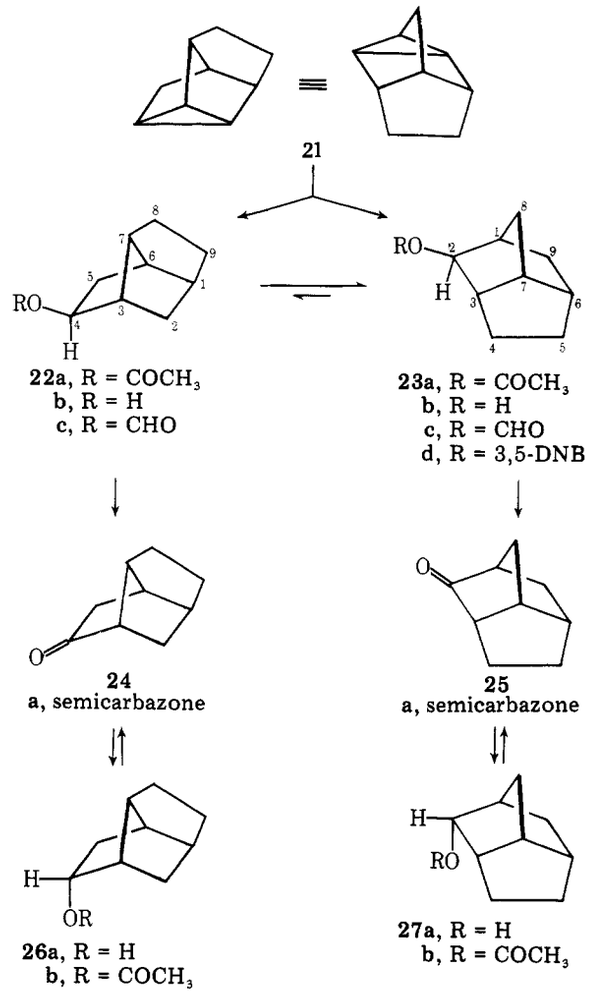
Our shortest route to deltacyclan-8-one (**19**) involved thermal cycloaddition of norbornadiene (**12**) and α-acetoxyacrylonitrile to produce a mixture of cyanohydrin acetates (**15** + **16**) in 28% yield. The presence of **15** as a minor component was inferred when saponification produced a 1:4 mixture of ketones, whose IR showed carbonyl absorption at 1770 cm^{-1} (cyclobutanone) as well as the 1740-cm^{-1} band for the major ketone, deltacyclan-8-one (**19**).[11a] The minor ketone, which still contains an olefin link, was removed by extraction with aqueous silver nitrate. Ketone **19** (and its semicarbazone **19b**) was reduced to liquid deltacyclane (**21**) by modified Wolff–Kishner methods.

III. Synthesis of Brex-4-yl and Brend-2-yl Systems. The cyclopropyl ring in deltacyclane (**21**) cleaves readily at room temperature in acetic acid/sulfuric acid. The products are *exo*-4-brexyl acetate (**22a**) and *exo*-2-brendyl acetate (**23a**), and the proportion of the latter acetate increases with time (Scheme IV). E.g., the brendyl/brexyl ratio (i.e., **23a/24a**) was about 1.5 after 20 min, but progressively increased to about 49 after 92 h. Clearly, the brendyl skeleton is the more stable, and the acid medium allows interconversion through a Wagner–Meerwein shift in their corresponding cations (viz. **3** → **4**). An acetate mixture from a 20-min run was separated by preparative gas chromatography and afforded **22a** and **23a** as clear liquids. Each acetate was readily saponified to its crystalline alcohol (**22b** and **23b,** respectively).

When our immediate objective was to prepare only the brend-2-yl compounds, we found it better to open deltacyclane in formic acid/sulfuric acid. After 20 h at room temperature, the formate esters **23c** and **22c** were present in the mixture in a ratio of ~50:1. Direct saponification gave crystalline *exo*-brendan-2-ol (**23b**) sufficiently pure (~95%) to carry forward. Acetylation of **23b** with Ac_2O/Py gave liquid **23a,** identical with that from the acetolysis route, and the 3,5-dinitrobenzoate derivative (**23d**) was crystalline.

The ketones **24** and **25** could be obtained individually by Brown oxidation of their respective pure exo alcohols. But we found it more practicable to prepare a mixture of the two ketones (by acetolysis of deltacyclane followed directly by saponification and oxidation) and then to separate them by preparative gas chromatography. Brexan-4-one (**24**) is a liquid, whereas brendan-2-one (**25**) is solid. Both show an infrared carbonyl band typical of a cyclopentanone (1745–1747 cm^{-1}), and brexan-4-one also absorbs at 1405 cm^{-1}, consistent with the presence of a $-CH_2CO-$. Both ketones were further characterized as their crystalline semicarbazones **24a** and **25a.** Evidence for location of the carbonyl groups as well as independent structural proof for the brexyl and brendyl skeletons are presented later in part V. The individual ketones were

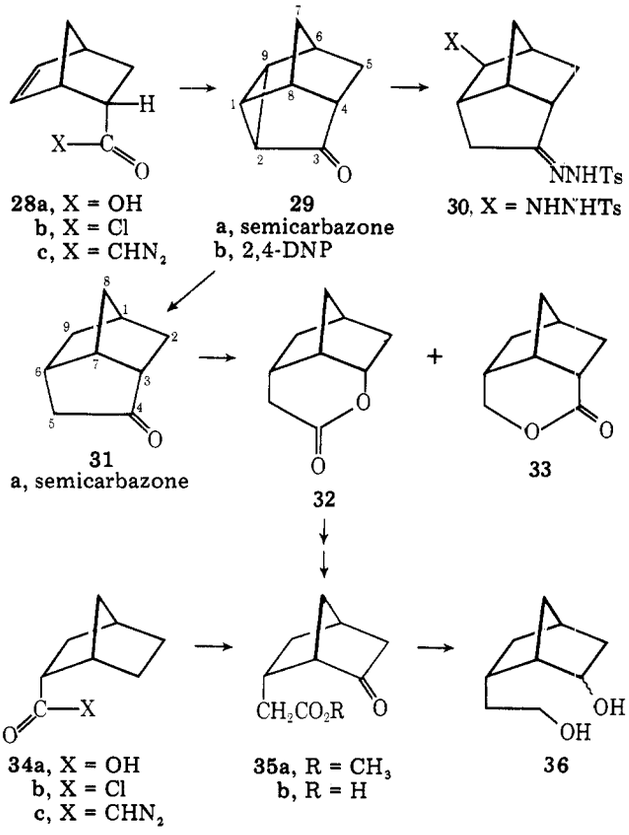
Scheme IV. Synthesis of Brex-4-yl and Brend-2-yl Systems



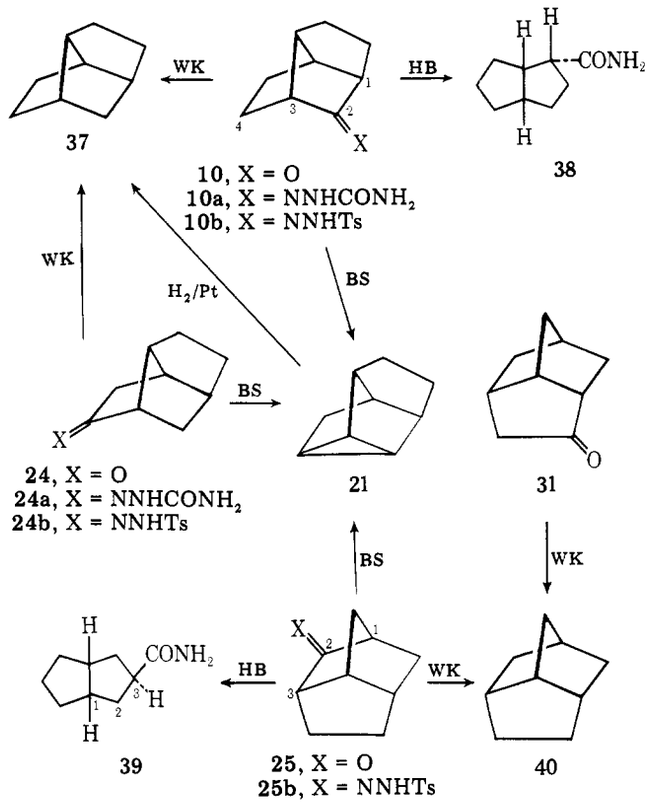
reduced with lithium aluminum hydride to the corresponding endo alcohols (liquid **26a** and solid **27a**), each of which was reoxidized to its parent ketone and readily acetylated (Ac_2O/Py) to acetates **26b** and **27b,** respectively.

IV. Synthesis and Structure Proof of Brendan-4-one (31). We found a convenient entry to the brendane system functionalized at C-4 from *endo*-5-norbornene-2-carboxylic acid (**28a**). This acid was converted to its acid chloride (**28b**) with oxalyl chloride and then to its diazomethyl ketone (**28c**) with diazomethane (Scheme V). Both **28b** and **28c** were liquids and were handled without purification. Intramolecular carbenoid addition of the diazomethyl group was effected with copper bronze, which gave the crystalline tetracyclic ketone **29** in an overall yield of 31% from **28.** Characteristic spectral features of this rigid, cyclopropyl ketone included a cyclopropyl C–H stretching band at 3048 cm^{-1}, a carbonyl stretching band at 1734 cm^{-1}, and UV λ_{max} (EtOH) 271 nm (ε 50). Ketone **29** gave a semicarbazone (**29a**) and a 2,4-dinitrophenylhydrazone (**29b**), whose analytical and spectral data indicated they were conventional derivatives. Interestingly, however, an unexpected result occurred on attempted routine preparation of a *p*-toluenesulfonylhydrazone. The derived product had combined with two molecules of the tosylhydrazine reagent and was soluble in dilute hydrochloric acid. We tentatively assign structure **30** to this bisfunctionalized product and presume it arises by a Michael-like addition to the "conjugated" cyclopropyl ketone, with cleavage of the more strained "conjugated" bond. This regioselectivity in cleavage is observed in the next synthetic step, opening of **29** to the target ketone **31,** either by catalytic hydrogenation (Pd/C) or by Li/NH_3 reduction. The crude brendan-4-one

Scheme V. Synthesis and Structure Proof of Brendan-4-one



Scheme VI. Structural Correlations in Brexyl and Brendyl Systems



(~86–89% yield) may be purified through a sodium bisulfite addition product or through hydrolysis of its high-melting semicarbazone (**31a**). Pure brendan-4-one shows carbonyl absorption at 1744 cm^{-1} (with slight splitting at 1703) and a methylene bending vibration at 1407 cm^{-1} characteristic of a $-CH_2CO-$ unit. Both enolizable hydrogens were exchanged completely by deuterium on reflux in $MeOD/D_2O$ containing K_2CO_3. To rule out the possibility of unexpected molecular rearrangements, we carried out an independent proof of structure for ketone **31** as follows.

Baeyer–Villiger oxidation of **31** with trifluoroperoxyacetic acid gave a mixture of the two δ-lactones **32** and **33.** We could not separate them directly, but found that saponification of the mixture followed by acidification at 0 °C regenerated lactone **33** and left the other component as the hydroxy acid. Without separation this mixture was treated with diazomethane, oxidized with Brown's reagent, and again saponified and acidified to reclose lactone **33.** An alkaline extraction readily separated lactone **33** from keto acid **35b,** and each was purified and characterized. Diazomethane converted **35b** to a pure sample of keto methyl ester **35a.** And this liquid ester was identical (IR and ^1H NMR) with authentic material that we synthesized from known keto acid **34a** by a three-step Arndt–Eistert homologation via acid chloride **34b** and diazomethyl ketone **34c.** The keto ester **35a** was reduced with $LiAlH_4$ to a crystalline diol (**36**), which probably has an *endo*-OH but for which we have no positive evidence.

V. Structural Correlations in Brexyl and Brendyl Systems. Because the brexyl and brendyl ketones in Schemes II–V play key roles in a variety of mechanistic studies, we wanted to confirm their structures by independent means. We used Haller–Bauer (HB) reactions, Wolff–Kishner (WK) reductions, and carbene insertions via Bamford–Stevens (BS) reactions as summarized in Scheme VI.

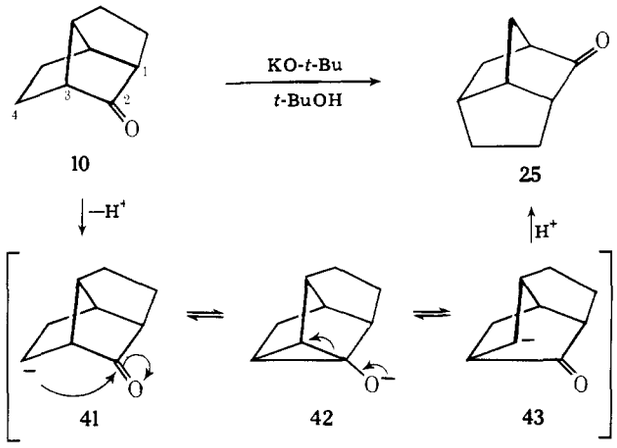
Haller–Bauer cleavage of the nonenolizable brexan-2-one (**10**) with sodium amide in diisopropyl ether produced *cis*-bicyclo[3.3.0]octane-*cis*-2-carboxamide (**38**). The melting point (161 °C), mixture melting point, and infrared absorption of this amide were identical with those of an authentic sample.[12]

A similar Haller–Bauer reaction opened brendan-2-one (**25**). Unlike the symmetrical brexan-2-one, however, brendan-2-one has two bonds that could potentially rupture, viz. 1,2 or 2,3. After repeated recrystallization of the crude cleavage product, we isolated an amide whose melting point (136–137 °C) agrees with that reported[13] for **39,** in which the H at C-3 is trans to the angular hydrogens. The cis epimer of **39** is reported to have mp 153 °C. Since C-2–C-3 cleavage of **25** should produce the cis geometry initially, we infer that the $CONH_2$ group epimerized in the alkaline medium. This inference is reasonable because Granger et al. have shown for the *cis*-bicyclo[3.3.0]octane skeleton that a CO_2CH_3 group at C-3 is more stable in the configuration corresponding to **39** than in the epimeric one.[13]

That brexan-2-one (**10**) and brexan-4-one (**24**) have identical carbon skeletons was shown by Wolff–Kishner reductions of their corresponding semicarbazones (**10a** and **24a**) to the same liquid tricyclic hydrocarbon, brexane (**37**). Likewise, Wolff–Kishner reductions of brendan-2-one (**25**) and brendan-4-one (**31**) produced the same crystalline hydrocarbon, brendane (**40**).

Finally the three ketones **10, 24,** and **25** were interrelated with one another and with deltacyclan-8-one (**19**) by preparation of their corresponding *p*-toluenesulfonylhydrazones (**10b, 24b,** and **25b,** respectively), followed by thermolysis (~150–160 °C) of their sodium salts in aprotic solvent (Bamford–Stevens reaction). Each substrate was converted to the same hydrocarbon, deltacyclane (**21**). In aprotic media such thermal Bamford–Stevens reactions produce carbenes and, for the cases at hand, these carbenes form the cyclopropyl ring in deltacyclane by 1,3 insertion. Hydrogenation of hydrocarbon **21** with Pt in acetic acid at 95 °C produced brexane (**37**), as well as brendyl and brexyl acetates from electrophilic ring cleavage.[14]

Scheme VII. Skeletal Isomerization via Homoenolate Ions



VI. Skeletal Isomerization via Homoenolate Ions. The nonenolizable nature of the brex-2-yl and brend-2-yl ketones and their structural relationship to each other led us to explore homoenolization to isomerize ring skeletons.[15] We found that prolonged treatment of brexan-2-one (**10**) in KO-*t*-Bu/*t*-BuOH at 185 °C transformed it to brendan-2-one (**25**). The change (Scheme VII) is interpreted as an abstraction of a C-4 proton in **10** to produce the homoenolate ion **41**, which is either in equilibrium with species **42** and **43** or is a resonance contributor to a hybrid ion represented by **41, 42,** and **43.** In any case protonation at the negative site in **43** gives brendan-2-one. To learn if brendanone could be partially reverted to brexanone, we treated **25** similarly with KO-*t*-Bu. The product contained no detectable brexanone (**10**), and consisted of starting ketone **25** with 4% of an unidentified contaminant. The driving force for the **10** → **25** isomerization lies, very likely, in the greater stability of the brendyl ring system. E.g., we noted earlier (Scheme IV) that *exo*-brend-2-yl acetate (or formate) is favored at equilibrium over the *exo*-brex-4-yl isomer by a ratio of nearly 50:1. And recent molecular mechanics calculations suggest an enthalpy difference of ~2.90 kcal/mol (12.1 kJ/mol) for the parent hydrocarbons brendane and brexane.[16] The ability to interconvert polycyclic ketones under alkaline conditions should be especially useful for optically active substrates. Thus, e.g., optically active brexan-2-one should produce optically active brendan-2-one with no attendant racemization and with predictable relative chirality.

Experimental Section

General. Melting points are corrected and rounded to the nearer half degree. Boiling points are uncorrected and refer to atmospheric pressure unless stated otherwise. Infrared band positions are calibrated and are expressed in reciprocal centimeters; the letters w, m, s, br, and sh refer to weak, medium, strong, broad, and shoulder, respectively. Proton magnetic resonance spectra were recorded on a 60-MHz instrument (Varian A-60) with internal tetramethylsilane as a standard. All chemical shifts are expressed in δ units and s, d, t, and m refer to singlet, doublet, triplet, and multiplet, respectively. Ultraviolet spectra were recorded on Beckman DK-2 or on Cary Model 14 recording spectrophotometers with 1-cm quartz cells. Gas chromatographic analyses (GLC) were performed on a Perkin-Elmer Model 226 Analytical instrument with a hydrogen flame ionization detector. Preparative GLC was done on a Wilkens Aerograph "Autoprep" Model A-700, with a thermal conductivity detector. The carrier gas was always helium. The following column designations are used. Model 226: Golay R, 150-ft Golay column (0.01-in. i.d.) with polypropylene glycol liquid phase (UCON-oil, LB-550-X); Golay Z, 200-ft Golay column (0.01-in. i.d.) with SE-30 silicone gum rubber liquid phase; Golay MBMA, 150-ft Golay column (0.01-in. i.d.) with 80% *m*-bis(*m*-phenoxyphenoxy)benzene plus 20% alumina-washed Apiezon-L; Golay Castorwax, 200-ft Golay column (0.02-in. i.d.), Castorwax liquid phase; Carbowax, 9-ft packed column (⅛-in. o.d.); Squalane, 9-ft packed column (⅛-in. o.d.), 15% squalane liquid phase on Chromosorb W support. Model A-700: Carbowax, 20 ft × ⅜ in. packed column with 30% Carbowax 20-M on Chromosorb W support; SE-30, 20 ft × ⅜ in. packed column with 30% SE-30 silicone gum rubber on Chromosorb P support; Castorwax, 20 ft × ⅜ in. packed column with 20% Castorwax on Chromosorb P support. The column designation and column temperature are reported for each GLC.

Mass spectra were recorded with a Consolidated Electrodynamics Corp. Mass Spectrometer Type 21-103C. Elemental analyses were performed by Mr. Joseph Walter of this Department.

"Semicarbazide acetate" solution was prepared from powdered semicarbazide hydrochloride (25 g), which was combined with powdered sodium acetate trihydrate (40 g). Methanol (75 mL) was added to the paste, and the slurry was stirred and allowed to stand overnight. The solid was collected and washed with methanol (25 mL). The filtrate and washings (~140 mL total) was the solution used for the preparation of semicarbazones.

For chromatography commercial pentane, hexane, and petroleum ether were first purified by 24 h of treatment with ca. one-third of its volume of a solution of 50% sulfuric acid and 50% fuming sulfuric acid. The hydrocarbon layer was washed with water, dried over magnesium sulfate, passed through a column of alumina (Alcoa), and distilled. Diethyl ether and diisopropyl ether were dried by distillation from lithium aluminum hydride. Benzene was dried over molecular sieves followed by distillation under nitrogen. Pyridine was dried by distillation of reagent grade material from barium oxide under nitrogen. Deuterium oxide (>99.5% d_2) was obtained from General Dynamics Corporation. Methanol-*O*-*d* was from Merck Ltd. of Canada and was >95% d_1. "Copper bronze" powder (lot no. 3165) was grade MD 101 and was kindly provided by the Metals Disintegrating Division of the Martin-Marietta Corporation, Elizabeth B, New Jersey. Solvent evaporations in vacuo were done on a rotary evaporator and refer to ~15-mm aspirator pressure.

2-Oxo-*syn*-7-bicyclo[2.2.1]heptanecarboxylic Acid (6a). A mixture of the exo and endo isomers of 2-bicyclo[2.2.1]hept-5-enecarboxylic acid (100 g, 0.72 mol, Aldrich Chemical Co.) was converted via lactones to *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylic acid in a manner similar to that reported by Beckman and Geiger[17] except that we handled much larger batches. All details are available in the Ph.D. dissertation of Swartz.[18] Beckman and Geiger oxidized the hydroxy acid to the desired keto acid (41% yield) with alkaline permanganate; however, we developed the following improved method. Crude hydroxy acid (78.0 g, 0.5 mol, mp 145–150 °C (reported[17] 155–157 °C)) was esterified with ethereal diazomethane[19] and the resulting ether solution of the ester [ν (neat) 3436, 1730 cm^{-1}] was filtered and treated with the Brown[20] oxidation reagent (500 mL; 1.0 mol) over a 30-min period. After an additional 16 h at room temperature, the stirred, two-layer mixture was diluted with water, and the water layer was extracted with ether. The combined ether layers were washed with saturated sodium bicarbonate and on workup left 73.4 g (87%) of yellow, liquid keto ester. Gas chromatography (Golay Castorwax, 150 °C) showed two minor impurities that totaled <5%. The keto ester was refluxed 2.5 h in a solution made up from potassium hydroxide (35 g) in 1 L of 75% aqueous methanol (v/v). Most of the methanol was removed on a rotary evaporator and the solution was made slightly acidic with dilute sulfuric acid. Addition of brine and thorough extraction with ether gave 64.9 g (97%) of the desired keto acid: mp 120.5–122.5 °C (reported[17] 122–123 °C). Our product was 97% pure as indicated by GLC (Golay R, 145 °C, 39 psi He) on a small sample esterified with diazomethane.

Methyl 2-Oxo-*syn*-7-bicyclo[2.2.1]heptaneacetate (7) by Arndt–Eistert Homologation. (a) Preparation of Sodium Salt. Distilled water (200 mL) was carefully added to a mixture of keto acid **6a** (38.5 g, 0.255 mol) and anhydrous sodium bicarbonate (21.3 g, 0.255 mol), and the solution was shaken occasionally for 2 h until CO_2 evolution had ceased. Most of the water was removed by rotary evaporation, dry benzene was added, and the benzene–water azeotrope was removed on the rotary evaporator. The solid sodium salt was triturated several times with ether and dried in a vacuum oven at 94 °C for 10 h; 43.8 g (99%).

(b) Conversion to Acid Chloride (6b). Oxalyl chloride (59.5 g, 0.47 mol, Aldrich Chemical Co.) in dry ether (200 mL) was added dropwise during 30 min to a magnetically stirred, cooled (0 °C) suspension of the keto acid sodium salt (43.8 g, 0.25 mol) in dry ether (1.5 L). The evolved gases (CO_2 and CO) escaped through a drying tube on the condenser. After an additional 1.5 h at 0 °C, the stirred mixture was filtered under vacuum through a cotton plug to remove suspended sodium chloride, and the ether was evaporated on a rotary evaporator, with moisture excluded. Dry benzene (50 mL) was added, and further evaporation removed both the benzene and any remaining oxalyl chloride. The cloudy, liquid keto acid chloride (**6b,** 37.8 g, 88%) showed the expected carbonyl bands [ν (neat) 1801, 1749 cm^{-1}] and was used without further purification.

(c) Preparation of Diazo Ketone (6c). The acid chloride **6b** (37.8 g, 0.22 mol) in dry ether (150 mL) was added slowly to an excess of ethereal diazomethane,[19] which was cooled in ice and rapidly stirred magnetically. During addition pale-yellow keto diazo ketone precipitated, as N_2 and CH_3Cl were evolved from solution. Stirring at 0 °C was continued 30 min after addition was completed, and the ether was aspirated to leave the 2-oxo-*syn*-7-diazomethyl ketone **6c:** 36.8 h, 94.5%; mp 100–105 °C (softens at 95 °C); IR ν (CCl_4) 3116 (m, CH of diazo ketone), 2108 (s, diazo unit), 1754 (C=O cyclopentanone), 1648 (C=O of diazo ketone unit). The entire batch was dissolved in a minimum amount of dry benzene and precipitated with *n*-pentane. The first crop (27.6 g, 71%, mp 106–107 °C) was pure enough to use in the next step. An analytical sample was obtained as pale-yellow crystals by recrystallization from benzene–pentane: mp 106.5–107.5 °C (gas evolved, softens at 105 °C).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.31; H, 5.70.

(d) Wolff Rearrangement. Silver benzoate was prepared from equimolar amounts of benzoic acid and silver nitrate in water and was dried overnight in a vacuum oven at 90 °C. The dry brown salt (10 g, 0.04 mol) was dissolved in trimethylamine (92 g, 0.91 mol, Eastman, undistilled but clear) and the dark mixture was filtered by gravity to give a yellow solution of the silver benzoate–triethylamine catalyst.[21] A few drops of catalyst solution was added to a stirred solution of the keto diazo ketone (25.0 g, 0.14 mol; mp 106–107 °C) in dry methanol (570 mL). Nitrogen was evolved slowly but steadily as the color deepened and colloidal silver formed. Stirring was continued at room temperature and more catalyst solution was added whenever gas evolution became slow. After addition of ~20 mL of catalyst (over 12 h) the mixture was refluxed for 20 min and gravity-filtered, and the methanol was removed on a rotary evaporator. The residue was taken up in 250 mL of ether, which was then filtered and washed successively with 5% sulfuric acid (3 × 20 mL), 5% sodium bicarbonate (2 × 20 mL), and brine (2 × 20 mL), and was treated with activated charcoal, dried ($MgSO_4$), and evaporated. The yellow, viscous liquid (22.4 g, 88%) was vacuum distilled. A middle fraction [bp 100 °C (0.2 mm)] consisted of 17.7 g (69.5%) of colorless liquid keto ester **7,** shown by GLC (Golay Castorwax, 150 °C) to be >99% pure; $n^{23}D$ 1.4803; IR ν (neat) 1736 (s, ester C=O), overlapped with 1748 cm^{-1} (s, ketone C=O); ^1H NMR ($CDCl_3$) δ 3.70 (s, 3, OCH_3), 2.65–1.40 (m, 11). The overall yield of **7** from **6** was 43%.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.70; H, 7.85.

2′-(*syn*-7-Bicyclo[2.2.1]heptan-2-ol)ethanol (8a). The homologated keto ester **7** (16.4 g, 0.09 mol) in dry ether (100 mL) was added dropwise over 1 h from a pressure-equalizing funnel to a magnetically stirred, cold (5 °C) suspension of $LiAlH_4$ (22.7 g, 0.80 mol) in dry ether (500 mL). The mixture was stirred 12 h at room temperature and then was successively treated dropwise with water (23 mL), 15% sodium hydroxide (23 mL), and water (68 mL). After an additional hour the granular inorganic solid was separated. Workup of the ether left a viscous, liquid mixture of epimeric diols (**8a,** 14 g, 98%): IR ν (neat) 3500–3100 (s, br, OH), 1095 (m), 1038 (m), 1008 cm^{-1} (m). For analysis a small amount was distilled twice in a vacuum sublimation apparatus [bath temperature 95–100 °C (0.25 mm)]. The center cut of the colorless liquid was dried under vacuum (0.25 mm) for 24 h at room temperature and 12 h at 40 °C: GLC (Golay Z, 120 °C) showed two peaks in the ratio 108:1 (t_R ~29 and 42 min, respectively); ^1H NMR ($CDCl_3$) δ 4.88–3.45 (m, 6), 2.45–0.73 (m, 10).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.89; H, 10.42.

Diol Monomesylate 8b. A solution of methanesulfonyl chloride (6.9 g, 0.06 mol, bp 162 °C) in dry pyridine (30 mL) was added to a cold (5 °C) solution of diol **8a** (9.9 g, 0.056 mol) in dry pyridine (40 mL). Pyridinium hydrochloride formed immediately in the orange reaction mixture, which was stirred 10 h in a cold room (5 °C). Water (1 mL) was added and after 30 min the mixture was poured into cold water and worked up with ether, which was washed in turn with cold 5% hydrochloric acid (5 × 40 mL), cold 5% sodium bicarbonate (40 mL), and cold brine (40 mL). The ether layer was concentrated to ~50 mL in a rotary evaporator, and this solution of the diol monomesylate was used directly in the next step. For spectral analysis a portion of the ether was dried over $MgSO_4$ for 30 min at −5 °C and evaporated in vacuo to leave **8b** as an oil: IR ν (neat) 3542 and 3391 (m, br, OH), 3020 (w, CH), 1353 and 1172 (s, sulfonate ester), 975 (m), 946 (m), 917 cm^{-1} (m).

7-*syn*-(2′-Mesyloxyethyl)bicyclo[2.2.1]heptan-2-one (Keto Mesylate 9). Brown's oxidation reagent (56 mL, 0.11 mol)[20] was added to the stirred ether solution of the diol monomesylate **8b,** all maintained at 5 °C in a cold room during addition and for 10 h thereafter. Conventional workup and removal of the ether on a rotary evaporator left the keto mesylate **9** as a slightly yellow oil (5.9 g, 45% from **8**): IR ν (neat) 3022 (m, CH), 1744 (s, C=O), 1352 and 1175 (s, sulfonate ester), 974 (s), 943 (s), 918 cm^{-1} (s). This product was used in the next step without purification. A sample in ether solution stored in the refrigerator for 6 months underwent little deterioration, based on infrared inspection.[22]

Tricyclo[4.3.0.0^{3,7}]nonan-2-one (Brexan-2-one) (10). Sodium hydride sand was prepared in a drybox under N_2 by repeated pentane trituration of a 50% suspension of sodium hydride in mineral oil (Metal Hydrides, Inc.) followed by collection on a filter funnel and thorough washing with dry pentane. The gray solid was dried under vacuum and stored in a desiccator. A solution of keto mesylate **9** (5.9 g, 0.025 mol) in dry, distilled *N,N*-dimethylformamide (100 mL, bp 153 °C) was degassed with a stream of nitrogen, and dry sodium hydride sand (2.4 g, 0.10 mol) was added all at once. After most of the gas evolution ceased (30 min), the flask was lowered into an oil bath (60 °C) and the brown mixture was stirred magnetically for 11 h. The excess of NaH was decomposed by careful, dropwise addition of methanol, and after an additional 1 h the stirred mixture was poured into water (300 mL) and extracted with pentane (5 × 50 mL), which was then washed with 5% hydrochloric acid and brine, and dried ($MgSO_4$). GLC at this stage (Golay R, 145 °C) showed the brexan-2-one to be 96% pure. The pentane solution was concentrated to 25 mL on an 18-in. spinning band distillation column with a 10:1 reflux ratio, and the ketone was isolated as a colorless, pure liquid (1.05 g, 32%) by preparative GLC (Carboxwax, 222 °C) with collectors cooled in dry ice–acetone. For elemental analysis the brexan-2-one was vacuum distilled [bath at 120–125 °C (35 mm)]: $n^{26}D$ 1.4951; M^+/e 136, prominent *m/e* peaks at 67 (100), 70 (40), 79 (79), 80 (99); IR ν (neat) 3466 (w, C=O overtone), 1841 (w) and 1746 (s, C=O), 1069 (s), 765 cm^{-1} (s); in CS_2 the C=O doublet is at 1844 (w) and 1748 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.31 (s, 4), 2.13–1.42 (m, 8). The ketone gave no precipitate when shaken at length with 40% aqueous sodium bisulfite and incorporated no deuterium when refluxed 7 days in D_2O/K_2CO_3.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.17; H, 9.07.

Brexan-2-one semicarbazone (10a) was obtained when the ketone (0.54 g) was heated in a methanolic semicarbazide acetate solution (see General) on the steam bath for 1 h, and then allowed to stand overnight. The derivative was precipitated with water, and the crude product (0.74 g) was recrystallized several times from hot methanol: 0.62 g; mp 188–189.5 °C; IR ν (KBr) 3475 (m), 3495 (m), and 3171 (s, NH), 1693 (C=O), 1580 cm^{-1} (C=N).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82. Found: C, 62.34; H, 7.89.

Tricyclo[4.3.0.0^{3,7}]nonan-2-ol (Brexan-2-ol) (11). Brexan-2-one (0.59 g, 0.0043 mol) in dry ether (25 mL) was reduced with $LiAlH_4$ (0.50 g, 0.013 mol) for 12 h at room temperature. The stirred solution was treated successively with water (0.5 mL), 15% sodium hydroxide (0.5 mL), and distilled water (1.5 mL). The ether was separated from the precipitated inorganic salts and, after workup and careful evaporation, left white brexan-2-ol (0.59 g, 98%); one vacuum sublimation [bath 55–65 °C (12 mm)] gave 0.56 g, mp 84–86 °C. A second sublimation gave the analytical sample (mp 84.5–86.5 °C), which showed only one GLC peak (Golay Z, 100 °C): IR ν (CCl_4) 3626 (m, free OH), 3352 (m, bonded OH), 1080 (s), 1058 (s), 1008 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.71 (d, 1, J = 6 Hz, CHOH), 2.30–1.83 (m, 5), 1.80–1.22 (m, 8). A sharp spike at ~2.13 disappeared on addition of D_2O and likely was the OH.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.46; H, 10.11.

Conventional oxidation with Brown's reagent[20] or with activated manganese dioxide in petroleum ether (25 °C, 104 h) regenerated brexan-2-one.

2-Brexyl Acetate (11a). Brexan-2-ol (0.096 g, mp 81–82 °C) in freshly distilled acetic anhydride (4 mL) and dry pyridine (0.5 mL) was heated at 60–70 °C for 2 h and kept at room temperature for 14 h. After dilution with water and repeated extraction with pentane, the organic layer was washed successively with water, saturated sodium bicarbonate, and water, dried, and passed through a column of alumina (2 g) to remove any traces of alcohol. Careful aspiration of the pentane followed by three bulb-to-bulb distillations of the residue at 60–80 °C (3 mm) gave the pure acetate: $n^{23}D$ 1.4795; IR ν (CCl_4) 1735 (s), 1248 (s), 1046 (s), 1019 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 4.47 (d, 1, J = 5–6 Hz, CHO). The acetate was pure by GLC (Golay R, 145 °C), although at block temperatures of 240 °C some pyrolysis to deltacyclane occurs.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.21; H, 8.86.

Brexan-2-ol α-Naphthylurethane (11b). This derivative was

obtained when the alcohol (0.069 g) and α-naphthyl isocyanate (0.085 g) were heated on the steam bath for 20 min and allowed to stand overnight at room temperature. For analysis the derivative was recrystallized three times from 95% ethanol: white crystals; 0.094 g; mp 139–139.5 °C.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89. Found: C, 78.37; H, 7.11

Brexan-2-ol 3,5-Dinitrobenzoate (11c). A pyridine solution of the alcohol and 1 equiv of 3,5-dinitrobenzoyl chloride (mp 67–69 °C) was stirred 10 h at room temperature. Conventional workup gave a crude solid (mp 104–130 °C), which was repeatedly recrystallized from benzene–hexane, followed by chromatography on alumina and a final recrystallization: feathery, pale yellow crystals; mp 136 °C (33%); ^{1}H NMR ($CDCl_3$) δ 4.82 (d, 1, J = 6 Hz, CHOCO).

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85. Found: C, 57.59; H, 4.91.

The parent alcohol was regenerated from this ester by saponification with KOH/methanol (10-h reflux) or by reduction with lithium aluminum hydride in ether.

8-Cyanotetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (17a). This nitrile was prepared from norbornadiene and acrylonitrile as reported by Hall:[8] bp 124–126 °C (16 mm); n^{24}D 1.5136; 15.1% yield [reported bp 124–126 °C (17 mm); n^{24}D 1.5053; 12.4% yield].

Tetracyclo[4.3.0^{2,4}.0^{3,7}]nonane-8-carboxylic Acid (17b). Hall's method was used to hydrolyze the nitrile to this carboxylic acid: bp 96–98 °C (0.1 mm); n^{24}D 1.4973; 18%.[8]

8-Hydroxytetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane-8-carboxylic Acid (18). Alkaline permanganate oxidation of **17b** as reported[8] gave hydroxy acid **18,** but our yields were variable (3.6%, mp 102–112 °C to 11.1%, mp 98–107 °C) and consistently lower than that reported (16.9%, mp 102–110 °C). We oxidized the hydroxy acid to deltacyclan-8-one (**19**) with dichromate as described, but obtained low yield (17–29%).

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane-8-carboxamide (20a). A solution of the nitrile **17a** (97.5 g), 30% hydrogen peroxide (200 mL), sodium hydroxide (6 N, 30 mL), and 95% ethanol (400 mL) was heated on the steam bath for 15 min then allowed to stand 45 min. More hydrogen peroxide (100 mL) was added and the mixture was heated for 1 h. The amide (65 g, mp 185–203 °C) was collected, washed with water and 95% ethanol, and dried in vacuo. Two recrystallizations gave mp 211–213 °C (48 g, 31%): IR ν (KBr) 3365 (s) and 3205 (s, NH), 3069 (m, cyclopropyl CH), 1655 (s) and 1627 (s, $CONH_2$), 790 cm^{-1} (s, cyclopropyl C–C deformation).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.76; H, 7.94.

Hofmann rearrangement[23] of amide **20a** (9.9 g) with sodium hydroxide (14.9 g) and bromine (3.6 mL) in water (120 mL) gave the primary amine **20b,** distilled as a colorless liquid: 2.8 g (34%); bp 80–82 °C (0.25 mm); with appropriate IR characteristics. However, the amine readily turned yellow on standing, and the hydrochloride and hydrobromide salts were hygroscopic and discolored.

8-(Carbomethoxyamino)tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (20c). A solution of sodium (4.6 g, 0.2 mol) dissolved in methanol (160 mL) was added to a stirred solution of amide **20a** (16.3 g, 0.1 mol, mp 211–213 °C) in methanol (100 mL) at 0 °C. After 20 min, bromine (16 g, 0.1 mol) was added at 0 °C during 15 min, and the solution was stirred 15 min at room temperature followed by 30 min on the steam bath. The mixture was cooled, the solvent was removed in vacuo, water (100 mL) was added, and the solid was collected and washed with water. One crystallization from absolute ethanol gave 13.8 g (72%), mp 78–83 °C. The analytical sample of the white urethane (from ethanol–water) had: mp 84.5–86 °C; IR ν (KBr) 3309 (m, NH), 3050 (w, cyclopropyl CH), 1720 (s, C=O), 800 cm^{-1} (m, cyclopropyl C–C deformation).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 78.37; H, 7.82. Found: C, 68.51; H, 7.93.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (Deltacyclane) (21) by Decarboxylation. Attempts to replace the carboxyl group of **17b** by halogen through the Hunsdiecker reaction[24] or the Cristol modification[25] of that reaction were unsuccessful. Wiberg's[9] three-step method for decarboxylation was tried, and provided deltacyclane in ~10% yield. Thionyl chloride (10.7 g, distilled) was added during 10 min to a stirred, cold (0 °C) solution of acid **17b** (15.0 g) and dry pyridine (7.13 g) in dry ether (100 mL). After an additional 1 h, the insoluble salts were filtered off and washed with dry ether. The ether filtrate provided 15.8 g of the oily acid chloride **17c:** IR ν (neat) 3051 (m, cyclopropyl CH), 1801 (s, C=O), 801 (s, cyclopropyl C–C deformation). Without purification the acid chloride (15.8 g) was added during 1.5 h to a stirred, cold (0 °C) solution of *tert*-butyl hydroperoxide (12.4 g, Lucidol Corp.) and dry pyridine (18.7 g) in *p*-cymene (62 mL; bp 175–176 °C, Fisher Certified). After an additional 1 h the stirred mixture was poured onto ice and the water was extracted with *p*-cymene, which was then washed successively with cold 8% sulfuric acid, ice water, 5% sodium bicarbonate, and ice water. The *p*-cymene solution containing the *tert*-butyl perester was dried over $MgSO_4$ for 1 h at 0 °C and was transferred to a flask equipped for distillation. The solution was heated until gas evolution began (145 °C). After 1 h at this temperature any distillate was returned to the solution, which was then distilled in portions through an 18-in. spinning-band column. Fractions collected between 120 and 175 °C (760 mm) totaled 3.41 g of liquid, which contained about equal amounts of deltacyclane, *p*-cymene, and an unknown compound, as revealed by gas chromatography (Golay Z, 95 °C) peak enhancement with authentic samples. We found it difficult to separate the deltacyclane efficiently from this mixture, and therefore alternative routes to the tetracyclic hydrocarbon were developed.

8-Acetyltetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (13). (a) By Addition of Methyllithium to Acid 17b.[26] A solution of methyllithium was prepared by addition, over 3 h, of methyl iodide (110 g) in dry ether (350 mL) to a suspension of lithium wire (14.8 g) in dry ether (350 mL). The filtered solution was added during 3 h to the carboxylic acid **17b** (30.0 g) in anhydrous ether (300 mL) at a rate that maintained gentle reflux in the stirred solution. After 30 min longer the mixture was poured into ice water (150 mL). Conventional workup of the ether (dried over $MgSO_4$) left 16.5 g of crude, liquid ketone. A portion (3.75 g) was chromatographed on alumina (120 g, Alcoa). Elution with petroleum ether containing 3–5% benzene gave 2.27 g of liquid, which was colorless after distillation: 2.01 g; bp 82–84 °C (1.2 mm); n^{28}D 1.4980; IR ν (neat) 3052 (m, cyclopropyl CH), 1706 (s, C=O), 1357 (m, CCH_3 deformation), 1168 (s), 802 cm^{-1} (s). Gas chromatography (Golay R, 140 °C) showed the two methyl ketone epimers **13** in a ratio of 2.6:1: ^{1}H NMR (neat) δ 3.25–2.73 (m, 1), 2.42–1.55 (m, 8, prominent $COCH_3$ singlet at 2.07), 1.47 (s, 2), 1.20–0.67 (m, 3, cyclopropyl H).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.55; H, 8.63.

(b) By Homoconjugative Diels–Alder Reaction. Commercial norbornadiene (500 g, Shell Corp.), methyl vinyl ketone (400 g, Monomer-Polymer Laboratories), and cupric acetate (2 g) were heated (200 °C) in a steel bomb for 12 h. The mixture was poured into hexane (5 L) and then filtered through Celite. The hexane was evaporated on the steam bath, and the residue was distilled to get a fraction (67 g), bp 60–90 °C (0.4 mm). A solution of this liquid in ether (600 mL) was extracted with 1.5 M aqueous silver nitrate solution (2 × 150 mL) and then with water (2 × 100 mL), dried ($MgSO_4$) overnight, and evaporated. The product was distilled through a Vigreux column and a fraction (46.8 g), bp 62–64 °C (0.4 mm), was collected. GLC (Golay R, 140 °C) revealed the two epimeric methyl ketones in a ratio 1.56:1. The infrared spectrum (neat) was the same, except for relative peak intensities, as that from the ketone epimers obtained by method a above. In a run where hydroquinone (~2 g) was used in place of the cupric acetate and the reaction was run at 188 °C and worked up by steam distillation (to remove bicycloheptadiene and to collect the 8-acetyldeltacyclane), a higher yield (74 g) of the product mixture was obtained. We also tried the homoconjugative Diels–Alder reaction catalyzed by $Ni(CN)_2{\cdot}2P(C_6H_5)_3$.[27]

In a run with norbornadiene (20 mL), methyl vinyl ketone (20 mL), and catalyst (0.65 g, mp 212 °C) in a sealed Pyrex tube at 120 °C for 15 h, we obtained 7 g of the epimeric ketones by steam distillation and ether extraction.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-8-ol (14b) by Baeyer–Villiger Oxidation.[28] **Method A.** A trifluoroperoxyacetic acid solution was prepared by dropwise (1.5 h) addition of trifluoroacetic anhydride (127 mL) at 0 °C to a stirred, cold suspension of 90% hydrogen peroxide (20.5 mL) in methylene chloride (130 mL). After another 15 min this cold (0 °C) solution was slowly (1 h) dropped into a stirred, cold (0 °C) suspension of 8-acetyldeltacyclane (**13;** 81 g, epimeric mixture) and anhydrous disodium hydrogen phosphate (35.5 g) in methylene chloride (500 mL). After an additional 20 min, the stirred suspension was refluxed 1 h and filtered, and the insoluble salts were washed with methylene chloride. The filtrate was washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation left a colorless liquid, which was distilled: 62.3 g; bp 54–60 °C (0.7 mm); IR ν (neat) 3053 (s, cyclopropyl CH), 1776 (m, C=O of $OCOCF_3$), 1734 (s, C=O of $OCOCH_3$), 1375 (m), 1357 (m), 1241 (s), 1027 (s), 803 (s, cyclopropyl C–C deformation). GLC (Golay R, 140 °C) showed two peaks in the ratio 1:20. This ester mixture (55.7 g) was refluxed for 3 h under nitrogen in a solution of potassium hydroxide (23 g) and methanol (250 mL). Evaporation of the methanol, addition of water, and extraction with ether gave on normal workup a colorless liquid, which was distilled: 41.7 g; bp 60–62 °C (0.5 mm); n^{23}D 1.5194; IR ν (neat) 3332 (s, br, OH), 3054 (cyclopropyl CH), 1072 (s), 1036 (s), 991 (m), 802 cm^{-1} (s, cyclopropyl C–C deformation). GLC (Castorwax, 174 °C) showed

only one peak, but the alcohol **14b** is likely a mixture of epimers.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.23; H, 8.72.

A **3,5-dinitrobenzoate (14c)** was prepared with anhydrous pyridine and 3,5-dinitrobenzoyl chloride. Several recrystallizations from 95% ethanol gave the analytical sample with constant mp 91.5–93 °C. This derivative probably represents a single epimer.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27. Found: C, 58.07; H, 4.34.

Method B. An epimeric mixture of methyl ketones (16.7 g, 0.10 mol) and *m*-chloroperoxybenzoic acid (33 g, 0.16 mol, Food Machinery Corp., 85% minimum purity) in methylene chloride (300 mL) was refluxed for 12 h. The solid *m*-chlorobenzoic acid was removed from the cold mixture and washed with methylene chloride, which was then extracted thoroughly with saturated sodium bicarbonate solution (3 × 300 mL) followed by brine (1 × 300 mL), and was filtered through dry, powdered sodium bicarbonate. Evaporation of the clear solution left 17.5 g (95.5%), and vacuum distillation [bp 88–90 °C (1.6 mm)] gave 14.6 g (81%) of the colorless, sweet-smelling acetates **14a.** The acetate mixture was saponified with potassium hydroxide (12.3 g) in methanol (135 mL) and water (12 mL). After 3 h at reflux and 15 h at room temperature the methanol was evaporated and the mixture was worked up conventionally with pentane. The colorless, tetracyclic alcohol **14b** was distilled: 19.2 g; bp 90–92 °C (1.4 mm). It remains liquid at room temperature, but partly solidified in the cold condenser.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-8-one (Deltacyclan-8-one) (19). Brown's oxidation reagent[20] (61 mL) was added during 20 min to a cold (0 °C) stirred solution of the liquid tetracyclic alcohol **14b** (15.0 g) in ether (50 mL). After 2 h at room temperature the ether layer was worked up normally, and the product on distillation gave a colorless liquid with a strong characteristic odor: 12.6 g (85%); bp 88–90 °C (11 mm); GLC (Castorwax, 162 °C) showed only one peak; IR ν (neat) 3068 (m, cyclopropyl CH), 1748 (s, C=O), 1405 (w, CH_2 α to C=O), 798 cm^{-1} (s, cyclopropyl C–C deformation). This spectrum was superimposable on that of an authentic sample of tetracyclic ketone **19** kindly supplied by Dr. H. K. Hall, Jr.[8] Oxidation of the alcohol **17b** with the Sarett reagent (CrO_3/Py)[29] also gave this ketone, but in lower yield (43%).

The **2,4-dinitrophenylhydrazone (19a)** precipitated when the ketone (0.05 g) and 2,4-dinitrophenylhydrazine (0.2 g) in ethanol (10 mL) containing concentrated hydrochloric acid (3 drops) sat overnight in the refrigerator: 0.11 g (93.5%); mp 189–191 °C. The analytical sample (from ethanol) had mp 193.5–194 °C.

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49. Found: C, 57.04; H, 4.42.

To get the **semicarbazone (19b)** the ketone (0.094 g) in methanol (2 mL) containing 3 drops of pyridine was treated with semicarbazide hydrochloride (0.222 g) in water (1.0 mL) on the steam bath for 5 min and then allowed to sit overnight in the refrigerator. This derivative (0.12 g, 89%, mp 209.5–211 °C) was recrystallized from methanol for analysis, mp 213.5–214 °C.

Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85. Found: C, 62.98; H, 6.65.

The parent ketone was regenerated when the semicarbazone was hydrolyzed with sodium hydroxide in water–ethanol.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (Deltacyclane) (21) by Modified Wolff–Kishner Reduction.[30] Anhydrous hydrazine (45 mL, bp 113–114 °C, prepared by distillation of 95% hydrazine from an equal weight of potassium hydroxide) was added to deltacyclan-8-one (**19**; 13.4 g, 0.1 mol) dissolved in dry, freshly distilled diethylene glycol (150 mL). The mixture was refluxed 1 h and the excess of hydrazine was distilled out until the distillation temperature reached 220 °C. A solution of sodium (2.5 g) in diethylene glycol (90 mL) was added and when heating was resumed nitrogen started to evolve and the hydrocarbon distilled out continuously as it formed. Nitrogen evolution was almost quantitative and at the end of the reaction the distillation temperature rose to 230 °C. The condenser was washed with pentane, which was combined with the distillate, washed with water, dried (Na_2SO_4), and distilled at 760 mm. The deltacyclane, bp 152–153 °C, weighed 9.45 g (79%): n^{25}D 1.4928; IR ν (neat) 3057 (m, cyclopropyl CH), 1306 (m, CH bend), 796 cm^{-1} (s, cyclopropyl C–C deformation); ^{1}H NMR (CS_2) δ 1.90 (s, 2), 1.70–1.42 (m, 7), 1.10–0.70 (m, 3, cyclopropyl H).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.91; H, 9.86.

Wolff–Kishner reduction of the semicarbazone (**19b**) of deltacyclan-8-one with sodium dissolved in diethylene glycol or with dry powdered KOH at 185–200 °C gave deltacyclane in lower yields (~50%). However, the KOH method has the attraction that the product distills from the reaction mixture directly in 95–98% purity.

Deltacyclan-8-one (19) from α-Acetoxyacrylonitrile. A mixture of norbornadiene (27.6 g, 0.33 mol), α-acetoxyacrylonitrile[31] (33.3 g, 0.3 mol), and hydroquinone (0.3 g) under nitrogen in a sealed *glass* tube was heated at 160 °C for 15 h. When cold, the dark brown mixture was poured into ether (600 mL), and the polymeric material that precipitated (12 g) was filtered off. The filtrate was evaporated and the residue was distilled in vacuo. Preliminary fractions [bp up to 165 °C (20 mm)] contained largely the starting reagents; the product was collected at bp 170–180 °C (20 mm), 17.2 g (28%). This mixture of isomeric cyanohydrin acetates in a solution of sodium hydroxide (30 g) in 10% H_2O–90% ethanol (300 mL) was refluxed 2 h. The mixture was steam-distilled until the distillate was clear (~300 mL), and the distillate was extracted with ether (4 × 75 mL), which was then washed with brine (2 × 75 mL), dried over Na_2SO_4, and evaporated. At this stage the residual liquid (7.2 g) showed two IR carbonyl bands (1740 and 1770 cm^{-1}) and consisted of a 4:1 mixture (GLC, 20% silicone grease, 190 °C) of deltacyclan-8-one (**19**) and the unsaturated cyclobutanone from a [2 + 2] addition pathway.

For separation of the two ketones, the mixture in pentane (30 mL) was vigorously extracted (10 min) with 25% aqueous silver nitrate (30 mL) and then again with 12% silver nitrate (40 mL). The pentane was then washed with water, dried with Na_2SO_4, and evaporated. Vacuum distillation of the residue gave pure (GLC) deltacyclan-8-one (**19**), 5 g, bp 88–90 °C (10 mm), identical with an authentic sample.[8] Overall yield from norbornadiene typically was 12–13%. (The silver nitrate extracts on workup gave 2.5 g of a mixture of the two ketones in ~1:1 ratio, by GLC.)

Acetolysis of Deltacyclane. Isolation of *exo*-4-Brexyl Acetate (22a). A mixture of deltacyclane (2.0 g), glacial acetic acid (100 mL), and 97% concentrated sulfuric acid (0.50 g) was stirred at room temperature. The mixture soon became homogeneous, and a brown color developed and gradually deepened. Aliquots were removed periodically and worked up by dilution with water and extraction with pentane, which was then washed with saturated sodium carbonate and water, dried over $MgSO_4$, and carefully evaporated at the water aspirator with no heat. GLC analysis (Golay R, 145 °C) showed that the ratio of *exo*-2-brendyl acetate/*exo*-4-brexyl acetate increased with time as follows: 1.5 (20 min); 2.3 (2.5 h); 2.9 (4 h); 49 (92 h). These ratios are based on peak heights only and are approximate. In all aliquots the starting hydrocarbon deltacyclane was evident in the GLC, but its proportion seemingly fluctuated with time. We also found that if the injection block temperature is too high (>220 °C) *exo*-4-brexyl acetate partly isomerizes to *exo*-2-brendyl acetate and partly decomposes to deltacyclane. (The brendyl acetate also pyrolyzes to deltacyclane at high block temperatures, but less readily.) Typically, the yield of mixed acetates from acetolysis was ~90%.

A mixture of the acetates (2.5 g; brendyl/brexyl ratio ~1.5) in pentane was separated by preparative gas chromatography (Autoprep-700, Carbowax, 165 °C, block 205 °C, He 195 cm^3/min, with sample injection directly onto the column with a 6-in. hypodermic needle. An early hydrocarbon fraction contained deltacyclane. The *exo*-2-brendyl acetate (t_R ~65 min) and *exo*-4-brexyl acetate (t_R ~80 min) were separately collected at dry ice–acetone temperature, and intermediate fractions were recycled. (Total recovery from preparative GLC 55–60%.) The liquid *exo*-4-brexyl acetate (**22a**) was >99.5% pure by analytical GLC (Golay R, 145 °C, block 200 °C): n^{25}D 1.4798; IR ν (CCl_4) 1740 (s) and 1725 (sh, C=O), 1242 (s), 1215 (m), 1148 (m), 1057 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3, CH_3CO_2), 4.59 (d, 1, J = 6 Hz, CHO). The doublet has additional fine splitting.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 8.88.

The ***exo*-2-brendyl acetate (23a)** was >99.5% pure: n^{24}D 1.4810; IR ν (neat) 1740 (s), 1730 (s, C=O doublet), 1380 (m), 1365 (m), 1245 (s), 1028 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 1, CHO), 1.95 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.55; H, 8.84.

***exo*-Brexan-4-ol (22b).** A solution of 4-brexyl acetate (0.030 g) and potassium hydroxide (0.35 g) in methanol (4 mL) and water (0.5 mL) was refluxed 5 h and then let stand at room temperature overnight. Addition of water, extraction with pentane, and normal workup gave, after one sublimation, white crystals (0.017 g, 72%), mp 51.5–53 °C. Resublimation for analysis gave: mp 52.5–53 °C; IR ν (CCl_4) 3595 (s), 1062 (s), 989 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) both before and after addition of D_2O, δ 3.71 (d, 1, J = 6 Hz, CHO; fine splitting is evident).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.35; H, 9.93.

***exo*-Brendan-2-ol (23b).** Pure *exo*-2-brendyl acetate was saponified in a solution of KOH (0.4 g) in methanol (7 mL) and water

(1 mL). After 6 h at reflux and 15 h at room temperature, the solution was diluted with water and worked up normally with pentane. The solid *exo*-brendan-2-ol was sublimed with water pump aspiration, mp 131–134 °C (0.68 g). Resublimation gave the analytical sample: mp 133.5–134.5 °C; IR ν (CCl_4) 3605 (s, free OH), 3525–3150 (br, bonded OH), 1150 (m), 1063 (s), 1021 cm^{-1} (s); ^1H NMR ($CDCl_3$) 3.30 (s, 1, CHO) before and after addition of D_2O.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.34; H, 10.20.

The 2-brendyl series is more efficiently arrived at by formolysis of deltacyclane as described below.

Formolysis of Deltacyclane. Preparation of *exo*-Brendan-2-ol (23b). A heterogeneous mixture of deltacyclane (0.95 g, ~90% pure), formic acid (45 mL, 97%) and concentrated sulfuric acid (0.20 g, 97%) was shaken at room temperature for 20 h. The homogeneous solution was diluted with water and worked up with pentane, which was washed successively with saturated sodium bicarbonate and water, dried ($MgSO_4$), and evaporated by water aspiration with no heat (0.88 g, 73%). GLC (Golay R, 145 °C) showed ~90% *exo*-2-brendyl formate and *exo*-4-brexyl formate in a ratio of ~50:1 (the brendyl ester has the shorter t_R) and minor peaks (total ~10%) due to deltacyclane and impurities. The formate mixture was saponified by 2 h of reflux in a solution of methanol (8 mL), water (1 mL), and potassium hydroxide (0.6 g). Dilution with water and normal pentane workup left the crude solid (0.72 g), which was sublimed at 12 mm (0.6 g, mp 87–95 °C). Recrystallization from the minimum amount of pentane or isooctane at dry ice temperature raised the melting point to 112–115 °C (sealed tube). Neither sublimation nor recrystallization (without severe loss) effectively removes residual *exo*-brexan-4-ol, small quantities of which are also difficult to detect by GLC. Nevertheless the purity of this *exo*-brendan-2-ol (~95%) is adequate for conversion to the acetate or the ketone, either of which is readily purified by gas chromatography.

The alcohol (0.1 g, mp 112–115 °C) was converted to its *acetate* **23b** in 96% yield by 2 h of reflux in acetic anhydride (4 mL, freshly distilled) and dry pyridine (0.5 mL). The acetate was worked up with pentane and distilled bulb-to-bulb, bp 60–80 °C (1 mm). It was identical in all respects with that obtained from the acetolysis route.

The **3,5-dinitrobenzoate** of *exo*-brendan-2-ol was prepared from the alcohol (0.6 g, mp 112–115 °C) and pure 3,5-dinitrobenzoyl chloride (0.20 g) in dry benzene (5 mL) and dry pyridine (0.75 mL) after 30 min of reflux. Normal workup gave: 0.13 g; 90%; mp 87–88 °C. The analytical sample of **23d,** repeatedly recrystallized from ethyl acetate–pentane, had: mp 98.5 °C; IR ν (CCl_4) 3080 (m), 1725 (s), 1485 (s), 1340 (s), 1275 (br), 1165 (s), 968 (m), 720 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 4.58 (s, 1, CHO).

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85. Found: C, 57.95; H, 5.01.

Brexan-4-one (24) and Brendan-2-one (25). Each of these ketones can be obtained by Brown oxidation of its respective pure exo alcohol. A more convenient route is as follows. A mixture (7.0 g) of 2-brendyl and 4-brexyl acetates (ratio 2.9:1) from acetolysis of deltacyclane was saponified by 27 h of reflux with KOH (22 g) in 95% ethanol (15 mL) and water (60 mL). Workup with water and ether gave 5.1 g (0.037 mol) (94%) of mixed alcohols, which was dissolved in ether (75 mL, previously treated with oxidizing agent to ensure inertness) and oxidized with the Brown reagent (37 mL, 0.074 mol). After 3 h at room temperature the heterogeneous mixture was worked up normally. Careful evaporation of the dried ether with a stream of dry N_2 and gentle heat left a waxy, white solid, 4.33 g (96%). The ratio of brendan-2-one and brexan-4-one was 2.6:1 (Golay R, 145 °C) and therefore there was no significant isomerization of ring skeletons during the oxidation. The ketones in pentane were separated[32] by preparative GLC (Autoprep-700, Carbowax, 160 °C, injector 205 °C, He 300 cm^3/min) and collected in receivers cooled in dry ice–acetone. Under optimum GLC conditions the total ketone recovery was as high as 70%.

The **brendan-2-one** was eluted first, and was camphorlike, mp 114–118 °C (1.27 g), pure by analytical GLC (Golay R, 145 °C). Two vacuum sublimations (water-pump) gave: mp 118.5–119.5 °C (softens 111 °C); IR ν (CCl_4) 1747 (s, C=O), 1169 (m), 1022 cm^{-1} (m); ^1H NMR δ 2.85–1.38 (m, 11), 1.10–0.75 (m, 1).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.57; H, 9.04.

The **semicarbazone** of **brendan-2-one** was obtained when the ketone in absolute methanol was heated for 3 min with semicarbazide acetate (2 equiv) reagent (see General) and let stand overnight at room temperature. Normal workup followed by recrystallization from water–methanol and finally from absolute methanol gave white, starlike crystals of **25a,** mp 159.5–162 °C.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.16; H, 7.82. Found: C, 62.08; H, 7.88.

The **brexan-4-one** (0.59 g) was liquid, and pure by analytical GLC: $n^{25}D$ 1.4968; IR ν (CCl_4) 1745 (s, C=O), 1405 (m, CH_2 α to C=O); IR ν (neat) 1744 (s), 1407 (m), 1161 (m), 1122 cm^{-1}; H NMR ($CDCl_3$) δ 2.45–2.03 (m, 6), 2.00–1.25 (m, 6).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.27; H, 8.73.

The **semicarbazone (24a)** of **brexan-4-one,** prepared as described above for the brendyl ketone, had mp 202–204 °C (from methanol).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.16; H, 7.82. Found: C, 62.21; H, 7.91.

Pure ketone **24** was regenerated when the semicarbazone (**24a,** 0.26 g), water (6 mL), and oxalic acid dihydrate (0.35 g) were heated together until 6 mL of distillate was collected. The distillate was worked up with pentane, and the product was distilled [bath 110–115 °C (15 mm)] to give 0.13 g of brexan-4-one, pure by GLC.

***endo*-Brexan-4-ol (26a).** Pure brexan-4-one (0.50 g) in dry ether (20 mL) was reduced with lithium aluminum hydride (2 g) in dry ether (125 mL) for 5 h at reflux. Workup as in the brendyl series gave a liquid alcohol (~92% endo, 8% exo by GLC on acetylated mixture) that was distilled at 60–80 °C (1.2 mm), 0.43 g, 85%. Sublimation onto a cold finger gave a white solid, which is a viscous liquid at room temperature: $n^{25}D$ 1.5100; IR ν (CCl_4) 3602 (s), 1123 (m), 1093 (s), 1078 (s), 1021 cm^{-1} (s); ^1H NMR ($CDCl_3$) before and after shaking with D_2O, δ 4.20 (m, 1, CHO). No epimeric exo alcohol was detectable by IR or NMR.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.10.

Oxidation of the alcohol (0.020 g) in ether (8 mL) with Brown's reagent[20] (1 mL) at room temperature for 6 h and normal workup regenerated the parent brexan-4-one (0.015, 80%, after one sublimation of the liquid on a cold finger).

***endo*-4-Brexyl Acetate (26b).** Pure *endo*-brexan-4-ol (0.11 g) was acetylated in acetic anhydride (4.5 mL) and pyridine (0.5 mL) at 60–70 °C for 2 h, and left at room temperature overnight. Conventional workup with water and pentane left the acetate, which was distilled twice bulb-to-bulb at 60–80 °C (2 mm); colorless, fragrant liquid (0.12 g, 80%); $n^{24}D$ 1.4807; IR ν (CCl_4) 1740 (s), 1725 (s), 1246 (s), 1238 (s), 1068 (s), 1037 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3, CH_3), 4.90 (m, 1, CHO).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.95; H, 8.75.

***endo*-Brendan-2-ol (27a).** A solution of brendan-2-one (0.17 g, mp 118 °C) in dry ether (10 mL) was added slowly to a stirred, ice-cooled suspension of powdered lithium aluminum hydride (0.60 g) in dry ether (100 mL). The mixture was refluxed 3 h and, when cold, was carefully treated with saturated sodium sulfate (10 mL) to decompose the excess of hydride, followed by dilute sulfuric acid (10 mL, 2%). Normal workup of the ether layer left a solid (endo/exo ~95:5) that gave white crystals after sublimation: 0.5 g (84%); mp 165–166 °C (174–175 °C in a sealed capillary). Melting points can vary widely on a given sample owing to ease of sublimation and do not necessarily reflect variation in purity: IR ν (CCl_4) 3620 (s), 1112 (m), 1076 (s), 1056 cm^{-1} (m); ^1H NMR ($CDCl_3$) before and after shaking with D_2O, δ 4.11 (d, br, complex, 1, J = 8 Hz, CHO).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.31; H, 10.02.

Oxidation in ether with Brown's reagent[20] for 5 h at room temperature regenerated the parent ketone, mp 117–118 °C after sublimation.

***endo*-2-Brendyl Acetate (27b).** The endo alcohol (0.80 g, mp 155 °C) was heated at 60–70 °C for 2 h with freshly distilled acetic anhydride (3.5 mL) and dry pyridine (0.5 mL). After 48 h at room temperature the solution was again heated at 60–70 °C for 2 h. Ice water was added to the cooled solution and after a conventional pentane workup the colorless product was distilled twice (bulb-to-bulb) to furnish the sweet-smelling liquid acetate: $n^{22}D$ 1.4835; IR ν (CCl_4) 1738 (s), 1720 (sh), 1248 (s), 1052 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3, CH_3), 4.90 (d, br, complex, 1, J = 8 Hz, CHO). The acetate was 99% pure by GLC (Golay R, 145 °C), although with this column the epimeric exo acetate had the same retention time and would not be resolved.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 8.88.

Tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]nonan-3-one (29). *endo*-5-Norbornene-2-carboxylic acid (**28a;** 69 g, mp 44–44.5 °C), obtained pure from a mixture of endo and exo epimers by Berson's method,[33] was converted to its sodium salt by treatment with a solution of sodium bicarbonate (46 g), and the residue was dried at 75 °C (0.5 mm) for 24

h. The dry sodium salt (79.5 g) suspended in dry ether (500 mL) at 0 °C was added dropwise (30 min) to a stirred solution of oxalyl chloride (67 g) in anhydrous ether (150 mL). After an additional 30 min, the mixture was filtered, the filtrate was evaporated in vacuo, and two successive portions of dry benzene (30-mL each) were added and each evaporated in vacuo. The oily acid chloride (**28b**; 64 g) had IR ν (neat) 1801 (s, C=O) and 701 (s, C=C deformation).

The acid chloride (62 g) in dry ether (250 mL) was gradually added (30 min) to a stirred solution of ethereal diazomethane[34] at 0 °C. After an additional 30 min at 0 °C, evaporation in vacuo left the diazomethyl ketone **28c** as an oil (61.2 g): IR ν (neat) 3062 (m, olefinic CH), 2105 (s, diazo), 1633 (s, C=O), 708 (s, C=C deformation).

A suspension of the diazo ketone (61.2 g), copper-bronze powder (12 g), and dry tetrahydrofuran (2 L, distilled from sodium) was refluxed 50 h. The cooled mixture was filtered, the solvent was removed in vacuo, and the residue (36 g) was triturated with 600 mL of ether. Precipitated solid was removed, the ether was evaporated in vacuo, and the residue (33 g) in pentane was chromatographed on Woelm alumina (900 g, neutral, Grade II). Elution with pentane through pentane–ether (3:1) gave preliminary impure fractions (total 16 g) followed by pure fractions (total 12.2 g) monitored by GLC. Sublimation [62–66 °C (0.5 mm)] of the combined pure fractions gave white, tetracyclic ketone **29** (11.4 g), mp 90.5–92.5 °C, which showed only one peak on GLC (Golay R, 146 °C), and a molecular ion at *m/e* 134: IR ν (CCl_4) 3048 (m, cyclopropyl CH), 1734 (s, C=O), 1303 (s), 1279 (m), 903 (s), 872 cm^{-1} (s); ^1H NMR (CCl_4) δ 3.00–2.38 (m, 4), 2.38–1.40 (m, 6). UV λ_{max} (95% ethanol) 271 nm (ϵ 50); (isooctane) 278 nm (ϵ 66).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.60; H, 7.39.

Rechromatography of the impure fractions (16 g) and sublimation led ultimately to an additional 9.7 g of pure (mp 90–92 °C) tetracyclic ketone. The total overall yield of **29** from endo acid was 31%.

The **semicarbazone** (**29a**) of tetracyclic ketone was prepared with semicarbazide acetate in methanol conventionally (overnight in the refrigerator). A few drops of water were added, and after 15 h at room temperature the solid (mp 203.5–204 °C) was collected. Two recrystallizations from methanol for analysis gave **29a** with mp 204–205 °C: IR ν (KBr) 3445 (NH), 2060 (cyclopropyl CH), 1680 (C=O), 1590 cm^{-1} (C=N).

Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85. Found: C, 63.01; H, 6.73.

The **2,4-dinitrophenylhydrazone (29b)** was obtained by treatment of ketone **29** (overnight in the refrigerator) in 95% ethanol with 1.0 equiv of reagent and 5 drops of concentrated hydrochloric acid. The precipitate was recrystallized four times from methanol: mp 210–211 °C; IR ν (KBr) 3305 (NH), 3105 (aromatic CH), 3035 (cyclopropyl CH); UV λ_{max} (95% ethanol) 372 (ϵ 23 400), 280 sh (ϵ 7800), 271 sh (ϵ 10 200), 234 nm (ϵ 18 020).

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49. Found: C, 57.09; H, 4.46.

Attempted Preparation of *p*-Toluenesulfonylhydrazone. A solution of tetracyclic ketone **29** (0.13 g) and *p*-toluenesulfonylhydrazine (0.19 g, 1.0 equiv) in 95% ethanol (1.5 mL) containing 5% hydrochloric acid (5 drops) stood overnight at room temperature. The derived solid (probable structure **30**) was crystallized from methanol: 0.11 g; mp 164.5–165.5 °C. The analytical sample (mp 165–165.5 °C) had strong IR bands (KBr) at 3400 and 3200 (NH), but otherwise was difficult to interpret.

Anal. Calcd for $C_{23}H_{28}N_4O_4S_2$: C, 56.54; H, 5.78. Found: C, 56.88; H, 5.71.

This product was extracted from ether by 5% hydrochloric acid and was released from the acid solution with sodium bicarbonate solution. For comparison we showed that camphenilone tosylhydrazone[35] was not extracted by dilute hydrochloric acid. We did not further explore product **30**, but presume its yield would increase markedly by use of 2 equiv of reagent.

Tricyclo[4.2.1.$0^{3,7}$]nonan-4-one (Brendan-4-one) (31). A. By Catalytic Hydrogenation. A stirred solution of tetracyclic ketone **29** (5.15 g) in ethyl acetate (7 mL) was hydrogenated with 10% Pd/C (0.51 g) at 22.5 °C (744 mm) until hydrogen absorption ceased (22 h; 107% of theoretical). The filtrate in pentane (40 mL) was repeatedly washed with water and dried ($MgSO_4$). Evaporation in vacuo left a white solid (4.62 g, 89%), mp 114–116.5 °C. Hydrogenation in ether gave comparable results (86%), mp 113–118 °C. Sublimation [65–70 °C (12 mm)] gave mp 116.5–118.5 °C. The analytical sample of brendan-4-one, mp 120–120.5 °C, was obtained by regeneration from the semicarbazone (see below): IR ν (CCl_4) 1744 (s, C=O), 1703 (w), 1448 (CH_2 scissor), 1407 (m, CH_2CO scissor); ^1H NMR (CCl_4) δ 2.90–2.02 (m, 8), 2.00–1.53 (m, 3), 1.45 (s, 1), 1.25 (s, 1), 1.03 (s, 1), 0.83 (s, 1); GLC (Golay R, 148 °C) showed only one peak; molecular ion at *m/e* 136.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.63; H, 8.90.

The **semicarbazone 31a** was obtained from crude brendan-4-one (2.0 g, mp 114–116.5 °C) and semicarbazide acetate–methanol reagent (20 min on steam bath, then overnight at room temperature). The precipitate (2.9 g, mp 195–197 °C) was recrystallized from methanol for analysis: mp 195–196 °C; IR ν (KBr) 1691 (s, C=O), 1596 (m, C=N).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82. Found: C, 62.20; H, 7.85.

A stirred suspension of semicarbazone (0.75 g), oxalic acid dihydrate (1.5 g), and water (15 mL) was distilled until the distillate became clear. Pentane extraction of the distillate gave, on workup, brendan-4-one, mp (after one sublimation) 120–120.5 °C (~45% yield).

B. By Li/NH_3 Reduction. A solution of tetracyclic ketone (2.5 g) in anhydrous ether (75 mL) was rapidly added to a solution of freshly cut lithium (1.30 g) in liquid ammonia (150 mL) in a flask equipped with an overhead stirrer and a dry ice–acetone cooled condenser. The solution was stirred and allowed to reflux 4 h. Solid ammonium chloride (5.0 g) was added, the mixture was stirred an additional 10 min, and the condenser was removed to allow the ammonia to evaporate from the stirred mixture. Conventional water–pentane workup left a semisolid (1.78 g), whose GLC (Golay R, 145 °C) revealed brendan-4-one (86%), three unknowns (total 4%), and starting ketone (10%) in that order of elution. The crude product was shaken for 3.5 h with 40% aqueous sodium bisulfite (15 mL). The derived white precipitate (1.86 g) was collected and stirred 15 h in a solution of sodium carbonate (3 g) in water (15 mL). Conventional pentane workup gave pure brendan-4-one (0.63 g, mp 116–117.5 °C) identical in infrared absorption with that of the analytical sample prepared above.

Deuterium Exchange in Brendan-4-one (31). A solution of brendan-4-one (0.10 g, mp 119–120 °C), D_2O (0.5 mL), methanol-*O*-*d* (2 mL), and potassium carbonate (0.10 g) was refluxed 7 days in a drybox. The solution was extracted with purified petroleum ether (bp 35–40 °C), which was then washed with D_2O, dried ($MgSO_4$), and evaporated in vacuo. Two sublimations of the solid residue [bath 60–80 °C (15 mm)] gave: mp 118.5–119.5 °C; one peak on GLC (Golay R, 137 °C); IR ν (CCl_4) 2215 (w) and 2132 (w, CD), 1738 (s, C=O), 1189 (s), 1160 (m), 1129 (m), 1076 (m), 1019 cm^{-1} (s). The characteristic CH_2CO "scissor" band at 1407 cm^{-1} was absent. Mass spectral assay showed 99.5% d_2; 0.5% d_1; 0% d_0.

Baeyer–Villiger Oxidation of Brendan-4-one (31). A solution of trifluoroperoxyacetic acid[28] prepared from trifluoroacetic anhydride (5.08 mL), methylene chloride (10 mL), and 98% hydrogen peroxide (0.85 mL) was added during 10 min to a cold (0 °C) stirred solution of brendan-4-one (2.72 g, mp 118–120 °C), disodium hydrogen phosphate (13.0 g), and methylene chloride (30 mL). After an additional 15 min at 0 °C, 30 min at room temperature, and 30 min at gentle reflux, the mixture was filtered. The methylene chloride was washed with saturated sodium bicarbonate and then brine, dried ($MgSO_4$), and evaporated in vacuo to leave a semisolid mixture of lactones **32** and **33** (2.71 g), IR ν (neat) 1739 cm^{-1}. (This material could be crystallized from pentane at 0 °C, but the derived solid, mp 102–104 °C, showed an IR spectrum little changed from that of the semisolid.)

The semisolid lactone mixture (2.71 g), sodium hydroxide (1.0 g), and water (25 mL) were shaken on the steam bath for 45 min. The cooled alkaline solution was washed with ether, saturated with solid sodium chloride, and, at 0 °C, acidified with 10% hydrochloric acid, followed by rapid extraction with ether (5 × 15 mL). Each ether extract was immediately poured into an ethereal solution of diazomethane, which was then reduced in volume to ~30 mL, dried ($MgSO_4$), and evaporated in vacuo. The residual oil (2.61 g) had: IR ν (neat) 3442 (m, br, OH), 1741 (s, sh on low frequency side, C=O, methyl ester and δ-lactone).

This mixture (2.60 g) of hydroxymethyl ester and δ-lactone (**33**) in ether (9 mL) was oxidized with Brown's reagent (15 mL)[20] for 12 h at 0 °C. The layers were separated, and normal workup of the ether layer left 1.97 g: IR ν (neat) 1740 (s, sh on high frequency side, C=O; ester, lactone, cyclopentanone); GLC (Golay Castorwax, 132 °C) showed the keto ester **35a** (eluted first) and the δ-lactone **33** in the ratio 1:1.2.

This mixture (1.90 g) of keto ester and δ-lactone was stirred and heated on the steam bath for 1 h with sodium hydroxide (0.65 g) and water (20 mL). The cooled, clear solution was washed with ether (3 × 5 mL) and acidified with 20% hydrochloric acid. After 5 min the acid mixture was made alkaline with solid sodium carbonate, and the lactone **33** was extracted with ether (4 × 4 mL).

The alkaline layer was acidified with 20% hydrochloric acid and the keto acid **35b** was extracted with ether (4 × 4 mL), and the acid solution was then reextracted continuously for 24 h with ether (10 mL). Workup of the combined ether extracts left keto acid **35b** as an oily solid (0.62 g), which was washed with petroleum ether and crystallized to constant melting point from benzene–petroleum ether: 0.51 g; mp 98.5–99 °C; IR ν (KBr) 1703 (s, acid C=O), 1738 (s, C=O cyclopentanone), 1425 (s), 1306 (s), 1296 (s), 1251 (s), 1224 (s), 926 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.95–1.66 (m, 11), 1.25–0.83 (m, 1).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.53; H, 7.19.

Treatment of keto acid **35b** with ethereal diazomethane gave the colorless, liquid methyl ester **35a** after one distillation [bath 110–115 °C (0.4 mm)], $n^{23}D$ 1.4757. Its IR and ^1H NMR spectra were superposable on those of an authentic sample prepared from **34a** by an Arndt–Eistert sequence described below.

The ether extracts from above, containing the lactone **33**, were washed with water, dried ($MgSO_4$), and evaporated in vacuo. The solid δ-lactone **33** (0.61 g) was repeatedly recrystallized at 0 °C from minimum amounts of pentane: 0.31 g; mp 125–126.5 °C; GLC (Golay Castorwax, 129 °C) indicated >99.5% purity; IR ν (KBr) 1738 (s, C=O), 1240 (s), 1221 (s), 1143 (s), 1078 (s), 1053 (s), 1002 cm^{-1} (s); ^1H NMR (CCl_4) δ 4.42 (s, 2, CH_2O), 2.66–1.08 (m, 10).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.99; H, 8.01.

Synthesis of Keto Ester 35a by Arndt–Eistert Homologation of Keto Acid 34. Purified thionyl chloride (5.4 g) in dry ether (50 mL) was added during 20 min to a stirred, cold (0 °C) solution of 6-oxobicyclo[2.2.1]heptane-*endo*-2-carboxylic acid (**34a**, 7.0 g, mp 102–103 °C, prepared as reported[17]) and dry pyridine (3.7 g) in dry ether (240 mL). After 1.5 h the mixture was rapidly filtered through sintered glass, and the ether was evaporated in vacuo. Traces of thionyl chloride were removed by two successive additions of dry benzene (15 mL) and evaporation. The residual oily acid chloride **34b** (6.9 g) had: IR ν (neat) 1802 (s, C=O of acid chloride), 1747 (s, C=O cyclopentanone), 1410 (m), 1000 cm^{-1} (s).

The acid chloride (6.9 g) in dry ether (50 mL) was added during 5 min to a cold (0 °C) stirred solution of diazomethane (~3.9 g) in ether (~250 mL).[34] About 15 min after vigorous N_2 evolution had ceased, the solvent was evaporated in vacuo, the oily residue was dissolved in dry benzene (~20 mL), and hexane was added until the solution became cloudy. After 3 h in a freezer (−20 °C) the clear supernatant solution was decanted from some oil that had formed and was kept in the freezer overnight. Pale yellow crystals of the diazomethyl ketone **34c** precipitated: 4.5 g; mp 66–73 °C; IR ν (CCl_4) 3106 (m, CH), 2114 (s, diazo), 1751 (s, C=O cyclopentanone), 1653 (s, C=O diazomethyl ketone), 1409 (m), 1310 (m), 1043 cm^{-1} (s).

A clear solution (2.8 g) of silver benzoate in triethylamine (made from 1.0 g of silver benzoate in 9.0 g of triethylamine) was added dropwise during 30 min to a stirred solution of the diazomethyl ketone **34c** (4.4 g) in methanol (50 mL). After an additional 30 min, the mixture was heated on the steam bath for 10 min, the solvent was evaporated in vacuo, and the residue was taken up in ether (75 mL), which was washed successively with 5% sulfuric acid, 5% sodium bicarbonate, and water, and dried ($MgSO_4$). The liquid keto ester (2.8 g), which contained about 5% of an impurity as revealed by GLC (Golay R, 146 °C), was chromatographed on alumina (85 g, which we prepared by shaking 100 g of Woelm alumina, neutral, Grade I with 3 g of water for 1 h). Graded elution with pentane up to pentane–ether (15:1) gave 1.83 g of homogeneous product, as judged by GLC (Golay Castorwax 100 °C). Two bulb-to-bulb distillations [bath 110–115 °C (0.5 mm)] gave the colorless, liquid keto ester **35a** (1.5 g), 99.5% pure by GLC (Golay R, 146 °C): $n^{23}D$ 1.4757; IR ν (neat) 1740 (s, br, C=O of ester and ketone), 1454 (m), 1438 (s), 1411 (m), 1374 (m), 1291 (s), 1205 (s), 1169 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.71 (s, 3, OCH_3), 2.83–0.83 (m, 11).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.22; H, 7.78.

2′-(2-Hydroxy-*endo*-6-bicyclo[2.2.1]heptyl)ethanol (36). The keto ester **35a** (0.40 g) in dry ether (10 mL) was added during 5 min to a cold (0 °C), stirred suspension of $LiAlH_4$ (0.30 g) in dry ether (50 mL). After 2 h at 0 °C more $LiAlH_4$ (0.10 g) was added, and stirring was continued 10 h at room temperature. After water (3 mL) was carefully added, followed by 10% aqueous sulfuric acid (30 mL), the mixture was stirred 30 min, and the ether layer was separated, washed with 5% sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The diol **36** (0.31 g) was crystallized once from benzene–pentane: 0.25 g; mp 67.5–70 °C. It was sublimed once [bath 110–115 °C (0.5 mm), 0.21 g, mp 70.5–73 °C] and recrystallized for analysis: 0.20 g; mp 73–74.5 °C; IR ν (KBr) 3350 (OH), 1128 (m), 1071 (m), 1044 (s), 989 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 4.62–3.58 (m, 6), 2.57–1.66 (m, 6), 1.45–0.78 (m, 4). On addition of D_2O a peak at δ 4.15 disappeared.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.51; H, 10.21.

Haller–Bauer Cleavage of Brexan-2-one (10). A stirred suspension of brexan-2-one (0.08 g), sodium amide (0.40 g), and diisopropyl ether (5 mL; distilled from $LiAlH_4$) was refluxed 8 h. Water (1 mL) was carefully added to decompose the excess of reagent, and the mixture was worked up with water and ether. The ether layer was washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and brine, and dried ($MgSO_4$). Evaporation left a crude solid (0.047 g, mp 157–161 °C), which was recrystallized from hot water and finally from benzene–pentane, mp 161–161.5 °C undepressed on admixture with an authentic sample[12] (mp 161 °C) of *cis*-bicyclo[3.3.0]octane-*cis*-2-carboxamide (**38**). The infrared spectra (KBr) were also identical.

Haller–Bauer Cleavage of Brendan-2-one (25). A suspension of brendan-2-one (0.16 g), sodium amide (0.60 g), and dry diisopropyl ether (10 mL) was refluxed 9 h. When cool, the liquid phase was decanted, water was carefully added to the residual sodium amide, and the resulting aqueous solution was extracted with chloroform. The isopropyl ether solution was evaporated in vacuo, water was added, and the mixture was extracted with chloroform. The chloroform extracts were combined, washed with water, dried ($MgSO_4$), and evaporated in vacuo: 0.13 g (74%); mp 115–130 °C; IR ν ($CHCl_3$) 3484 (m, free NH), 3379 (m, bonded NH), 1678 (s, $CONH_2$). Gas chromatography (Golay Z, 200 °C) showed two peaks in the ratio 1:13. Recrystallization from hot CCl_4 and then from benzene–pentane gave a constant mp 136–137 °C (0.050 g). Chromatography of the mother liquors on alumina (Woelm neutral, Grade I) gave a second crop (0.031 g): mp 136.5–138.5 °C (from ether); IR ν (KBr) 3379 (s) and 3193 (s, NH), 1657 (s) and 1628 (s, $CONH_2$), 1423 (m), 1291 (m), 1127 cm^{-1} (m). The reported melting point for *cis*-bicyclo[3.3.0]octane-*trans*-3-carboxamide (**39**) is 135–136 °C, and that for the C-3 epimer is 153 °C.[13]

Tricyclo[4.2.1.$0^{3,7}$]nonane (Brendane) (40). A. By Wolff–Kishner Reduction of Brendan-4-one (31). A solution of brendan-4-one (0.55 g, mp 118–120 °C) and 95% hydrazine (2.5 mL) in diethylene glycol (7 mL) was heated slowly from 25 to 135 °C during 1 h, while nitrogen gas was bubbled through gently. Around 135 °C distillate started to collect, and distillation was continued until the temperature reached 220 °C. When cool, the solution of hydrazone was treated with a clear solution of freshly cut sodium (0.20 g) in deoxygenated diethylene glycol (3 mL). While being purged with a nitrogen stream, the solution was heated, and at 180 °C gas was evolved and a white, waxy solid began to sublime into the collector. After continued heating at 200–215 °C for 4 h the collected sublimed solid in CS_2 (10 mL) was successively washed with water, 5% hydrochloric acid, and brine, and dried ($MgSO_4$). GLC (5% squalane on Chromosorb, 135 °C) at this stage showed 98% of one component. Preparative GLC with the same column gave 0.093 g: IR ν (CS_2) 1310 (m), 1287 (m), 1252 (w), 1148 cm^{-1} (m); IR ν (CCl_4) 1453 (m), 1311 (m), 1288 (m), 1251 (w), 1149 cm^{-1} (m); ^1H NMR (CCl_4) δ 2.33–1.38 (m), 0.87 (s), 0.70 (s). Because of overlap, accurate relative intensities were not obtained. Sublimation for analysis [bath 80–90 °C (760 mm)] gave white brendane (**40**): mp 98–99 °C (N_2 filled, sealed tube); molecular ion at *m/e* 122.[36]

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.20; H, 11.54.

B. By Wolff–Kishner Reduction of Brendan-2-one (25). The reduction of brendan-2-one (0.40 g, mp 118.5–119.5 °C) was conducted as described for brendan-4-one with proportional amounts of reagents. Preparative GLC of the CS_2 solution gave 0.053 g of brendane, whose IR in CS_2 and NMR in CCl_4 were superposable on those of the hydrocarbon from part A. After sublimation, it had mp 98.5–99 °C (N_2 filled, sealed tube) with softening at 70 °C. A mixture melting point with brendane from part A had mp 98–99 °C.

Tricyclo[4.3.0.$0^{3,7}$]nonane (Brexane) (37). A. By Wolff–Kishner Reduction of Brexan-2-one Semicarbazone (10a). A mixture of brexan-2-one semicarbazone (0.43 g, mp 188–189.5 °C) and powdered potassium hydroxide (0.57 g) in a bulb-to-bulb distillation apparatus was slowly heated in an oil bath while the receiver bulb was cooled in dry ice. At 180 °C gas evolution began and heating was continued at 185–200 °C for 2 h. The distillate was dissolved in CS_2, which was successively washed with water, 5% hydrochloric acid, 5% sodium bicarbonate, and water, and dried ($MgSO_4$). Purification by preparative GLC (Carbowax on Chromosorb W, 147 °C) gave 0.11 g of liquid, which was dried with $MgSO_4$ and distilled [bath 120–150 °C (760 mm)] from $LiAlH_4$ to give colorless brexane (**37**) (0.072 g): one peak on GLC (squalane, 132 °C); $n^{25}D$ 1.4845; IR ν (CCl_4) 1462 (m), 1307 (m); ^1H NMR (CCl_4) 2.05–1.73 (m, 4), 1.73–0.92 (m, 10); molecular ion at *m/e* 122.

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.55; H, 11.50

B. By Wolff–Kishner Reduction of Brexan-4-one Semicarbazone (24a). Brexan-4-one semicarbazone (0.35 g, mp 202–204 °C) was reduced with powdered potassium hydroxide (0.45 g) in a manner essentially the same as that described above in part A. After preparative GLC the colorless product (0.063 g) had n^{25}_D 1.4843 and its IR in CCl_4, its retention time on GLC (squalane, 132 °C), and its mass spectral cracking pattern were identical with those of brexane obtained by method A.

Brexan-2-one *p*-Tosylhydrazone (10b). A solution of brexan-2-one (0.050 g) and *p*-toluenesulfonylhydrazine (0.075 g, mp 110–111 °C) in methanol (1 mL) was refluxed 30 h. Removal of the solvent in vacuo left a white solid (0.093 g, mp 140–143 °C), which was recrystallized from methanol–water for analysis: 0.068 g; mp 148–149.5 °C; IR ν (KBr) 3200 (s), 1671 (m), 1600 (m), 1344 (s), 1162 (s), 815 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 63.39; H, 6.71.

Brendan-2-one *p*-Tosylhydrazone (25b). A solution of brendan-2-one (0.013 g) and *p*-toluenesulfonylhydrazine (0.038 g) in absolute methanol (1 mL) was heated gently on a steam bath for 30 min. Water (1 mL) was added and the solution was heated briefly and allowed to cool. The first crop of crystals (~70%) was recrystallized twice from methanol–water (1:1), mp 146.5–147.5 °C.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 63.30; H, 6.66.

Brexan-4-one *p*-Tosylhydrazone (24b). This derivative was prepared from brexan-4-one in the same manner as used for brendan-2-one. Recrystallization from absolute methanol gave mp 192.5–193.5 °C dec.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 62.76; H, 6.52.

Bamford–Stevens Reaction on Brexan-2-one Tosylhydrazone (10b). A stirred mixture of brexan-2-one tosylhydrazone (0.685 g, mp 146–148 °C), sodium methoxide (0.833 g, freshly prepared and thoroughly dried), and bis(2-ethoxyethyl) ether [4.5 mL, dried repeatedly over KOH and distilled, bp 78–79 °C (15 mm)] was heated on an oil bath. At 140 °C (bath temperature) nitrogen was vigorously evolved. After 2 h at 140–150 °C, water was added to the cooled solution, which was then extracted with pentane. The extract was washed with water and dried over $MgSO_4$, and the solvent was removed on an 18-in. spinning-band column (reflux ratio 5:1) until the boiling point reached 60 °C. The residual pot solution was preparatively gas chromatographed (20% SE-30 on Chromosorb P, 132 °C). The colorless liquid (0.142 g) had n^{23}_D 1.4921, showed only one GLC peak (Golay R, 118 °C), and its IR (neat) and ^1H NMR (CCl_4) were superposable on those of authentic deltacyclane (**21**).

Bamford–Stevens Reaction on Brexan-4-one Tosylhydrazone (24b). A stirred mixture of the tosylhydrazone (0.161 g, mp 192–192.5 °C), dry sodium methoxide (0.15 g), and purified bis(2-ethoxyethyl) ether (2.5 mL) was heated on an oil bath. Gas was evolved around 155 °C and heating was continued for 1.5 h at 155–160 °C. After a water–pentane workup, the dried pentane layer gave 0.024 g of liquid after preparative GLC (20% SE-30 on Chromosorb P, 130 °C), n^{25}_D 1.4928. It showed only one peak on GLC (squalane, 132 °C), and its IR (CCl_4) and mass cracking pattern were identical with those of authentic deltacyclane (**21**).

Bamford–Stevens Reaction on Brendan-2-one Tosylhydrazone (25b). This reaction was conducted on 0.304 g of brendan-2-one tosylhydrazone (mp 140–144 °C) as described above for the brexan-4-one analogue, with proportional quantities of reagents. After preparative GLC the product (0.049 g; n^{25}_D 1.4928) showed only one peak on GLC (squalane, 132 °C) and had an IR (neat) that was identical with that of authentic deltacyclane (**21**).

Brexane (37) from Catalytic Hydrogenation of Deltacyclane (21). The tetracyclic hydrocarbon **21** (0.12 g), platinum oxide (0.040 g), and acetic acid (10 mL) were hydrogenated at 95 °C and 100 psi for 4.5 h. After conventional workup, GLC on squalane showed deltacyclane and brexane in the ratio of 2:1. (Possibly a small proportion of brendane may have escaped detection in the tailing peak.) *exo*-2-Brendyl acetate and *exo*-4-brexyl acetate were not detected with the squalane column, but were principal products, as revealed by use of appropriate columns (polypropylene coated Golay).

Isomerization of Brexan-2-one (10) to Brendan-2-one (25) by Alkali. A solution of brexan-2-one (0.20) and potassium *tert*-butoxide [0.51 g, M.S.A. Corp., sublimed twice at 135–140 °C (0.3 mm)] in *tert*-butyl alcohol (5.7 mL, twice distilled under nitrogen from sodium) was heated in a sealed Pyrex tube for 150 h at 185 °C in a bomb with external *tert*-butyl alcohol as a pressure equalizer. Water (15 mL) was added, and the mixture was extracted with pentane (5 × 4 mL), which was then washed with water and brine, dried with $MgSO_4$, and concentrated to ~4 mL with an 18-in. spinning-band distillation column. The remaining solvent was removed in vacuo and the residue was sublimed [bath 60–80 °C (13 mm)] to give a white solid (0.12 g, 57%), mp 117.5–118.5 °C undepressed by an authentic sample of brendan-2-one. Their IR spectra (CCl_4) were also identical. GLC (Golay R, 124 °C) showed >99% brendan-2-one and <1% brexan-2-one.

In a control homoenolization experiment conducted similarly (185 °C for 120 h) on **brendan-2-one,** the product (~100%) was brendan-2-one, which contained (GLC on Golay Castorwax, 110 °C) ~4% of an unidentified compound, which was not brexan-2-one. A second control run on brendan-2-one for 60 h at 205 °C and similar workup again gave no brexan-2-one, but led to extensive decomposition. The crude product (~35% yield by weight) showed five peaks on GLC (Golay Castorwax, 100 °C) in the ratio 2:2:1:4:10. The first peak corresponds to brendan-2-one.

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Registry No.—**6a,** 57722-41-5; **6a** sodium salt, 57722-42-6; **6b,** 57722-43-7; **6c,** 1703-68-0; **7,** 1703-69-1; *exo*-**8a,** 66840-95-7; *endo*-**8a,** 66840-96-8; *exo*-**8b,** 66840-97-9; *endo*-**8b,** 66840-98-0; **9,** 1703-77-1; **10,** 1703-78-2; **10a,** 1703-79-3; **10b,** 66787-57-3; **11,** 1521-91-1; **11a,** 66787-64-2; **11b,** 66787-65-3; **11c,** 66787-66-4; **12,** 121-46-0; **13** epimer 1, 66808-07-9; **13** epimer 2, 66808-08-0; **14a** epimer 1, 29415-45-0; **14a** epimer 2, 66808-09-1; **14b** epimer 1, 13927-45-2; **14b** epimer 2, 13927-44-1; **14c,** 66787-58-4; **15,** 66787-59-5; **16,** 66787-60-8; **17a,** 1007-04-1; **17b,** 29412-43-9; **17c,** 21519-81-3; **18,** 66787-61-9; **19,** 16282-07-8; **19a,** 66787-62-0; **19b,** 66787-63-1; **20a,** 939-84-4; **20b,** 21519-84-6; **20c,** 21519-85-7; **21,** 6567-11-9; **22a,** 61800-16-6; **22b,** 61800-18-8; **22c,** 61800-17-7; **23a,** 61800-14-4; **23b,** 14805-44-8; **23c,** 61800-15-5; **23d,** 66787-54-0; **24,** 53439-20-6; **24a,** 66787-55-1; **24b,** 66787-56-2; **25,** 1521-92-2; **25a,** 1521-93-3; **25b,** 1521-73-9; **26a,** 66808-03-5; **26b,** 66808-04-6; **27a,** 66808-05-7; **27b,** 66808-06-8; **28a,** 1195-12-6; **28a** sodium salt, 66787-51-7; **28b,** 37750-50-8; **28c,** 35964-13-7; **29,** 1719-13-7; **29a,** 1719-09-1; **29b,** 1521-79-5; **30,** 66787-52-8; **31,** 1521-78-4; **31a,** 1521-77-3; **32,** 26433-43-2; **33,** 66787-53-9; **34a,** 42392-37-0; **34b,** 66787-45-9; **34c,** 66787-46-0; **35a,** 1719-08-0; **35b,** 1521-76-2; **36,** 66787-47-1; **37,** 3104-87-8; **38,** 66787-50-6; **39,** 7067-97-2; **40,** 1521-75-1; *exo*-2-bicyclo[2.2.1]hept-5-enecarboxylic acid, 934-30-5; *endo*-2-bicyclo[2.2.1]hept-5-enecarboxylic acid, 1195-12-6; *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylic acid, 66808-01-3; methyl *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylate, 66787-49-3; methyl *syn*-2-oxo-7-bicyclo[2.2.1]heptane carboxylate, 66808-02-4; α-naphthyl isocyanate, 86-84-0; 3,5-dinitrobenzoyl chloride, 99-33-2; methyl vinyl ketone, 78-94-4; α-acetoxyacrylonitrile, 3061-65-2; methyl 6-hydroxy-2-bicyclo[2.2.1]-heptaneacetate, 66787-48-2.

References and Notes

(1) (a) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87**, 1613 (1965); (b) presented at the 149th Meeting of the American Chemical Society, Detroit, Michigan, April, 1965, Abstracts 2P.

(2) The parent hydrocarbon **1** (Z = H) is tricyclo[4.3.0.0^{3,7}]nonane, and can be viewed as a norbornyl system with an extra two-carbon bridge that uses an *exo*-norbornyl bond. The convenient trivial name *brexane* derives from the words *bridge* and *exo*.

(3) For a recent review, see: H. C. Brown, "The Nonclassical Ion Problem", Plenum Press, New York, N.Y., 1977.

(4) The parent hydrocarbon **5** (Z = H) is tricyclo[4.2.1.0^{3,7}]nonane. A convenient name for the skeleton is *brendane*, which emphasizes the existence of a *bridge* involving an *endo*-norbornyl bond.

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(6) Several research groups have contacted us for comparison samples, spectral data, experimental procedures, and mechanistic or other details about various brexyl, brendyl, and related derivatives. We wish to acknowledge mutually beneficial correspondence from J. H. Richards (California Institute of Technology); R. S. Bly (University of South Carolina); R. M. Moriarty (University of Illinois, Chicago Circle); W. R. Adams, D. Heywood, and E. Marcus (Union Carbide Corp., South Charleston, W. Va.); M. Julia (University of Paris); A. Krantz (State University of New York, Stony-

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(7) The fourth letter of the Greek alphabet led to the convenient name *deltacyclane* for this key tetracyclic hydrocarbon, whose full IUPAC name is given in the Experimental Section. We avoided prefixes like *quad* or *tetra* to prevent confusion with the tetracyclic hydrocarbon, quadricyclane, and with the "tetracycline" class of antibiotics.
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Marine Natural Products: Halitoxin, Toxic Complex of Several Marine Sponges of the Genus *Haliclona*[1]

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A complex mixture of high molecular weight toxic pyridinium salts designated halitoxin has been isolated from the sponges *Haliclona rubens, H. viridis,* and *H. erina.* The toxin has been separated into molecular weight range fractions of 500–1000, 1000–25 000, and > 25 000, each of which shows the same spectral and biological properties. A general structure for halitoxin has been proposed based on ^{1}H and ^{13}C NMR analyses and identification of a group of 3-alkenylpyridines obtained in good yield upon pyrolysis of the toxin. The oligomeric/polymeric toxin consists of 3-alkylpyridine units connected by the nitrogen of one ring and the terminus of the 3-alkyl chain of the next. No functionality other than the pyridinium ring has been detected. Halitoxin is cytotoxic, haemolytic, and toxic to fish and mice.

Sponges from several species of the genus *Haliclona* have been reported to give extracts toxic to fish.[2] Baslow and Turlapaty[3] found that a crude aqueous extract of *H. viridis* was toxic to mice (LD_{50} ~ 275 mg/kg) and also inhibited the growth of Ehrlich ascites tumors. These authors coined the name halitoxin for this crude toxic extract but did not report any effort to isolate a pure toxin. In our ongoing search[4] for pharmacologically active compounds from marine organisms, we found that extracts of *H. rubens* are toxic to mice (LD_{50} ~ 7 mg/kg) and fish and cytotoxic in the National Cancer Institute's KB cell culture bioassay.[5] We also have found that other species of the genus *Haliclona* contain what appears to be the same toxin. However, not all of the *Haliclona* sp. examined yielded the toxin. In this paper we report the partial purification, spectral characterization, and chemical degradation which have lead to a proposed gross structure for halitoxin from four different *Haliclona* species.

The sponge we have studied most extensively is *Haliclona rubens,* a red tubular sponge commonly found in shallow (15 ft or less) reef waters of the Caribbean. Samples of the sponge for chemical work have been preserved in various ways: air-dried, freeze-dried shortly after collection, and preserved in alcohol. The method of preservation appears to have little effect on the character of the toxin isolated as judged by biological activity and spectral analysis. The toxin is obtained easily from the sponge preserved by any of the above methods.

Isolation and Purification of Halitoxin. Toxin was obtained from air-dried *H. rubens* by first defatting the ground specimens with chloroform and then extracting them continuously with methanol. After removal of most of the solvent, the methanol extract was dissolved in water and extracted several times with 1-butanol. The 1-butanol fractions contained virtually all of the toxin as determined by spectral

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