Synthesis of Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (Homocubane) and Some of Its Derivatives[1]

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Homocubane-4-carboxylic acid (6) has been prepared by two routes both of which utilize a Favorskii-type ring contraction of an α-halo ketone to generate the homocubane skeleton. In the preferred route, ketone **5**, formed by photochemical ring closure of the Diels–Alder adduct, **4**, of cyclopentadiene and α-bromocyclopentadienone, gave acid 6 (in nearly quantitative yield) when heated with aqueous alkali. In the alternate route, ketone **7**, when heated with solid sodium hydroxide in benzene, gave a mixture of ring cleaved acid **8a** and the desired Favorskii product **9a** which was dehalogenated with lithium *t*-butyl alcohol to give acid *6*. The latter was converted into the aminomethyl derivative **13**, into the amine **14**, and into the parent hydrocarbon, homocubane (**17**). When ketone **7** was heated either with an aqueous solution of potassium hydroxide or with solid potassium hydroxide in benzene, acid **8a** was essentially the sole product. Nmr double resonance studies were carried out on ester **8b**.

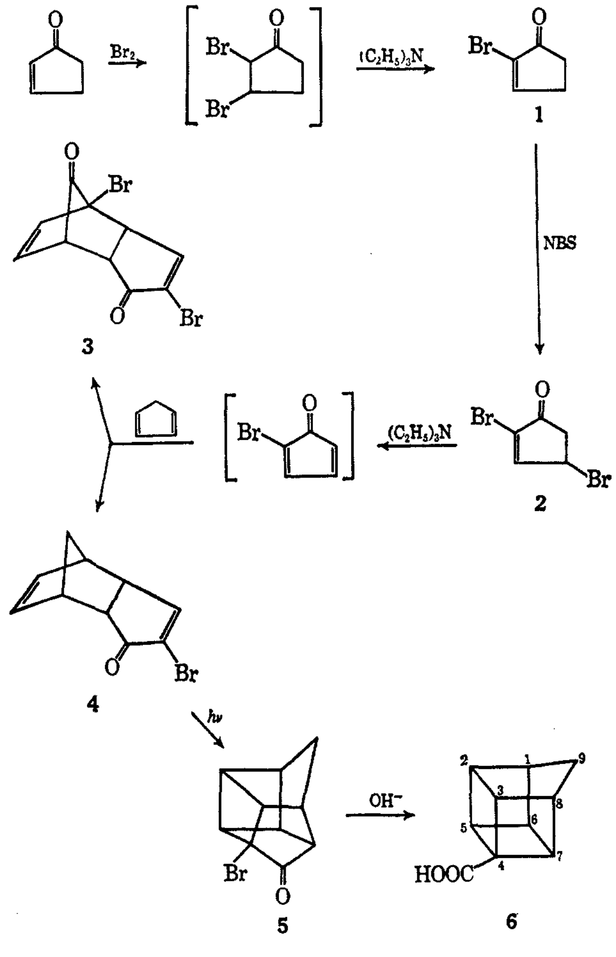
During an investigation of the biological activity of a variety of cage compounds it became necessary to devise a synthesis of monosubstituted pentacyclo-[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonanes. Soon after we began our work Scherer and coworkers[2] reported the synthesis of a polychlorinated compound containing this skeleton, for which they suggested the trivial name "homocubane." Since then several reports[3a–i] have described the synthesis and reactions of various substituted homocubanes. We wish to report now the results of our investigations on the synthesis of the parent hydrocarbon, homocubane,[4] and some of its monosubstituted derivatives.

Favorskii-type ring contraction of an appropriate halopentacyclodecanone has been used successfully to generate homocubane carboxylic acids containing halogen atoms and other functional groups.[3a,b] Since the requisite halopentacyclodecanones are conveniently prepared by photochemical cyclization of a Diels–Alder adduct, whose *endo* stereochemistry positions two carbon–carbon double bonds close enough together to allow internal cyclization to take place, we used this approach in two similar synthetic schemes.

The first sequence was based upon the fact that cyclopentadiene reacts with cyclopentadienone in a Diels–Alder reaction to give *endo*-dicyclopentadien-1-one.[5,6] By using an α-halocyclopentadienone[7] in this type of reaction we obtained α-bromo ketone **4**, which was ultimately transformed into homocubane-4-carboxylic acid (6) (Scheme I).

Our second route to the homocubanes (Scheme II) utilized polyhalopentacyclodecanones, which are readily prepared[8–10] from the stable tetrachlorocyclopentadienone ketals. The known tetrachloro ketone **7**, first prepared by Yates and Eaton,[9] provided a convenient starting point. The intermediate polyhalohomocubanes obtained by this sequence may then be dehalogenated to give the required product.

Scheme I



Of the two approaches, the pathway outlined in Scheme I was the more satisfactory. Bromo ketone **1** was prepared by bromination of 2-cyclopentenone followed by dehydrobromination of the intermediate 2,3-dibromocyclopentanone with triethylamine. The

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[1] A preliminary communication describing a portion of this work has appeared: G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *Tetrahedron Lett.*, 3737 (1966).

[2] K. V. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p 23N.

[3] (a) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 3157 (1964); (b) K. V. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, *Tetrahedron Lett.*, 1199 (1965); (c) K. V. Scherer, Jr., G. A. Ungefug, and R. S. Lunt, III, *J. Amer. Chem. Soc.*, **88**, 2859 (1966); (d) K. V. Scherer, Jr., and R. S. Lunt, III, *ibid.*, **88**, 2860 (1966); (e) W. G. Dauben and D. L. Whalen, *Tetrahedron Lett.*, 3743 (1966); (f) W. G. Dauben and D. L. Whalen, *J. Amer. Chem. Soc.*, **88**, 4739 (1966); (g) C. G. Chin, H. W. Cuts, and S. Masamune, *Chem. Commun.*, 880 (1966); (h) P. von R. Schleyer, J. J. Harper, G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Amer. Chem. Soc.*, **89**, 698 (1967); (i) G. C. Barborak and R. Pettit, *ibid.*, **89**, 3080 (1967).

[4] Dauben and Whalen (see ref 3e) also have synthesized homocubane, but by an entirely different route.

[5] K. Hafner and K. Goliasch, *Ber.*, **94**, 2909 (1961).

[6] C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).

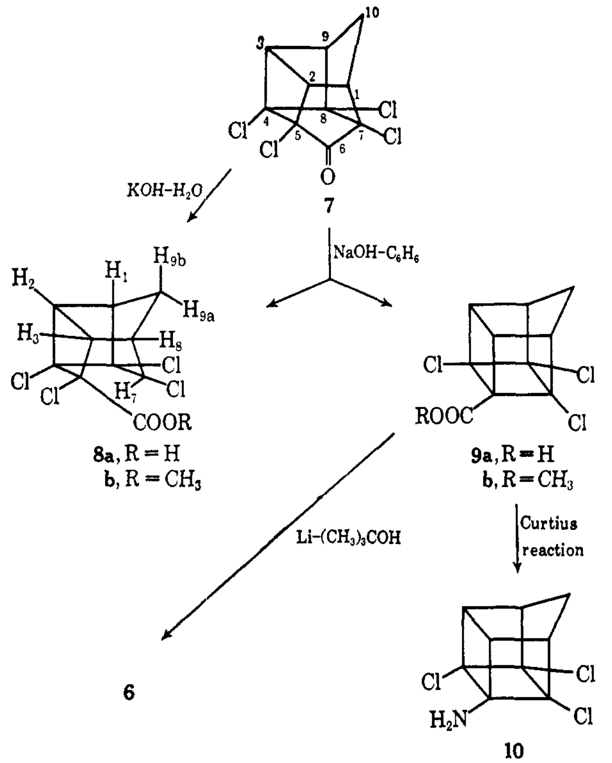
[7] P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962 (1964).

[8] P. E. Eaton, Ph.D. Dissertation, Harvard University, Cambridge, Mass., 1960.

[9] P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

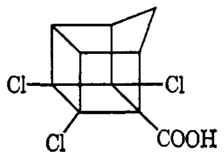
[10] G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964).

SCHEME II



structure of **1** is supported by its ultraviolet spectrum which shows a bathochromic shift[11] of 20 mμ from the absorption peak of 2-cyclopentenone and by the appearance of a single vinylic proton in its nmr spectrum.[12] Allylic bromination of **1** with N-bromosuccinimide gave dibromoenone **2** in good yield. Dehydrohalogenation of **2** with triethylamine at low temperature generated the extremely reactive 2-bromocyclopentadienone which immediately condensed with the cyclopentadiene present in the reaction mixture to form the Diels–Alder adduct **4** in low yield.[13] The expected *endo* stereochemistry[14] of **4** was confirmed by its ready photochemical cyclization to **5**. When **5** was treated with hot aqueous alkali, acid **6** was obtained in almost quantitative yield. The nmr spectrum of **6** shows a singlet[15] (δ 1.72) for the bridge methylene which would be expected for its symmetrical structure.

In the alternate route to homocubanes (Scheme II), tetrachloro ketone **7**, when heated with solid sodium hydroxide in boiling benzene, gave a mixture of three acids shown by glpc to be present in the ratio 11:8:1. The two major components[16] were separated by Florisil column chromatography of their methyl esters. The ester present in larger quantity (55%) was hydrolyzed to give a tetrachloro acid (**8a**) (see discussion below). The second major ester component (**9b**) was shown to be the product of a Favorskii-type ring contraction from analytical and spectral information. Since the ring contraction of **7** can proceed in either of two directions, the parent acid of ester **9b**, shown by glpc on several columns to be a single compound, may have structure **9a** or **11**. It has been assigned structure **9a**



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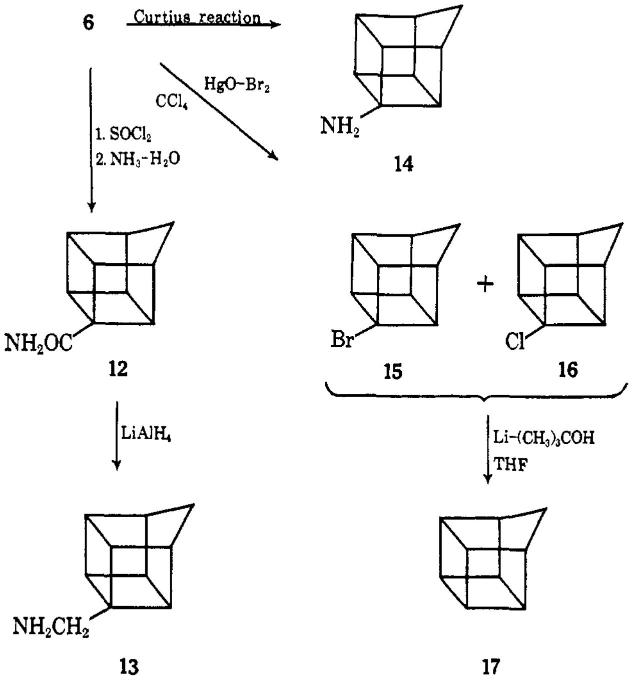
on the basis of the following evidence. When this acid was dechlorinated with lithium *t*-butyl alcohol, a semisolid acidic product was obtained which was homogeneous by glpc though its nmr spectrum indicated the presence of some olefinic acid, presumably a result of ring fission. The mixture was treated with bromine, a gummy precipitate was removed, and the residue was subjected to repeated fractional sublimation. A small sample of a pure acid was obtained and was shown by comparison of physical and spectral properties to be identical with homocubane-4-carboxylic acid (**6**) obtained earlier (Scheme I).

Acid **6** was converted (Scheme III) into the aminomethyl derivative **13** by lithium aluminum hydride reduction of amide **12**. Amine **14** was obtained from **6** *via* a Curtius reaction. When **6** was subjected to a Hunsdiecker reaction (Cristol modification)[17] in carbon tetrachloride the glpc of the product showed it to be a 1:1 mixture of two components. Although the components were not separated and individually identified it seems likely that they were 4-bromohomocubane (**15**) and 4-chlorohomocubane (**16**). The chloro compound **16** could have been formed by attack of the 4-

SCHEME III



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[11] L. F. Fieser and M. Fieser, *Steroids*, 19 (1959).

[12] C. H. DePuy, C. E. Lyons, and L. B. Rodewald [*J. Chem. Eng. Data*, **11**, 102 (1966)] reported that the nmr spectrum of 2-cyclopentenone showed a β-vinylic proton at δ 7.63 (sextet) and an α-vinylic proton at 6.11 (sextet). Compound **1** shows a triplet at δ 7.86 which is the expected pattern based on DePuy's results.

[13] The low yield encountered in this step apparently is due to the formation of a by-product which we assume has structure **3** since the infrared spectrum of the crude reaction product showed carbonyl absorption at 5.50 μ (see ref 7) in addition to the peaks at 5.88 and 6.35 μ expected for **4**.

[14] See J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961), for a review of the stereochemistry of the Diels–Alder reaction.

[15] The half-height width of the methylene peak is 2.5 Hz compared to 1 Hz for TMS. Any coupling between the bridge methylene protons and the adjacent bridgehead methines is therefore probably less than 1 Hz.

[16] The minor acid component (5%) remains unidentified.

[17] S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

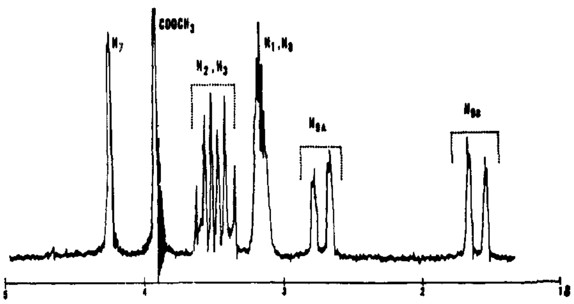


Figure 1.—Nmr spectrum (100 MHz) of tetrachloro ester **8b** in $CDCl_3$.

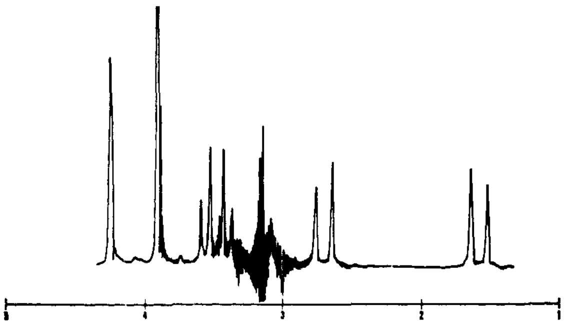
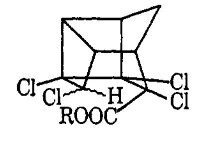


Figure 2.—Nmr spectrum of **8b** with irradiation of the H_1, H_8 peak.

homocubyl radical on the solvent (CCl_4).[18] Indirect support for this assumption follows from the lithium *t*-butyl alcohol dehalogenation of the mixture. Glpc of the reaction product after dehalogenation showed a single component which was isolated in low yield and shown to be pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]nonane (**17**), homocubane. This hydrocarbon, a very volatile solid, showed a simple infrared spectrum with no significant absorption between 3.6 and 7.3 μ. Its nmr spectrum was identical with that reported by Dauben,[3e] though our melting point was slightly higher.

The formation of **9a** as the only product of Favorskii ring contraction of **7** was rather surprising, though Scherer and coworkers[19] have reported a similar result with a ketone closely related to **7**. Examination of a molecular model of **7** shows that the C-5 chlorine is almost eclipsed with the C-2 hydrogen giving rise to some torsional strain and nonbonding interaction. However, the C-7 chlorine is conformationally *skewed* with respect to the C-1 hydrogen and apparently has no nonbonded interactions as severe as that shown by the C-5 chlorine. It is possible then, that the torsional[20] and nonbonded strains on the C-5 chlorine may be relieved as the ring contraction proceeds, with gradual lengthening of C-5 carbon–chlorine bond and with angle change, thus favoring formation of **9a** over **11**.

The tetrachloro acid, obtained as a major by-product from the reaction of ketone **7** with solid sodium hydroxide in boiling benzene, also was obtained almost exclusively (94%) when **7** was heated either in aqueous alkali or in benzene containing solid potassium hydroxide.[21] Elemental analysis (see the Experimental Section) and the nmr spectrum of its methyl ester, which showed a 1 H singlet at δ 4.27 indicative of a proton in a –CHCl grouping, indicated that this acid was a product of Haller–Bauer cleavage of ketone **7** and therefore must have structure **8** or **18**.



18a,R = H
b,R = CH_3

Scherer and coworkers[22] have shown that Haller–Bauer ring cleavage of octachlorohomocubanone proceeds with over-all retention of configuration; *i.e.*, both the carboxyl group and the proton are inside the cage. By analogy we have depicted the two alternatives, **8** and **18**, as the products resulting from ring cleavage with retention of configuration. Double resonance studies of ester **8b** (or **18b**) were carried out at 100 MHz[23] to determine the direction of ring opening. The 100-MHz nmr spectrum of **8b** (or **18b**) is shown in Figure 1. The additional multiplicity in the H-9a, H-9b doublets at δ 1.58 (1 H) and at 2.71 (1 H)[24] and the H-7 peak at δ 4.27 (1 H, –CHCl) in **8b** indicated the presence of weak spin–spin coupling. The spectrum also shows a sextet at δ 3.6–3.3 (2 H) and a broad peak at 3.25–3.05 (2 H). Irradiation of the δ 3.25–3.05 peak (Figure 2) caused the two upfield doublets and the downfield singlet to sharpen considerably, while the sextet collapsed to an AB quartet (J_{AB} = 7 Hz). Irradiation of the δ 3.6–3.3 sextet produced no observable change in the two upfield doublets or the downfield singlet. Irradiation of the δ 4.27 peak caused a slight change in the δ 3.25–3.05 peak only. These results are readily interpreted in terms of the structure shown above for **8b** with the assignments indicated on the spectrum (Figure 1), but not for the alternate structure **18b**. If the structure were **18**, irradiation of the bridge-

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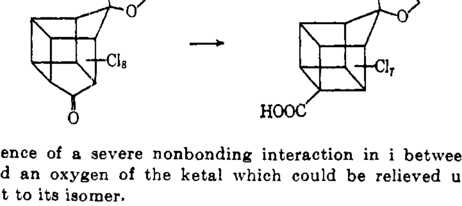
(18) F. W. Baker, H. D. Holtz, and L. M. Stock [*J. Org. Chem.*, **28**, 514 (1963)] have shown that brominative decarboxylation of bicyclo[2.2.2]-octane-1-carboxylic acid under the conditions suggested by Cristol in carbon tetrachloride leads to a mixture of the 1-chloro (68%) and 1-bromo (32%) derivatives. These authors suggest that the chloro derivative may be formed by attack of the 1-bicyclo[2.2.2]octyl radical on carbon tetrachloride.

(19) These investigators (see ref 3b) showed that ii was the exclusive product of ring contraction of i. In this case the exclusiveness was attributed to the presence of a severe nonbonding interaction in i between the C-7 chlorine and an oxygen of the ketal which could be relieved upon going to ii but not to its isomer.



(20) Schleyer [*J. Amer. Chem. Soc.*, **89**, 701 (1967)] has discussed recently the importance of considering torsional effects in the stereochemistry of attack and departure in norbornane derivatives.

(21) G. W. Kenner, M. J. T. Robinson, C. M. B. Tylor, and B. R. Webster [*J. Chem. Soc.*, 1756 (1962)] obtained different products when sodium hydroxide was substituted for potassium hydroxide in a study of the Haller–Bauer cleavage of fluorenone.

(22) K. V. Scherer, Jr., G. A. Ungefug, and M. G. Ly, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p O9. The X-ray data reported at this meeting indicated that the configuration of the ring cleaved acid was opposite to that first postulated by these workers (see ref 3b).

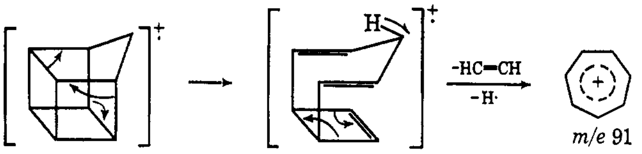
(23) We are grateful to Japan Electron Optics Laboratory, Medford, Mass., for performing the double resonance experiments.

(24) The low field doublet (δ 2.71) has been tentatively assigned to the methylene proton (H-9a) *syn* to the C-6, C-7 chlorines. The nmr spectra of some dihalonorbornenes [P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965)] showed a large downfield displacement of the bridge methylene proton *syn* to *exo* halogens.

head protons H-1, H-8 should have shown that they are coupled only to the bridge methylene and H-2, H-3 protons and not to the -CHCl proton. We have considered only vicinal coupling to be important in the appearance of the spectrum. Though some small long range coupling between H-7 and H-9b might be expected and indeed might exist we have no real evidence to support it here.

The nmr spectrum of bromo ketone **5** showed a multiplet (1 H) at δ ∼2.4, about 0.5 ppm upfield from the closest methine resonance. We have assigned this peak to proton 7 and in our preliminary communication we discussed in some detail our reasons for favoring this assignment. We noted also that this peak was about 0.13–0.15 ppm upfield from the methine signals of the parent hydrocarbon. Tetrachloro ketone **7** shows no upfield methine signals. This apparently anomalous behavior of protons α to a carbonyl in caged systems also has been noted by Stedman and coworkers.[25]

The mass spectrum of homocubane (**17**) shows a low intensity molecular ion peak of relative abundance (RA) 13 at *m/e* 118 and a base peak (RA, 100) at *m/e* 117, corresponding to loss of one hydrogen. The second most intense peak (RA, 39) in the spectrum was at *m/e* 91 which might be attributed to the tropylium ion, generated from **17** by loss of a hydrogen and acetylene. The mass spectra of other cage systems, both structurally similar with[26] and structurally different from[27] homocubane also have shown a significant peak at *m/e* 91 suggestive of a tropylium ion. The spectrum of homocubane contains almost all the peaks shown in the mass spectrum of cycloheptatriene, which has been postulated to dissociate to the tropylium ion on electron impact.[28]



Experimental Section[29]

2-Bromo-2-cyclopentenone (**1**).—A solution of bromine (160 g, 1 mol) in CCl_4 (500 ml) was added dropwise during 45 min to a cold (0°) solution of 2-cyclopentenone (82 g, 1 mol) in CCl_4 (500 ml). After stirring 5 min at 0° a solution of triethylamine (210 ml, 151 g, 1.5 mol) in CCl_4 (500 ml) was added dropwise during 45 min while maintaining the temperature at 0°. When the addition was complete, the mixture was stirred at room temperature for 2 hr, then the precipitated triethylammonium bromide was filtered and washed well with CCl_4. The combined filtrate and washings were extracted with dilute HCl and with water and then dried. The solvent was removed at 40° *in vacuo* and the residue was distilled to give 82 g of 2-bromo-2-cyclopentenone (**1**), bp 52–56° (0.3 mm), which solidified in the receiver. One recrystallization from ether–hexane gave 68 g (42%) of **1** as colorless plates: mp 39–39.5°; ultraviolet maximum at 238 mμ (ε 8470); infrared absorption at 5.91 (C=O) and 6.32 μ (C=C); and nmr peaks at δ 7.86 (1 H triplet, *J* = 3 Hz) and at 2.88–2.43 (4 H multiplet).

Anal. Calcd for C_5H_5BrO: C, 37.30; H, 3.13; Br, 49.63. Found: C, 37.31; H, 3.11; Br, 49.32.

***endo*-2-Bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one** (**4**).—A mixture consisting of 2-bromo-2-cyclopentenone (**1**) (80 g, 0.50 mol), N-bromosuccinimide (98 g, 0.55 mol), azobisisobutyronitrile (ABIN) (2.5 g), and 1 l. of CCl_4 was heated at reflux. Additional 1-g portions of ABIN were added after 3 and 7 hr and then reflux was continued for a total of 24 hr.[30] The mixture was cooled to room temperature, and the succinimide was filtered and washed with CCl_4. The combined filtrate and washings were extracted with 5% aqueous $NaHCO_3$ solution and with water and then dried. The solvent was evaporated at 25° *in vacuo* to give 118 g of crude 2,4-dibromo-2-cyclopentenone (**2**)[31] as a dark liquid.

A solution of the dibromoenone **2** (118 g) in anhydrous ethyl ether (2 l.) was added dropwise during 2 hr to a solution of freshly distilled cyclopentadiene (570 ml) and triethylamine (145 ml, 105 g, 1.04 mol) in anhydrous ether (1 l.) cooled to −10°. The temperature was maintained between −10 and 0° during addition. The mixture was stirred for 15 min, the precipitated triethylammonium bromide (75 g, 82%) was collected and washed with ether. The combined filtrate and washings were extracted with dilute HCl, water, 5% aqueous $NaHCO_3$, and water and then dried. Evaporation of the ether *in vacuo* gave 137 g of residual oil. Thin layer chromatography on silica gel G with benzene showed four components. The residue was dissolved in hexane (900 ml), decanted from some insoluble gum and chromatographed on neutral alumina (6 lbs, Woelm, activity grade I). Elution with hexane (12 l.) gave some dicyclopentadiene; elution with benzene (32 l.) gave 31 g of 2-bromo-3a,4,7,-7a-tetrahydro-4,7-methanoinden-1-one (**4**); elution with 1:1 benzene–chloroform (10 l.) gave another 5 g of **4**. Further elution with benzene–chloroform or chloroform gave mixtures of desired product and what we presume to be 2,4-dibromo-3a,-4,7,7a-tetrahydro-4,7-methanoinden-1,8-dione (**3**) based on a strong peak at 5.50 μ in its infrared spectrum.

The combined solids from the benzene and 1:1 benzene–chloroform eluates (36 g) were recrystallized from petroleum ether (30–60°) to give 32.8 g (29%) of **4**: mp 56–57°; ultraviolet maximum at 246 mμ (ε 6000); infrared absorption at 5.75 (C=O) and 6.27 μ (C=C); and nmr peaks at δ 7.56 (1 H doublet, *J* = 2.8 Hz), at 3.52–3.18 (2 H multiplet), at 3.18–2.75 (2 H multiplet), and at 1.71 (2 H complex triplet).

Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.50. Found: C, 53.38; H, 4.03; Br, 35.87.

5-Bromopentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-6-one (**5**).—A solution of ketone **4** (24 g, 0.103 mol) in ethyl acetate (1 l.) was irradiated with a 450-W Hanovia medium pressure mercury vapor lamp for 32 hr in a Pyrex immersion photolysis apparatus. The solvent was removed *in vacuo* and the dark residue was heated with boiling petroleum ether (400 ml). A small amount of insoluble dark solid was removed by filtration; the filtrate was treated with Darco and then cooled in a freezer. The desired product **5** was collected as colorless crystals (19 g, 79%): mp 39–40°; ultraviolet spectrum showed end absorption only; infrared absorption at 5.56 (m), 5.60 (sh), 5.63 (s), 5.67 (s), and 5.70 (s) μ (C=O);[32] and nmr peaks at δ 3.68–2.72 (6 H

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(25) R. J. Stedman and L. S. Miller, *J. Org. Chem.*, **32**, 35 (1967); R. J. Stedman, private communication, Smith Kline and French Laboratories, Philadelphia, Pa., 1967.

(26) (a) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211 (1967); (b) W. L. Dilling and M. L. Dilling, *ibid.*, **23**, 1225 (1967).

(27) (a) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 286 (1964); (b) C. Cupas, P. von R. Schleyer, and D. J. Trecker, Jr., *J. Amer. Chem. Soc.*, **87**, 917 (1965).

(28) S. Meyerson, J. D. McCollum, and P. N. Rylander, *ibid.*, **83**, 1401 (1961).

(29) Melting points were determined in open capillary tubes using a Thomas–Hoover Unimelt apparatus and are corrected. Ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 recording spectrophotometer. Infrared spectra, unless indicated otherwise, were obtained in Nujol mull using a Perkin-Elmer Infracord; infrared spectra in solution were determined on a Perkin-Elmer Model 521 grating spectrophotometer. Nmr spectra were obtained in deuteriochloroform solution (unless indicated otherwise) on a Varian A-60 spectrophotometer using TMS as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-D spectrometer operated by Morgan-Schaffer Corp., Montreal, Canada. Glpc were performed on an F & M Model 700 gas chromatograph equipped with a thermal conductivity detector. All solvents used in anhydrous reactions were dried over Linde 4A Molecular Sieve. Tetrahydrofuran was dried over a mixture of 4A and 13X sieves. Magnesium sulfate was used as drying agent for organic extracts.

(30) Tlc of the reaction after 1 hr showed the presence of unreacted starting compound **1**. The above conditions were necessary to force the reaction to completion.

(31) Because **2** tended to polymerize on distillation it was used in the next step without purification.

(32) Similar carbonyl multiplicity has been noted in other caged ketones and has been attributed to combination bands and/or Fermi resonance: P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 3157 (1964); P. E. Eaton and T. W. Cole, Jr., *ibid.*, **86**, 962 (1964).

multiplet) at ~2.4 (1 H multiplet), and an AB pattern centered at δ 1.79 (broad singlet with $w^1/_2 = 3$ Hz,[33] $J_{AB} \sim 11$ Hz).

Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.50. Found: C, 53.18; H, 4.05; Br, 35.19.

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (6).—A solution of ketone **5** (21 g, 0.093 mol) in hot 30% aqueous KOH (350 ml) was heated at reflux for 4 hr. After cooling to room temperature, the solution was extracted with ether and then acidified with dilute HCl. The mixture was extracted with ether, the combined extracts were dried, treated with Darco, and then evaporated *in vacuo* to give 15 g (99%) of **6**, mp 92–93°. A sample (600 mg) was further purified by vacuum sublimation at 80–90° (1 mm) to give 500 mg of the acid: mp 93–95°; infrared absorption at 5.96 μ (acid C=O); and nmr peaks at δ 11.45 (1 H singlet, COOH), at 3.72–3.05 (7 H multiplet), and at 1.72 (2 H singlet).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.12; H, 6.17.

4,5,7,8-Tetrachloropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (**7**).[34]— A solution of 2,3,3a,7a-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (10 g, 0.035 mol) in 400 ml of ethyl acetate was irradiated for 1.5 hr with a 450-W Hanovia mercury vapor lamp in a quartz immersion photolysis apparatus. The solvent was evaporated by heating *in vacuo* to give 9.7 g of crude solid which was sublimed at 90–120° (1 mm) to give 7.9 g (79%) of ketone **13**: mp 113–115° (lit.[34] 113.5–114.5°); infrared absorption (CH_2Cl_2) at 5.52 μ (C=O); and nmr peaks at δ 3.91–2.96 (4 H multiplet) and an AB quartet with A at 2.54 and B at 1.91 ($J_{AB} = 13$ Hz).

Reaction of 4,5,7,8-Tetrachloropentacyclo[5.3.0.0^{2,5}.0.^{3,9}0^{4,8}]-decan-6-one (**7**) **with NaOH in Benzene.**—Ketone **7** (14.2 g, 0.05 mol) was added in one portion to a stirred suspension of powdered NaOH (10 g, 0.25 mol) in 1125 ml of benzene and the mixture was heated at reflux under a Dean–Stark trap overnight. After cooling to room temperature 500 ml of water was added and the mixture was agitated vigorously for a few minutes. The dark aqueous layer was separated, the benzene layer was washed with water, and the washings were combined with the original aqueous layer. Two methods of isolation were used.

Method A.—The aqueous solution was cooled (5–10°) and the pH was adjusted to 5–7 with concentrated HCl. Using a pH meter (Beckman Zeromatic) the solution was carefully adjusted to pH 3.5 by dropwise addition of 2 *N* HCl. If the pH drifted above 3.65 it was readjusted to 3.5. When the pH no longer rose above 3.65 (after 30 min) the precipitated solid was collected to give 3.5 g (26%) of **5,6,7-trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic acid** (9a), mp 212–214°. One recrystallization from aqueous methanol gave colorless prisms: mp 214–216°; infrared absorption at 5.90 μ (acid C=O); and nmr peaks (DMSO-d_6) at δ 3.70–3.34 (4 H multiplet) and an AB quartet with A at 2.14 and B at 1.80 ($J_{AB} = 13.5$ Hz).

Anal. Calcd for $C_{10}H_7Cl_3O_2$: C, 45.23; H, 2.66; Cl, 40.06; neut equiv, 265. Found: C, 45.13; H, 2.89; Cl, 40.39; neut equiv, 265.

Acidification of the filtrate to pH <0.5 gave 10 g of acidic product which was shown by glpc,[35] after treatment with ethereal diazomethane, to consist of 8% closed acid **9a** and 92% open acid **8a**.

Method B.—Alternatively, the aqueous layer was acidified to a pH <0.5 with concentrated HCl and extracted with ether to give a mixture of acids. In a typical experiment 40 g of tetrachloro ketone **7** gave 33 g of crude acid mixture. A portion of the mixture (31 g) was esterified with ethereal diazomethane.[36] The esters were separated by column chromatography on Florisil (1 kg). Elution with 1:3 benzene–hexane gave 16 g (38%) of ester **8b**: mp 134–135°; infrared absorption at 5.76 μ (ester C=O); and nmr peaks at δ 4.27 (1 H broad singlet), at 3.90 (3 H singlet), at 3.6–3.28 (2 H multiplet), at 3.28–3.02 (2 H multiplet), and an AB quartet with A at 2.71 and B at 1.58 ($J_{AB} = 12$ Hz).

Anal. Calcd for $C_{11}H_{10}Cl_4O_2$: C, 41.81; H, 3.19; Cl, 44.88. Found: C, 41.86; H, 3.19; Cl, 44.60.

Elution with 1:1 benzene–hexane gave 8.7 g (24%) of ester **9b**, mp 62–63°. Sublimation at 50° under high vacuum raised the melting point to 63–64°. An infrared absorption peak was located at 5.80 μ (C=O ester); and nmr peaks were at δ 3.82 ($-OCH_3$, singlet) and 4.10–3.42 (multiplet, 7 H) with an AB quartet having A at 2.34 and B at 1.83 ($J_{AB} = 13$ Hz).

Anal. Calcd for $C_{11}H_9Cl_3O_2$: C, 47.26; H, 3.24; Cl, 38.05. Found: C, 47.26; H, 3.30; Cl, 38.22.

4,5,6,7-Tetrachlorotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane-4-carboxylic Acid (**8a**).—A solution of ketone **7** (1.0 g, 3.5 mmol) in a mixture of 30% aqueous KOH (20 ml) and dioxane (7.5 ml) was heated at reflux for 4 hr. The mixture was cooled and extracted with ether. The aqueous layer was then acidified with concentrated HCl, extracted with ether and the combined extracts were washed with water and dried. The tan solid remaining after evaporation of the solvent was dissolved in ether, the solution was filtered to remove a small amount of insoluble material and then the filtrate was evaporated *in vacuo* to give 1 g (94%) of off-white solid, mp 212–215°.

A portion of the acid was esterified with ethereal diazomethane and analyzed by glpc on a 6-ft column of 5% SE-30 at 200°. The chromatogram showed 2% of an unknown component, 4% of ester **9b**, and 94% of ester **8b**.

Two recrystallizations from methanol–water gave colorless crystals, mp 214–216°. Glpc[33] of an esterified sample showed 100% **8a**; an infrared absorption peak appeared at 5.81 μ (C=O, acid), and nmr peaks (pyridine) were at δ 5.29 (1 H broad singlet), at 3.70–3.48 (2 H multiplet), and at 3.48–3.01 (2 H multiplet) with an AB quartet having A at 2.62 and B at 1.46 ($J_{AB} = 12$ Hz).

Anal. Calcd for $C_{10}H_8Cl_4O_2$: C, 39.77; H, 2.67; Cl, 46.96; neut equiv, 302. Found: C, 40.03; H, 2.81; Cl, 47.13; neut equiv, 298.

The acid also was prepared by alkaline hydrolysis of ester **8b** obtained in method B above. Samples of the acid obtained from the two routes were shown to be identical upon comparing their physical and spectral properties.

4-Amino-5,6,7-trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (**10**).—A solution of acid **9a** (5.0 g, 0.019 mol) in 75 ml of thionyl chloride was heated at reflux for 2.5 hr, the solution was evaporated *in vacuo*, the residue was taken up in benzene and evaporated again to give 5.1 g of solid acid chloride. This was taken up in 160 ml of acetone, the solution was cooled in an ice bath, and then a solution of sodium azide (1.53 g, 0.024 mol) in 15 ml of water was added. After stirring in the cold for 15 min the mixture was diluted with 240 ml of water. The turbid mixture was extracted with ether and the combined dried extracts evaporated at 25° *in vacuo* to give 4.4 g of azide. The azide was dissolved in 35 ml of benzene and the solution heated at reflux for 1 hr. Removal of the solvent *in vacuo* yielded 3 g of isocyanate. A solution of the isocyanate in a mixture of tetrahydrofuran (120 ml) and concentrated HCl (30 ml) was heated at reflux for 1 hr and then heated *in vacuo* to remove the THF. The aqueous residue was diluted with water (75 ml), basified with 10% aqueous NaOH, and extracted with ether. Treatment of the dried ethereal solution with ethereal HCl precipitated 2.0 g (38%) of **10** hydrochloride. The hydrochloride was purified by recrystallization from ethanol–ether: mp 192–195° dec; nmr peaks (D_2O–DCl)[37] at δ 3.98–3.52 (4 H multiplet) and an AB quartet with A at 2.38 and B at 1.93 ($J_{AB} = 13$ Hz).

Anal. Calcd for $C_9H_9Cl_4N$: C, 39.60; H, 3.32; Cl, 51.95; N, 5.13. Found: C, 39.69; H, 3.24; Cl, 51.98; N, 5.15.

A sample of the free base **10** was prepared by basification of an aqueous solution of the hydrochloride, the precipitate was collected and recrystallized from hexane, mp 89–91° dec; infrared absorption ($CHCl_3$) appeared at 2.90 and 2.95 ($-NH_2$ stretching) and at 6.20 μ ($-NH_2$ bending).

Anal. Calcd for $C_9H_8Cl_3N$: C, 45.70; H, 3.41; Cl, 44.97; N, 5.92. Found: C, 45.69; H, 3.36; Cl, 45.17; N, 5.80.

Dechlorination of 5,6,7-Trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]-nonane-4-carboxylic Acid (**9a**).—To a solution of **9a** (10.6 g, 0.04 mol) in dry THF (200 ml) containing *t*-butyl alcohol (23 ml, 0.24 mol) was added finely cut pieces of lithium wire (3.3 g, 0.48 mol). Within a few minutes the mixture began to reflux spontaneously. As the reaction subsided (15 min) external heat was applied to maintain reflux for 15 min. A 12-ml quantity of *t*-butyl alcohol and 1.7 g of finely cut lithium wire were

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[33] The half-height width ($w^1/_2$) of TMS was 1 Hz.

[34] We have used a modification of the procedure described by P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

[35] Gas chromatographic analyses were carried out at 190° on a 4-ft column of 10% SE-30 on Diatoport S.

[36] Glpc of the esterified mixture showed that it contained 5% unknown material, 40% ester **9b**, and 55% ester **8b**.

[37] 3-Trimethylsilyl-1-propanesulfonic acid sodium salt was used as internal standard.

added and the mixture was heated at reflux for 3 hr to complete the reaction. The mixture was cooled, poured into an ice–water mixture (1 l.) and after the excess lithium had decomposed the aqueous solution was extracted with ether. The aqueous layer was separated, acidified with concentrated HCl, and extracted with ether. The dried ether layer was evaporated *in vacuo* to give 5.2 g of a semisolid acid mixture. Although glpc showed a single peak, nmr data indicated the presence of unsaturation.

A portion of the acid mixture (1.8 g) was treated with bromine in carbon tetrachloride, the precipitated solid filtered and the filtrate evaporated. The filtrate residue (1.6 g) was twice recrystallized from petroleum ether to give 0.70 g of crude acid. Repeated fractional sublimation finally gave a pure sample of acid (40 mg), mp 91.5–93°. This acid was shown by spectral comparisons and mixture melting point to be identical with the homocubane-4-carboxylic acid (6), obtained by the alternate route (Scheme I).

Pentacyclo[$4.3.0.0^{2,5}.0^{3,8}.0^{4,7}$]nonane-4-carboxamide (12).—A solution of acid **6** (5.0 g, 0.031 mol) in 25 ml of thionyl chloride was heated at reflux for 1 hr and then allowed to stand overnight at room temperature. The thionyl chloride was removed by heating *in vacuo*, the crude acid chloride was dissolved in 15 ml of THF and added dropwise (3 min) to 75 ml of cold concentrated NH_4OH. After stirring 1 hr, the mixture was diluted with 25 ml of water and the precipitate was collected, mp 261–263°. Recrystallization from 1:1 acetonitrile–isopropyl alcohol gave 3.8 g (76%) of off-white crystals: mp 261–263°; infrared absorption at 2.95, 3.10, 6.00, and 6.19 μ; and nmr peaks (CF_3COOH) at δ 3.90–3.18 (7 H unsymmetrical doublet) and at 1.85 (2 H singlet).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.65; H, 7.06; N, 8.74.

Pentacyclo[$4.3.0.0^{2,5}.0^{3,8}.0^{4,7}$]nonane-4-methylamine (13) Hydrochloride.—Amide 12 (3.0 g, 0.0186 mol) was added portionwise (1 hr) under nitrogen to a slurry of lithium aluminum hydride (3.04 g, 0.08 mol) in 400 ml of hot THF. The reaction was heated at reflux for 46 hr, cooled in ice and the excess lithium aluminum hydride decomposed by cautious addition of water (4 ml) followed by a saturated aqueous Na_2SO_4 solution. The white suspension was filtered through a Celite pad and the filtrate evaporated to a small liquid residue *in vacuo*. The residue was dissolved in ether, a small amount of water was separated and then the dried organic solution was treated with ethereal HCl to give 1.5 g (44%) of **13** hydrochloride as a colorless solid. Recrystallization from 1:1 isopropyl alcohol–ethyl acetate gave 1.0 g of crystalline hydrochloride: mp >300°; infrared absorption at 6.20 (sh), 6.27, 6.36, 6.62 μ; and nmr peaks (D_2O-DCl) at δ 3.42–2.98 (9 H unsymmetrical doublet) and at 1.67 (2 H singlet).

Anal. Calcd for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; Cl, 19.30; N, 7.63. Found: C, 65.54; H, 7.65; Cl, 19.03; N, 7.54.

4-Aminopentacyclo[$4.3.0.0^{2,5}.0^{3,8}.0^{4,7}$]nonane (14) Hydrochloride.—A solution of acid **6** (11.6 g, 0.072 mol) in thionyl chloride (50 ml) was allowed to stand for 18 hr at room temperature then heated at reflux for 1 hr. Excess thionyl chloride was removed *in vacuo* and the remaining liquid acid chloride was dissolved in acetone (60 ml), cooled to 0–5°, and treated with a solution of sodium azide (7.5 g) in water (75 ml). After stirring at 0–5° for 30 min the mixture was diluted with water (800 ml) and extracted with benzene, and the combined extracts were dried. The benzene solution was heated at reflux for 1 hr, the solvent was removed *in vacuo* and the residual isocyanate was heated in a refluxing mixture of tetrahydrofuran (500 ml) and concentrated HCl (120 ml). The solution was concentrated to 0.25 volume *in vacuo*, diluted with water (300 ml), and extracted with ether. The aqueous solution was basified with 10% aqueous NaOH solution and extracted with ether. The combined dry extracts were treated with excess ethereal HCl and the precipitate was collected (8 g). Recrystallization from isopropyl alcohol–ethyl acetate gave 5.3 g of **14** hydrochloride, mp 188–190° dec. The mother liquor yielded a second crop upon further cooling (1.5 g), mp 188–190° dec, to give a total of 6.8 g (56%); infrared absorption appeared at 6.29 and 6.39 μ; and nmr peaks (D_2O-DCl) were at δ 3.68–3.17 (7 H multiplet) and at 1.73 (2 H singlet).

Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 63.78; H, 7.19; N, 8.13; Cl, 20.71.

Pentacyclo[$4.3.0.0^{2,5}.0^{3,8}.0^{4,7}$]nonane (Homocubane) (17).—A solution of bromine (2.5 g, 0.0156 mol) in 25 ml of CCl_4 was added dropwise (1 hr) to a solution of acid **6** (2.50 g, 0.0152 mol) in 65 ml of boiling CCl_4 containing red mercuric oxide (2.50 g, 0.0115 mol). When addition was complete the mixture was heated at reflux for 2 hr, cooled to room temperature and then filtered. The filter cake was washed with CCl_4 and the combined filtrate and washings were extracted with five 25-ml portions of 10% aqueous NaOH. The dried ($CaSO_4$) organic solution was concentrated to ~2 ml, diluted with pentane, and then chromatographed on 75 g of neutral alumina (Woelm, activity grade I) in pentane. The initial pentane eluates gave 1.2 g of liquid as a mixture of 4-chloro- (**16**) and 4-bromohomocubane (**15**).[38]

A portion of the mixture (0.5 g) was dissolved in 15 ml of dry THF containing *t*-butyl alcohol (0.42 g, 5.7 mmol), then finely cut pieces of lithium wire (0.08 g, 11.4 mmol) were added. The mixture was heated at reflux for 1.5 hr, cooled to room temperature and poured onto 150 g of crushed ice. After the excess lithium had decomposed, the mixture was extracted with pentane. The combined dried pentane extracts were distilled until no further volatile distillate collected. The residue[39] was taken up in a few drops of warm methanol, then cooled in ice to give a colorless solid, 50 mg. A second crystallization from methanol gave **17** as a colorless, volatile solid: mp 107.5–108.5° (sealed capillary); infrared absorption peaks (CCl_4) at 3.41, 7.82, 8.01, 8.12, 8.42, 10.85, 11.24, and 11.42 μ; and nmr peaks at δ 3.40–3.00 (8 H unsymmetrical doublet) and at 1.69 (2 H singlet). The mass spectrum shows principal peaks at *m/e* 118, 117, 115, 103, 91, 78, 77, 65, 63, 53, 52, 51, 50, 39, and 27.

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.19; H, 8.47.

Registry No.—**1,** 10481-34-2; **4,** 10481-35-3; **5,** 15844-10-7; **6,** 15844-05-0; **8a,** 15892-95-2; **8b,** 15892-96-3; **9a,** 15892-97-4; **9b,** 15892-98-5; **10,** 15892-99-6; **10** HCl, 15893-00-2; **12,** 15844-06-1; **13** HCl, 15844-07-2; **14** HCl, 15844-09-4; **17,** 15844-08-3.

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[38] Glpc at 100° on a 6-ft column of 5% SE-30 on Chromosorb W showed that two components were present in a 1:1 ratio, with retention times of 5.6 and 9.0 min.

[39] Glpc of the residue under the conditions of ref 38 showed it to contain a single component of retention time 2.3 min along with some solvent.