4-Homoisotwistane, 6,7-*exo*-Trimethylenebicyclo[3.2.1]octane, and Homoadamantane as Intermediates in Brønsted Acid Catalyzed Adamantane Rearrangement of Tricycloundecanes

Naotake Takaishi, Yoshiaki Inamoto,* and Koji Aigami

Industrial Research Laboratories, Kao Soap Company, Ltd. 1334 Minatoyakushubata, Wakayama 640-91, Japan

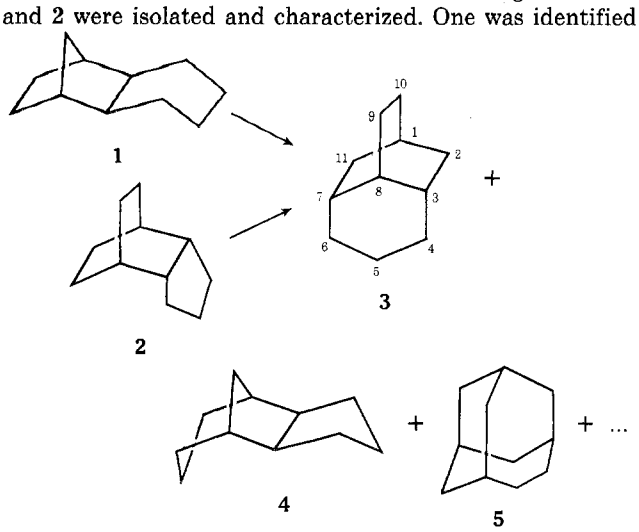
Received July 22, 1974

4-Homoisotwistane (tricyclo[5.3.1.0^{3,8}]undecane) (**3**), 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**4**), and homoadamantane (**5**), together with several, as yet unidentified tricycloundecanes, were discovered to be intermediates in the adamantane rearrangement of 2,3-*exo*-tetramethylenenorbornane (**1**) and 2,3-trimethylenebicyclo-[2.2.2]octane (**2**). ^{13}C nmr spectroscopy was the main tool in the structure determination of **3** and **4**. The structure of **4** was further confirmed by comparison with an independently synthesized authentic specimen. Brønsted acids (trifluoromethanesulfonic acid and sulfuric acid) were found to catalyze the rearrangement of these tricycloundecane precursors with almost quantitative yields of the products, the catalysis being milder and more specific than that by aluminum halides. A high yield synthesis of **3** was accomplished by a selective rearrangement of **2** catalyzed by sulfuric acid. An outline of the reaction scheme was deduced from the product studies of these Brønsted acid catalyzed rearrangements.

Acid-catalyzed isomerization of polycyclic saturated hydrocarbons to adamantanes (so-called adamantane rearrangement) has been widely studied since the discovery of the reaction by Schleyer.[1] Elucidation of the mechanism of the reaction, however, seems to have been less fruitful, except for the results by Whitlock[2] and Schleyer[3] on $C_{10}H_{16}$ rearrangement, when compared with many successful synthetic approaches in which a number of precursors has been found to give diamonoid molecules in good yields.[4] The difficulty involved in mechanistic studies will be fully understood by considering the abundance of isomeric polycycloalkanes[5] which may take part, to the degree their relative stabilities and reactivities will allow, in the rearrangement consisting of a complex network of competitive and/or consecutive reaction pathways. We also have been interested in the problem and studied mainly the rearrangement of C_{11} tricyclic hydrocarbons.

Only two tricycloundecane precursors, 2,3-*exo*-tetramethylenenorbornane (**1**)[6-9] and 2,3-*endo*-tetramethylenenorbornane,[9] were hitherto known to undergo adamantane rearrangement.[10] However no intermediate had been identified[12] until the existence of 4-homoisotwistane (**3**)[14] was established by Schleyer[13] in the rearrangement of **1**, and independently by us[15] in the rearrangement of **1** and 2,3-trimethylenebicyclo[2.2.2]octane (**2**), under aluminum chloride catalysis.

Now two further intermediates in the rearrangement of **1** and **2** were isolated and characterized. One was identified as homodamantane (**5**), which had been looked for but in vain in tricycloundecane rearrangements.[12,13] The other was determined by ^{13}C nmr spectroscopy to be one of four possible tricycloundecane isomers including 5,6-*exo*-trimethylenebicyclo[3.2.1]octane (**4**). Three other possibilities than **4** was unambiguously excluded by an independent synthesis of an authentic **4**.



Brønsted acids (trifluoromethanesulfonic acid and sulfuric acid) were found to be effective catalysts for the rearrangement of C_{11} tricyclic hydrocarbons. Indeed the sulfuric acid catalyzed isomerization of tetrahydro-Binor-S to diamantane[16] was the only example of Brønsted acid catalysis of the adamantane rearrangement of hydrocarbons. Although trifluoromethanesulfonic acid gave almost similar intermediate distributions as, but more slowly catalyzed the rearrangement than, aluminum chloride, sulfuric acid catalysis was fairly specific with respect to both reactant and product. Thus **2** was isomerized to **3** in a high yield in the presence of sulfuric acid.[17]

Slow catalysis by Brønsted acid made easier the study of time–conversion relationships in the rearrangement. Further isomerizations of isolated intermediates revealed the presence of some quasi-equilibriums. These results led us to draw an outline of the rearrangement scheme.

4-Homoisotwistane (3). Isomerization of **1** with 20 mol % of aluminum chloride in methylene chloride for 20 min at ambient temperature gave, together with a small amount of methyladamantanes, 45% **3** and three other major components in the amount of 23, 18, and 6%, respectively (run 1, Table I). The ir, ^{1}H nmr, and mass spectra did not tell much about the structure of **3**, except that molecular ion peak with relative intensity of 100 in the mass spectrum suggested a reasonably symmetrical cage structure. The ^{13}C nmr spectra of **3** showed the presence of eight different kinds of carbon atoms and the absence of methyl group in the molecule. Of the possible 70 tricycloundecanes containing neither three- nor four-membered rings,[5] only two isomers, **3** and **6**, are consistent with the above ^{13}C nmr spectra.

The structure **3** seems to explain better the methylene carbon resonance in an abnormally high field (15.2 ppm) than the alternative, **6**, does. Thus the methylene carbon resonance was assigned to 5-carbon atom in **3**, based on the calculated value (15.8 ppm) for the atom. The effect of 3(a)- and 4(e)-methyl group (or corresponding methylene groups in the fused ring system) on the chemical shift

Table I
Distribution of Intermediates in the Rearrangement of Tricycloundecanes[a]

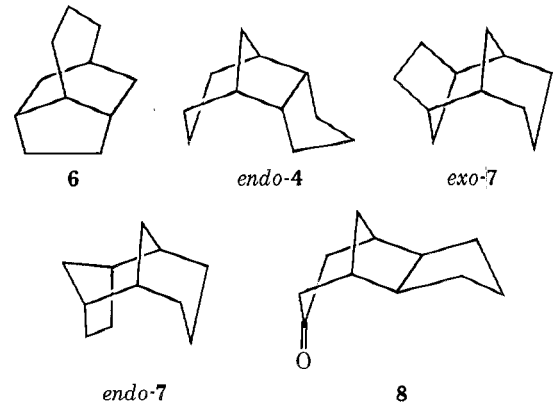
Run	Reactant	Reaction time, hr	Product,[b] %[c] Unknown A	1-Methyladamantane	Unknown B	Unknown C	2-Methyladamantane	4	1	3[d]	Unknown D[d]	2[d]	Unknown E	5
						Aluminum Chloride								
1	1[e]	0.3	0.6	2.4	23.0	17.6	0.6	6.1		44.7	3.8			1.2
		1.0		96.0			4.0							
2	2[e]	0.2			29.2	14.6		5.1		44.4	3.5			1.2
		1.0		96.3			3.7							
						Trifluoromethanesulfonic Acid								
3	1[f]	0.1			4.3	2.8			74.5	18.4				
		1.0	1.5	0.3	23.8	17.1	1.7	1.7	0.6	45.0	5.3			1.5
		24	2.6	6.8	18.9	15.6	6.0	6.8		37.2	2.8			2.1
4	2[g]	1.0			2.8	5.0		1.5		29.2	21.5	17.5	20.2	
		24	2.2	1.6	19.3	16.6	2.4	5.4		46.9	3.2			2.2
5	2[f]	1.0	0.3	1.0	8.1	16.6	1.4	3.9		60.2	4.4			2.3
		24	2.3	6.3	18.5	16.2	5.9	5.9		36.6	3.0			2.1
6	3[f]	1.0	0.5	1.6	10.3	19.6	3.2	4.1		51.8	4.5			2.3
		6.0	1.0	4.4	15.7	18.9	4.6	6.2		41.1	3.6			2.6
		24	2.4	5.3	19.6	16.8	5.8	6.5		36.3	2.8			1.8
		100	10.0	20.3	12.5	8.0	25.2	5.5		15.0	1.3			1.2
7	4[f]	5.0	1.7	2.1	7.3	7.5	2.5	53.4		24.2				0.7
		38	1.8	10.0	13.7	11.9	11.6	18.8		26.6	2.0			1.5
						Sulfuric Acid								
8[h]	2	2								38.3	20.7	28.7	8.9	
		7				3.5				93.5	2.8			

[a] 200 mg of reactant in 10 ml of methylene chloride at reflux, unless otherwise noted. [b] Yields of the intermediate mixtures as well as the final products (methyladamantanes) were always quantitative. Products are analyzed by conventional vpc and aligned in the order of the increasing retention time. See, however, footnote *d*. [c] That of the vpc peak area. [d] **3**, unknown D, and **2** could not be separated from each other by the usual vpc, but on a Golay column, from which proportions of **3**, unknown D, and **2** were calculated. [e] With 0.2 molar equiv to reactant of $AlCl_3$. The reaction was run at ambient temperature. [f] With 4.0 molar equiv of CF_3SO_3H. [g] With 1.0 molar equiv of CF_3SO_3H. [h] 500 mg of **2**, 3.2 ml of carbon tetrachloride, and 5 g of 95% sulfuric acid were stirred at ambient temperature. The reaction was heterogeneous, carbon tetrachloride layer being analyzed. The product was accompanied by some tarry materials, and the yield of crude **3** on isolation amounted to 81%.[17]

change of 1-carbon atom in chair form cyclohexane (26.9 ppm) has been calculated as −5.4 and −0.3 ppm, respectively.[18] A rational assumption that the additivity of chemical shifts in polycycloalkanes such as adamantane[19] also holds for **3** enabled us to calculate the chemical shift of the 5-carbon atom: 26.9 − 2 × 5.4 − 0.3. A good agreement between the observed and the calculated values indicates the existance of a trisubstituted cyclohexane partial structure and, hence, the structure **3** for the compound. The structure was later confirmed by the comparison of melting point and ^{13}C nmr spectrum with those described in the literature.[13,14]

6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (4). The sixth peak (6.1 %) in run 1 (Table I) was isolated and found to be homogeneous on several vpc columns. A large scale experiment allowed the separation and purification of the component on a preparative vpc. The ^{13}C nmr spectrum of the compound showed the presence of seven different kinds of carbon atoms among which three kinds had a relative spectral intensity of one. All of these three carbon atoms exhibited triplet absorptions in the off-resonance proton decoupled spectrum. Absence of methyl group was also indicated. The isomers[5] corresponding to the spectra are limited to four compounds: **4**, its *endo*-trimethylene isomer (*endo*-**4**), and 2,4-*exo*- and -*endo*-ethanobicyclo[3.3.1]nonane (*exo*-**7** and *endo*-**7**, respectively).

Since it is quite difficult to assign to the compound any of the four structures only by spectral method owing to the paucity in data for reference compounds, unequivocal synthesis seemed to be the shortest approach to the problem. We chose to synthesize **4** at first because no authorized route was established for the ever unknown 7's, and because *endo*-**4** might have little chance to be trapped as an intermediate owing to the relative instability. Synthesis of **4** was started by obtaining 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one (**8**) by the application of the method of Jefford, *et al.*,[20] to 5,6-*exo*-trimethylenenorborn-2-ene.[21] The ketone **8** was also obtainable, as a mixture with 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one and higher homologous ketones, on the ring expansion[22] of 5,6-*exo*-trimethylenenorbornan-2-one[23] by diazomethane. Wolff–Kishner reduction[24] of **8** gave an authentic **4**. Spectral properties, refractive index, and retention times on some



6 *endo*-**4** *exo*-**7** *endo*-**7** **8**

vpc columns of thus synthesized 4 were in complete agreement with those of the isolated intermediate under examination.

Homoadamantane (5). The last eluted component in the reaction mixture of run 1 was identified as homoadamantane (5) by comparison with an authentic specimen (retention times on vpc, melting point, and spectral properties). 5 has escaped[12,13] from the scrutiny of researchers probably because of its scarcity in reaction mixtures.

Unknowns. Structures of the compounds from other vpc fractions were left undetermined. This is mainly because they are mixtures. Capillary (Golay) column vpc revealed the presence of multiple components in them: unknown A, three; unknown B, three at the very beginning, and two in the later stage, of the rearrangement; and unknown C, four. Each of unknown D (Table I, footnote *d*) and E gave only one peak also in Golay vpc. Mass spectra are the only information available to us on these components at present, which were measured on a combined Golay vpc–mass spectrometer. All of the twelve components gave a molecular ion peak of *m/e* 150 with correct isotopic abundance corresponding to $C_{11}H_{18}$.[25] It was also possible by Golay vpc–mass spectrometry to establish the identities of each components from different precursors, 1–4.

^{1}H nmr spectra were taken on each of the isolated unknown fractions (A, B, C, and E) to show that the resonance was entirely absent in olefinic proton regions for the unknowns. These spectroscopic evidences indicate that no appreciable disproportionation had occurred under present reaction conditions.

Trifluoromethanesulfonic Acid Catalyzed Rearrangement of 2,3-*exo*-Tetramethylenenorbornane (1) and 2,3-Trimethylenebicyclo[2.2.2]octane (2). One of the reasons why we were successful in the detection of intermediates in adamantane rearrangements would lie in the use of milder catalyst system than had been used so far.[4] As an extention of this reasoning, it might be possible to detect a larger number of intermediates by making use of still milder catalyst systems. Selection of the catalyst may be made among Brønsted acids, trifluoromethanesulfonic acid, the strongest ever existed, being tried at first.

Trifluoromethanesulfonic acid in refluxing methylene chloride was found to catalyze the rearrangement of 1 and 2. Contrary to our expectations, the distribution of intermediates in these reactions was almost the same as in those catalyzed by aluminum chloride. However, a few characteristic features are to be noted. The catalyst has a very low activity in giving rise to methyladamantanes. Comparison of runs 1 and 3 shows that although both reactions proceed similarly up to the disappearence of 1, further reaction of the intermediates is very sluggish under trifluoromethanesulfonic acid catalysis. The catalyst also clearly demonstrated the difference between the reactivities and the reaction pathways in 1 and 2. 1 was so unreactive in the presence of 1.0 molar equiv of the catalyst that it was impracticable to study the reaction with this amount of the catalyst. 2 gave a new component (unknown E) and an increased proportion of unknown D (run 4), while none was observed with 1.

Trifluoromethanesulfonic Acid Catalyzed Rerrangement of the Isolated Intermediates (3 and 4). Treatment of the isolated intermediates, 3 and 4, with trifluoromethanesulfonic acid revealed an interesting feature of the rearrangement. The intermediate distributions in the reaction of 3 at 1 hr and 24 hr (run 6) are almost identical with those of 1 at 1 hr and 24 hr (run 3) as well as those of 2 with 4.0 *M* catalyst at 1 hr and 24 hr (run 5), respectively. The reaction of 4 (run 7) gave a little different intermediate distribution at the beginning of the reaction, but the proportion of unknowns A, B, C, and D, 3, and 5 in run 7 at sufficiently long reaction time (38 hr) is in quite a good agreement with that of the corresponding components in the reaction of 3 at a long reaction time (run 6, 24 hr) as well as those of the same components in the long reaction of 1 and 2.

Sulfuric Acid Catalyzed Rearrangement of 2,3-Trimethylenebicyclo[2.2.2]octane (2). A Convenient Synthesis of 4-Homoisotwistane (3). Sulfuric acid was also found to catalyze the rearrangement. The catalysis, however, was fairly specific with respect to reactant and product. Under the reaction conditions studied (Table I, footnote *h*), only 2 was isomerized, while 1, 3, and 4 were quite unreactive. Substitution of carbon tetrachloride in run 8 for methylene chloride did not change the product distribution at all, but gave a little inferior yield of 3 accompanied by an increased amount of tarry materials. These results led us to establish a convenient synthesis[17] of 3 which otherwise could be obtained so far only with difficulty.[13-15] Formation of unknown E and an increased proportion of unknown D at the beginning of the reaction (run 8, 2 hr) are in common with the reaction of 2 catalyzed by a small amount of trifluoromethanesulfonic acid (run 4, 1 hr); but the absence of unknowns A and B and 4 in run 8 is to be noted.

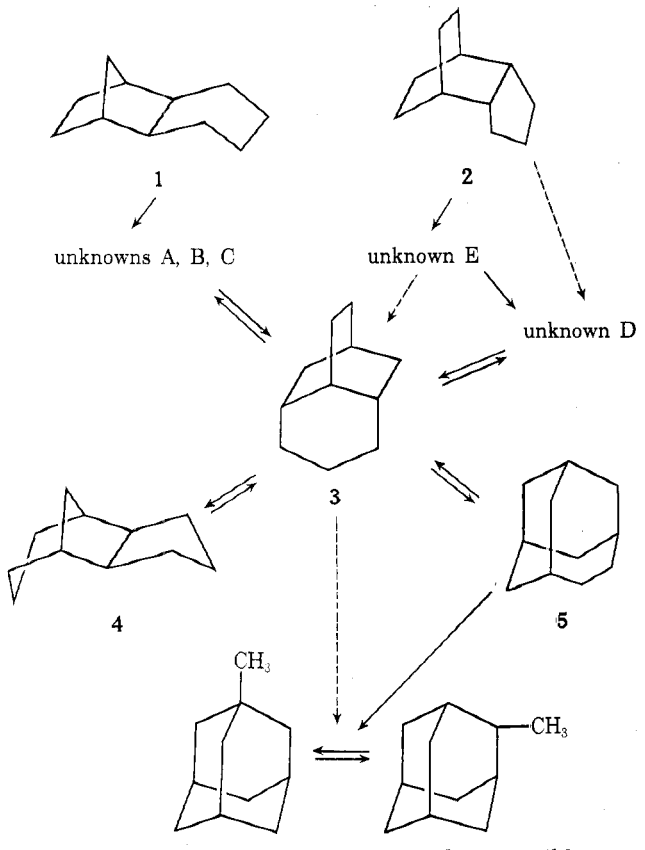
Discussion

Trifluoromethanesulfonic acid does not seem to have been examined as a catalyst in the adamantane rearrangement of tricyclic hydrocarbons. Sulfuric acid was successfully used for hydride transfer reduction–rearrangements,[14,26] but only a single example[16] can be cited for the sulfuric acid catalysis of adamantane rearrangement. Aspects of trifluoromethanesulfonic acid catalysis, especially concerning the product distributions, are fundamentally identical with those of aluminum chloride catalysis, although use of trifluoromethanesulfonic acid led to the detection of a new isomer, unknown E, in the reaction of 2 (run 4). However, this apparent difference vanishes if we expect unknown E to appear midway between 2 to 3 and to disappear quickly under the influence of stronger catalyst, aluminum chloride.

Sulfuric acid shows a little different catalytic activity from those of aluminum chloride and trifluoromethanesulfonic acid (runs 2, 4, and 8). Absence of unknown A and B as well as 4 in run 8 indicates that these three can be formed from 3 under aluminum chloride and trifluoromethanesulfonic acid catalysis, but are not under the influence of sulfuric acid. Difference between the activities of sulfuric acid and other two catalysts is better demonstrated in the formation of methyladamantanes from 3. Aluminum chloride and trifluoromethanesulfonic acid gave methyladamantane, although the reaction was very sluggish with the latter catalyst, while sulfuric acid did not. On the other hand, the fact also suggests faster reactions of 1 and 2 to 3 than that of 3 to methyladamantanes.

It is to be noted that 1 and 2 gave a similar distribution of intermediates on prolonged reaction. These proportions of intermediates are, in turn, quite similar to those in the further isomerization of either 3 or 4. An explanation for the results would be that the product distribution was the same as in the further isomerization of once formed 3, and this indicates that 3 would be one of the key intermediates in the whole sequence of the rearrangement. That 4 was formed from 3, but not directly from 1 or 2, is most probable in view of an almost exclusive formation of 3 from 2 (run 8), slow formation of 3 from 4 (run 7), and increase of

the amount of 4 after 1 or 2 had disappeared. An outline of the reaction scheme may be drawn based on these results.



The reactants 1 and 2 are quickly and irreversibly converted *via* unknowns to 3 which then slowly isomerized to final methyladamantanes. The rearrangement of 3 is indeed so slow under Brønsted acid catalysis that we may regard 3 to be in quasi-equilibriums with 4, 5, and some unknowns, the equilibriums slowly leaking to give methyladamantanes. 1 isomerizes to 3 with the intermediacy of unknowns A, B, and C, which, in turn, are in equilibrium with 3. 2 isomerizes to 3 *via* unknown E, and then *via* unknown D which is also in equilibrium with 3. It is not clear at present whether or not there exist any direct route from 2 to unknown D and that from unknown E to 3. 4 is most probably formed from and in equilibrium with 3. It is noteworthy that sulfuric acid fails to set up the equilibriums between 3 on one hand, and 4, unknown A, or unknown B on the other.

The scheme is quite obscure between 3 and methyladamantanes. What is certain at present is the intermediacy of 5. 3 gives rise to and is in equilibrium with 5, as shown by Majerski in his isomerization of homoadamant-4-yl cation to 3 and 2-methyladamantane[14] as well as in our experiments.[27] It seems to have been believed that 5 is the immediate precursor to methyladamantanes in view of the facile isomerization of 5 to methyladamantanes.[6b,13,14,28] Present experiments could not demonstrate whether or not the implicit allegation was correct, nor prove the presence of any pathways from 3 to methyladamantanes without the intermediacy of 5.

Present results are to be considered as a demonstration of the complexity, rather than the clear elucidation, of tricycloundecane rearrangements. Structures of unknowns and equilibriums as well as rate constants should be determined before the problem has been solved. However it is still evident from our incomplete studies that 3 is one of the largest energy minima on the tricycloundecane rearrangement surface.[13]

Experimental Section

All melting and boiling points are uncorrected. Infrared spectra were obtained for neat samples on a Hitachi 215 spectrophotometer. ^{1}H nmr spectra were obtained on a Varian T-60 instrument using deuteriochloroform as solvent. All chemical shifts are reported in parts per million downfield from an internal TMS standard (δ). ^{13}C nmr spectra were obtained at 15.1 MHz on a Varian NV-14 spectrometer. Mass spectra were measured on a Hitachi RMU-6D spectrometer with 75-eV ionization voltage. The vpc was accomplished on a Shimazu GC-4B-PTF chromatograph employing columns (¼ in. × 6 ft) packed with 60–80 mesh Chromosorb W containing 30% silicone SE-30, Carbowax 20M, Apiezon L, or DEGS. Golay vpc was done on a Perkin-Elmer 700 instrument using columns (0.01 in. × 150 ft) packed with Apiezon L or silicone SE-30 and operated between 60 and 70°. Golay vpc–mass spectrometry was made with a combination of JEOL JGC-20-KP gas chromatograph and JMS-D100 mass spectrometer. Preparative vpc was done on a Varian Aerograph 700 instrument. Elemental analyses were made on an automatic Yanagimoto CHN MT-2.

Materials. Trifluoromethanesulfonic acid is a commercial product of 3M Co. Methylene chloride was dried over anhydrous calcium chloride and distilled immediately before use. 2,3-Trimethylenebicyclo[2.2.2]octane (2) was prepared[17] by hydrogenation of the Diels–Alder adduct[29] of cyclopentadiene and cyclohexa-1,3-diene and purified on the preparative vpc. Homoadamantane (5) was synthesized according to the method of Stetter.[30] 4-Homoisotwistane (3) was obtained by the rearrangement of 2,3-trimethylenebicyclo[2.2.2]octane (2) catalyzed by sulfuric acid.[17] An authentic specimen of 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (4) was prepared by the application of the established synthesis of bicyclo[3.2.1]octan-3-one[20] to 5,6-*exo*-trimethylenenorborn-2-ene[21] as described below.

4-Homoisotwistane (3). A mixture of 50 g (0.33 mol) of crude 2, 320 ml of carbon tetrachloride, and 500 g of 95% sulfuric acid was stirred at ambient temperature for 7 hr. The organic layer was separated, and the sulfuric acid layer was extracted once with 100 ml of carbon tetrachloride. The combined organic layer and carbon tetrachloride extract were washed successively with each 100 ml of water, saturated sodium bicarbonate solution, and water and then dried over anhydrous calcium chloride. Carbon tetrachloride was evaporated off under slightly reduced pressure, and the residue was fractionally distilled *in vacuo* through a 1-ft Vigreux column. The fraction boiling at 92–94° (16 mm) gave 40.5 g (81%) of crude 3, mp 55–58°. The purity of crude 3 thus obtained was 94%, as calculated from the area ratio in the Golay vpc. Slow sublimation [60° (19 mm)] gave an analytical sample: mp 62–63° (lit. mp 56–58,[14] 57–59,[14] 66.6–67°[13]); ir 2925, 2890, 2870, 2850, 1480, 1465, 1450, 1440, 1340, 975, 940, 895, 845, cm^{-1}; ^{1}H nmr δ 1.0–2.0 (complex m); ^{13}C nmr (multiplicity, rel intensity) 15.2 (t, 1), 24.8 (d, 1), 26.3 (t, 1) 27.1 (t, 1), 30.9 (d, 2), 31.9 (t, 2) 32.2 (t, 2), 33.1 (d, 1); mass spectrum *m/e* (rel intensity) 150 (100, M$^+$), 122 (39), 121 (39), 109 (12), 108 (16), 107 (19), 93 (27) 81 (27), 80 (46), 79 (40), 67 (35), 55 (18), 41 (40).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.8; H, 12.2.

3,4-Dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene. To a mixture of 26.8 g (0.2 mol) of 5,6-*exo*-trimethylenenorborn-2-ene,[21] 40 g (0.74 mol) of sodium methoxide, and 150 ml of petroleum ether was added with efficient stirring 126 g (0.65 mol) of ethyl trichloroacetate at 0° over a period of 3 hr. The mixture was stirred at −5 to 0° for a further 4 hr and then allowed to warm gradually to ambient temperature overnight with continuously stirring. The reaction mixture was poured onto an equal volume of ice–water and the resulting mixture was set aside to separate an organic layer, the aqueous layer being extracted four times with ether. The combined organic layer and ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the solvent under slightly diminished pressure at room temperature, the residue was fractionally distilled to give 22.5 g (50%) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene: bp 138–140° (5 mm); $n^{25.6}$D 1.5320; ir 2945, 2850, 1620 (C=C), 1320, 1050, 958, 798, 693 cm^{-1}; ^{1}H nmr δ 0.9–3.0 (m, 12), 4.15 (d, 1, J = 3 Hz, CHCl), 6.12 (d, 1, J = 7 Hz, C=CH): mass spectrum *m/e* (rel intensity) 218 (3), 216 (4), 115 (14), 114 (9), 113 (41), 112 (17), 77 (29), 69 (100), 68 (15), 67 (19), 41 (14).

Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50; Cl, 32.65. Found: C, 60.5; H, 6.6; Cl, 32.8.

3-Chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene. To a cooled suspension of 6.45 g (0.17 mol) of powdered lithium aluminum hydride in 150 ml of ether and 450 ml of tetrahydrofuran was added dropwise with stirring a solution of 20.6 g (0.095 mol) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene obtained above over a period of 30 min. After the addition was completed, the reaction mixture was heated under gentle reflux for 22 hr. Any residual lithium aluminum hydride was decomposed by wet ether, and the resulting mixture was poured onto ice–water. The organic layer was separated, and the aqueous layer was, after acidification with 10% hydrochloric acid, extracted with ether (100 ml × 5). The combined organic layer and ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by fractional distillation gave 11.8 g (68%) of 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene: bp 77–79° (2 mm); $n^{25.6}$D 1.5223; ir 3045, 2935, 2855, 1640 (C=C), 1465, 1310, 1035, 957, 830, 680 cm^{-1}; ^{1}H nmr δ 0.8–2.8 (m, 14), 6.0 (d, 1, J = 7 Hz, C=CH); mass spectrum m/e (rel intensity) 182 (25), 115 (35), 114 (44), 113 (100), 112 (91), 79 (56), 77 (48), 69 (30), 67 (30), 41 (27).

Anal. Calcd for $C_{11}H_{15}Cl$: 73.32; H, 8.28; Cl, 19.40. Found: C, 72.5; H, 8.1; Cl, 19.4.

6,7-*exo*-Trimethylenebicyclo[3.2.1]octan-3-one (8). To 80 ml of 98% sulfuric acid cooled in an ice bath was added with efficient stirring 7.3 g (0.04 mol) of 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene in one portion, and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured onto cracked ice and extracted three times each with 150 ml of ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 3.6 g (55%) of 8: bp 75–77° (0.5 mm); $n^{25.6}$D 1.5031; ir 2945, 2850, 1710 (C=O), 1465, 1410, 1210, 1065, 825 cm^{-1}; ^{1}H nmr δ 0.7–2.5 (m); mass spectrum m/e (rel intensity) 164 (74, M$^+$), 121 (54), 120 (86), 95 (100), 79 (57), 68 (44), 67 (82), 41 (62).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.8; H, 10.2.

Ring Expansion of 5,6-*exo*-Trimethylenenorbornan-2-one. An Alternative Route to 8. To a cooled mixture of 30 g (0.2 mol) of 5,6-*exo*-trimethylenenorbornan-2-one,[23] 50 g (0.23 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, 60 ml of 95% ethanol, and 4 ml of water was added dropwise with gentle stirring a solution of 6 g of potassium hydroxide in 20 ml of 50% aqueous ethanol. The rate of addition was adjusted so that the temperature was maintained at 10–20°. After the addition was completed, the solution was stirred for an additional 30 min, acidified with 2 *N* hydrochloric acid, and extracted with petroleum ether. The organic layer was dried over anhydrous sodium sulfate, concentrated, and distilled. The fraction boiling at 77–79° (1 mm) gave 3.6 g (11%) of a mixture consisting of two components, as analyzed on the vpc. The first-eluted component (relative abundance 74%) was identical in all respects (ir and mass spectra and vpc retention times) with the authentic 8 obtained above.

The second component was assigned the structure of 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one on the basis of the method of synthesis[22] and the following properties: ir 2945, 2855, 1710 (C=O), 1470, 1450, 1420, 1240, 1090, 1030, 915, 780 cm^{-1}; mass spectrum m/e (rel intensity) 164 (23, M$^+$), 136 (12), 123 (25), 120 (100), 107 (16), 93 (20), 92 (23), 91 (27), 80 (33), 79 (68), 77 (27), 67 (40), 53 (20).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.3; H, 10.1.

6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (4). A mixture of 3.3 g (0.02 mol) of the ketone 8, 14 ml of 80% hydrazine hydrate, 11 g (0.2 mol) of potassium hydroxide, and 110 ml of diethylene glycol were heated under reflux for 3 hr. Water and excess hydrazine hydrate were then distilled off and the heating was continued under reflux (210°) for a further 5 hr.[24] After being cooled, the reaction mixture was poured onto cold water and extracted five times each with 100 ml of petroleum ether. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 2.4 g (80%) of 4: bp 63–65° (2 mm); n^{22}D 1.4967; ir 2930, 2860, 1460, 1340, 1300, 1290, 1230, 1120, 1070, 970, 918, 870 cm^{-1}; ^{1}H mnr δ 0.9–2.3 (m); mass spectrum m/e (rel intensity) 150 (51, M$^+$), 135 (13), 108 (24), 93 (22), 91 (19), 79 (50), 67 (82), 55 (25), 53 (37), 41 (100); ^{13}C nmr (multiplicity, rel intensity) 20.2 (t, 1), 28.1 (t, 1), 32.5 (t, 2), 34.1 (t, 2), 34.8 (t, 1), 41.4 (d, 2), 47.9 (d, 2).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.9; H, 12.1.

Acid Catalyzed Rearrangement of Tricycloundecanes. A 20-ml two-necked erlenmeyer flask was equipped with a reflux condenser connected to a calcium chloride tube which was connected to a nitrogen cylinder through a T-shaped joint, one end of which was connected for nitrogen pressure release to a glass tube dipped by half an inch into liquid paraffin. After the flask was thoroughly flashed with nitrogen stream, an appropriate amount of the catalyst and 5 ml of methylene chloride were added. The mixture was stirred at ambient temperature until complete dissolution of the catalyst resulted; to the mixture was added with stirring a solution of 200 mg (1.33 mmol) of tricycloundecane in 5 ml of methylene chloride. The reaction was started and run under a nitrogen atmosphere at specified temperature, while aliquots (each 100 μ) were withdrawn and quenched by cold water. A part of the methylene chloride layer was taken and, without drying, subjected to vpc analysis. The amount of the catalyst used was 36 mg (0.267 mmol) for $AlCl_3$ and 200 mg (1.33 mmol) or 800 mg (5.32 mmol) for CF_3SO_3H. Reactions were run at ambient temperature when aluminum chloride was used, and under reflux when trifluoromethanesulfonic acid was used.

In case 95% sulfuric acid was used as catalyst, 5 g of sulfuric acid was placed in the flask to which was added 500 mg (3.33 mmol) of a tricycloundecane in 3.2 ml of solvent (carbon tetrachloride or methylene chloride). The reactions were run at ambient temperature. Interruption of stirring allowed separation of the organic layer, from which aliquots were withdrawn for vpc analysis after quenching by cold water.

Acknowledgment. We thank Dr. S. Sato, Director of Application Research Laboratories, Nippon Electric Varian Co., for the measurements of the ^{13}C nmr spectra.

Registry No.—2, 53432-45-4; 3, 43000-53-9; 4, 53495-28-6; 5, 281-46-9; 8, 53432-46-5; 5,6-*exo*-trimethylenenorborn-2-ene, 10466-50-9; ethyl trichloroacetate, 515-84-4; 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene, 53432-47-6; 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene, 53432-48-7; 5,6-*exo*-trimethylenenorbornan-2-one, 34748-64-6; *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, 80-11-5; 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one, 53432-49-8.

References and Notes

(1) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **79**, 3293 (1957).
(2) H. W. Whitlock, Jr., and M. W. Siefken, *ibid.*, **90**, 4929 (1968).
(3) E. M. Engler, M. Farcasiu, A. Sevin, J. M. Cense, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 5769 (1973).
(4) Reference 3 and references cited therein.
(5) The number of isomers containing neither three- nor four-membered ring amounted to 16 for $C_{10}H_{16}$[2,3] and 70 for $C_{11}H_{18}$: E. Ōsawa, to be published.
(6) (a) P. v. R. Schleyer and R. D. Nicholas, *Tetrahedron Lett.*, 305 (1961); (b) K. R. Blanchard, Ph. D. Thesis, Princeton University, 1966.
(7) M. A. McKervey, D. Grant, and H. Hamill, *Tetrahedron Lett.*, 1975 (1970); D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Amer. Chem. Soc.*, **93**, 2798 (1971).
(8) N. S. Vorobeva, O. A. Arefev, V. I. Epshev, and A. A. Petrov, *Neftekhimiya*, **11**, 163 (1971).
(9) J. A. Bone, J. R. Pritt, and M. C. Whitting, *J. Chem. Soc., Perkin Trans. 1*, 2644 (1972).
(10) Schneider in his patent literature[11] referred to the possibility of preparing methyladamantanes by the isomerization of 2,3-trimethylenebicyclo[2.2.2]octane (2), but no experimental details on the preparation and characterization or rearrangement of 2 was described. Petrov[8] prepared and studied the isomerization to methyladamantanes of 6,7-trimethylenebicyclo[3.2.1]octane, but here again neither the characterization nor experimental details for the preparation of his 6,7-trimethylenbicyclo[3.2.1]octane of unspecified conformation was given.
(11) A. Schneider (Sun Oil Co.), U. S. Patent 3,356,751 (1967); British Patent 1,142,765 (1969).
(12) Blanchard[6b] isolated three intermediates in the rearrangement of 1, but it was not until 1973 that one of these intermediates was determined to be 3.[13]
(13) M. Farcasiu, K. R. Blanchard, E. M. Engler, and P. v. R. Schleyer, *Chemistry Lett.*, 1189 (1973).
(14) A trivial name assigned to tricyclo[5.3.1.0^{3,8}]undecane by K. M. Majerski and Z. Majerski, *Tetrahedron Lett.*, 4915 (1973). The compound was first synthesized by A. Krantz and C. Y. Lin, *Chem. Commun.*, 1287 (1971); *J. Amer. Chem. Soc.*, **95**, 5662 (1973).
(15) N. Takaishi, Y. Inamoto, and K. Aigami, *Chem. Lett.*, 1185 (1973).
(16) D. Faulkner, R. A. Glendinning, D. E. Johnston, and M. A. McKervey, *Tetrahedron Lett.*, 1671 (1971); T. Courtney, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Perkin Trans. 1*, 2691 (1972).
(17) N. Takaishi, Y. Inamoto, K. Aigami, K. Tsuchihashi, and H. Ikeda, *Syn. Commun.*, in press.
(18) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, p 44 ff.

(19) T. Pehk, E. Lipman, V. V. Sevostjanova, M. M. Krayuschkin, and A. I. Tatasova, *Org. Magn. Resonance*, **3**, 783 (1971).
(20) C. W. Jefford, J. Gunsher, D. T. Hill, P. Brun, J. Le Gras, and B. Waegell, *Org. Syn.*, **51**, 60 (1971).
(21) G. T. Youngblood and P. Wilder, Jr., *J. Org. Chem.*, **21**, 1436 (1956).
(22) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963); M. A. McKinney and P. P. Patel, *ibid.*, **38**, 4059 (1973).
(23) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **67**, 723 (1945).
(24) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).
(25) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N.Y., 1963, p 28.
(26) W. D. Graham and P. v. R. Schleyer, *Tetrahedron Lett.*, 1179 (1972); T. M. Gund and P. v. R. Schleyer, *ibid.*, 1959 (1973); J. S. Wishnok, P. v. R. Schleyer, E. Funke, G. D. Pandit, R. O. Williams, and A. Nickon, *J. Org. Chem.*, **38**, 539 (1973); J. Janjatovic, D. Skare, and Z. Majerski, *ibid.*, **39**, 651 (1974).
(27) Rearrangement of homoadamantane in the presence of Brønsted acid will be published separately.
(28) Z. Majerski and K. Milnaric, *Chem. Commun.*, 1030 (1972).
(29) N. Camelli, G. Salvetti, and G. Sartori (Montecatini Co.), Italian Patent 730,703 (1966); *Chem. Abstr.*, **69**, 51740y (1968).
(30) H. Stetter and P. Goebel, *Chem. Ber.*, **96**, 550 (1963).

Synthesis of 3-Keto-6-phenyl-8-methyl-9-oxa-$\Delta^{1,2}$-2-azabicyclo[4.3.0]nonane

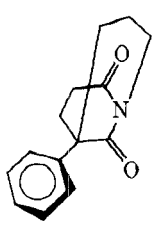
Edward E. Smissman,[1] Peter J. Wirth,*[2] and David R. Glynn

The Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045

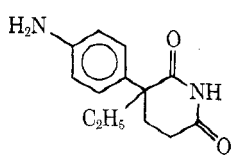
Received August 2, 1974

The synthesis and the study of the intramolecular cyclizations of ethyl 3-[3-phenyl-3-(2′-piperidonyl)]propionate (**3**), 2-(3-bromopropyl)-2-phenylglutarimide (**17**), and 2-(2-bromopropyl)-2-phenylglutarimide (**18**) are described. Although both N and O alkylations are possible, only the O-alkylated products were observed.

The synthesis of 5-phenyl-2,9-diketo-1-azabicyclo-[3.3.1]nonane (**1**), a bridged analog of aminoglutethimide (**2**), was undertaken in order to investigate the steric requirements of the antiepileptic action of drugs containing the ureide or imide moiety.



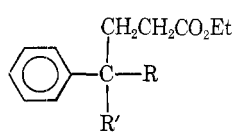
1



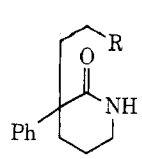
2

The initial approach to the synthesis of **1** involved the synthesis of ethyl 3-[3-phenyl-3-(2′-piperidonyl)]propionate (**3**). It was proposed that a base-catalyzed intramolecular attack by the amide nitrogen on the ester function would yield **1**.

Diethyl 2-phenylglutarate (**4**) was converted to diethyl 2-cyanoethyl-2-phenylglutarate (**5**) *via* cyanoethylation. Hydrogenation of **5** yielded the primary amine **6** which was converted without purification to the desired lactam ester **3**. Treatment of **3** with a variety of bases (sodium hydride, potassium *tert*-butoxide, thallous ethoxide, sodium hydroxide, and sodium ethoxide) in various solvent systems (dimethylformamide, dimethoxyethane, diethyl ether) failed to yield the desired bicyclic glutarimide **1**. The product isolated was identified as 3-[3-phenyl-3-(2′-piperidonyl)]propionic acid (**7**). This probably results from the initial

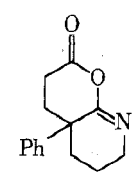


4, R′ = H; R = CO_2Et
5, R′ = CH_2CH_2CN; R = CO_2Et
6, R′ = $CH_2CH_2CH_2NH_2$; R = CO_2Et



3, R = CO_2Et
7, R = CO_2H

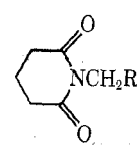
formation of **8** *via* intramolecular O-acylation followed by hydrolysis during isolation to give the acid **7**.



8

Attempts to cyclize compound **7** to the desired glutarimide **1** under various conditions (acetic anhydride, acetic anhydride and pyridine, thionyl chloride, dicyclohexylcarbodiimide, and polyphosphoric acid) yielded only starting material.

We previously reported[3] the light-catalyzed addition of hydrogen bromide to *N*-allylglutarimide (**9**) to yield *N*-(3-bromopropyl)glutarimide (**10**). If a small amount of acetic acid was added to the reaction *N*-(2-bromopropyl)glutarimide (**11**) was obtained. Attempts to cyclize **10** to the C-alkylated bicyclic system failed.



9, R = $CH{=}CH_2$
10, R = CH_2CH_2Br
11, R = $CHBrCH_3$

An alternate approach to the synthesis of **1** involved a base-catalyzed intramolecular alkylation of 2-(3-bromopropyl)-2-phenylglutarimide (**17**). We anticipated that the addition of a suitable base would lead to the abstraction of the relatively acidic imide proton and the resulting anion could afford nucleophilic displacement of the primary bromide of the propyl side chain to yield the desired compound **1**.

Phenylacetonitrile was allowed to react with allyl bromide and sodium hydride in dimethylformamide to yield 2-allylphenylacetonitrile (**12**). Cyanoethylation of **12** yielded 2-allyl-2-cyanoethylphenylacetonitrile (**13**) followed by hydrolysis to yield the diacid **14** which was converted to 2-allyl-2-phenylglutaric anhydride (**15**) with refluxing acetic