Biologically Active Polycycloalkanes. 2. Antiviral 4-Homoisotwistane Derivatives

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New derivatives of 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane) (**3**), the olefin (**8**), bromide (**4**), alcohols (**7**, **9**, **11**, and **14**), ketone (**10**), acid (**12**), esters (**13**, **18a**, and **18b**), amides (**5**, **16**, and **19a–d**), nitrile (**20**), and amines and their hydrochlorides (**6**, **17**, and **21**), were prepared, and antiviral activities of these compounds were determined in vitro on a monolayer culture of chick embryo fibroblasts against Newcastle disease virus. 4-Homoisotwist-3-ylamine hydrochloride (**6**) and 4-homoisotwist-3-ylmethylamine hydrochloride (**21**) were found 30–50 times more potent than amantadine hydrochloride in this assay. Methods of preparing the test compounds included those functionalization reactions of **3** which revealed many interesting features of the reactivity of the recently discovered polycyclic hydrocarbon **3**.

In the first paper[1] of this series, it was demonstrated that a variety of simple derivatives of adamantane, such as halides, alcohols, ketones, carboxylic esters, and nitriles, was found active as an antiviral agent when tested in vitro on a monolayer culture of chick embryo fibroblasts against Newcastle disease virus. In view of numerous examples of the use of polycycloaliphatic compounds for the modification of drugs, these results prompted us to examine the antiviral activities of compounds having polycyclic rings other than adamantane. In this paper, some derivatives of 4-homoisotwistane[2] (tricyclo[5.3.1.$0^{3,8}$]undecane) (**3**) were prepared and their antiviral activities were tested.

4-Homoisotwistane (**3**), a tricycloundecane having the skeleton of a sesquiterpene seychellene, was prepared for the first time by Krantz[4] in a stereoselectivity study on the intramolecular Diels–Alder reactions of 5-alkenylcyclohexa-1,3-dienes. Compound **3** was recently found independently by Schleyer,[5] Majerski,[3] and us[6,7] to arise as an intermediate in the adamantane rearrangement of various tricycloundecane precursors. The hydrocarbon **3** was also demonstrated theoretically[5] and experimentally[7] to be one of the most stable tricycloundecane isomers.[8] Indeed the stability of **3** is so large that it was possible to obtain **3**, in place of methyladamantanes, as the main product of the rearrangement by the use of a mild catalyst, trifluoromethanesulfonic acid.[7] A further study[9] showed the isomerization of 2,3-trimethylenebicyclo[2.2.2]octane (tricyclo[5.2.2.$0^{2,6}$]undecane) (**2**) under sulfuric acid catalysis offered a convenient synthesis of **3**.

Chemistry. Preparation of 4-homoisotwistane (**3**) and its derivatives is summarized in Scheme I. 2,3-Trimethylenebicyclo[2.2.2]octane (**2**), the precursor to **3** in the present synthesis, was prepared by hydrogenation over Raney nickel catalyst of the Diels–Alder adduct (**1**) of cyclohexa-1,3-diene and cyclopentadiene.[10] This Diels–Alder reaction was shown by Cameli et al.[10] to give *endo*-tricyclo[5.2.2.$0^{2,6}$]undeca-3,8-diene (**1**) with 98% selectivity.[11] The precursor **2** was isomerized in one step to **3** in the presence of sulfuric acid and carbon tetrachloride at room temperature.[9] The selectivity to **3** in the isomerization was as high as 95%. The mechanism of this rearrangement, however, remains yet to be clarified, although two major intermediates of unknown structure have been detected.[7]

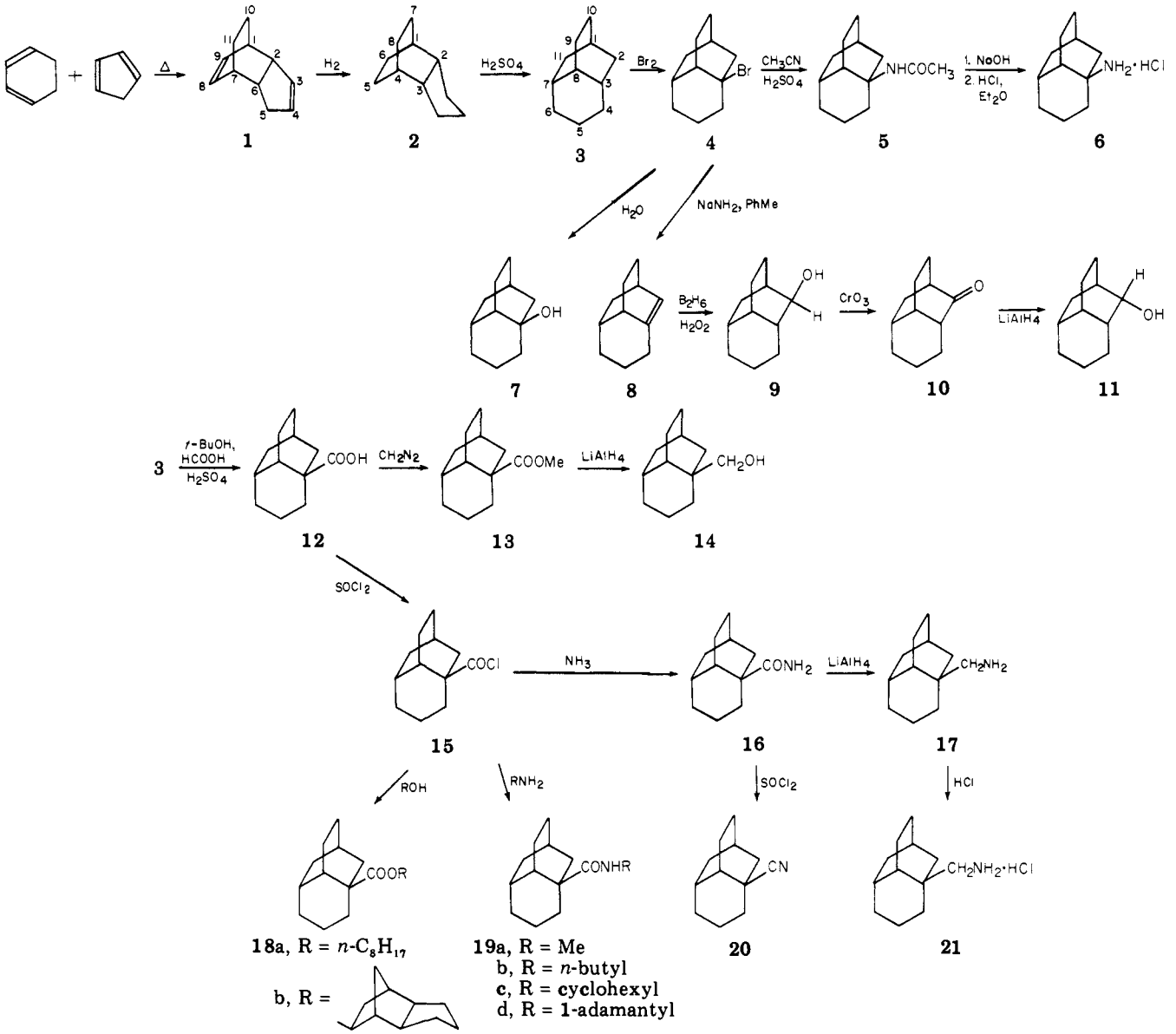
Bromination of **3** with liquid bromine at room temperature gave exclusively the 3-bromo derivative **4** in 85% yield.[12] The structure of the bromide **4** was established unambiguously on the following basis. Reduction of **4** with lithium metal in *tert*-butyl alcohol gave the original hydrocarbon **3**. The skeleton of 4-homoisotwistane thus remained intact during the bromination. The ^{1}H NMR spectrum of **4** did not contain any resonance assignable to the proton geminal to the bromine atom, demonstrating the substitution to have occurred at some bridgehead [the C-1, C-3 (C-7), or C-8]. The total proton-decoupled ^{13}C NMR spectrum of **4** comprised ten signals. This indicated the molecule to be asymmetrical and excluded the possibilities of **4** being either the 1- or the 8-bromide, both of which should give rise to eight signals owing to their C_s symmetries.

Of the three different kinds of bridgeheads in **3**, the C-3 was shown to be much more reactive than the two others in bromination. This would be readily explained based on the difference in the stabilities of the corresponding carbocations. Bingham and Schleyer[13] found an extensive correlation between bridgehead solvolysis rates and the stabilities of the corresponding carbocations in polycyclic halides and arenesulfonates. Particularly, the bicyclo[3.3.1]non-1-yl compound was 3×10^4 times more reactive than the bicyclo[2.2.2]oct-1-yl. The C-3 atom of **3** may be regarded as a bridgehead of bicyclo[3.3.1]nonane, while the C-1 and C-8 as that of bicyclo[2.2.2]octane. Therefore, the C-3 atom of **3** should react much faster than the C-1 and C-8 in bromination, that is, an ionic process involving carbocations.[14,15]

Hydrolysis of 3-bromo-4-homoisotwistane (**4**) was quite fast, in accordance with the high stability of its 3-cation. Reflux of **4** in aqueous acetone for 1 h caused a complete hydrolysis of **4** to 4-homoisotwistan-3-ol (**7**). Neither alkali nor silver ion[14] was required as catalyst for the reaction. The bromide **4** underwent readily Ritter reaction with acetonitrile, giving 3-acetylamino-4-homoisotwistane (**5**). Alkaline hydrolysis of **5** and subsequent neutralization of the product yielded 4-homoisotwist-3-ylamine hydrochloride (**6**).

The bromide **4** was found to give off hydrogen bromide to yield 4-homoisotwist-2(3)-ene (**8**) in 52% yield when treated with sodium amide in refluxing toluene.[16] Bridgehead olefins, so-called Bredt compounds, were obtained only with difficulty through a variety of elaborated methods,[14] and no example seems to have been found of the formation of the hoped-for olefins by the dehydrobromination method. Ready dehydrobromination in **4** could be attributed to the rigidity of the molecule. The 2-*exo*-hydrogen and 3-bromine atoms are tightly held in a completely eclipsed conformation, so that they would constitute an ideal arrangement of the atoms for the cis elimination transition state.[18] This interpretation also explains a high regioselectivity of the reaction, in which

Scheme I. Synthesis of 4-Homoisotwistane and Its Derivatives



neither 4-homoisotwist-3(4)-ene nor -3(8)-ene was obtained.[16] The olefin **8**, similarly as other Bredt compounds,[17] is a fairly unstable compound and polymerized in several hours in the presence of oxygen. However, it can be stored for months under nitrogen in a refrigerator.

Hydroboration–hydrogen peroxide oxidation[19,20] of the olefin **8** gave a mixture of 23% **7** and 77% 4-homoisotwistan-2-*exo*-ol (**9**) in 77% yield. The alcohols were easily separable on conventional preparative VPC. The 2-*exo*-ol **9** was oxidized by Jones reagent[21] to 4-homoisotwistan-2-one (**10**), which was then reduced by lithium aluminum hydride to 4-homoisotwistan-2-*endo*-ol (**11**). Two alcohols **9** and **11** had different physical and spectral properties that showed an epimerization at the C-2 center in the oxidation–reduction cycle. This result, together with the established preferential exo attack of diborane[19,20] and lithium aluminum hydride,[22] enabled the assignment of the configurations of the alcohols **9** and **11**.

Koch carboxylation of **3** through hydride transfer to the *tert*-butyl cation[23] gave 4-homoisotwistane-3-carboxylic acid (**12**). While the structure of **12** could be deduced with reference to that of the bromide **4** considering the carbonium ion nature of the Koch carboxylation, it was established unequivocally as follows. Lead tetraacetate decarboxylation[24] of **12** led to an acetoxy compound. Alkaline hydrolysis of this acetate gave 4-homoisotwistan-3-ol (**7**) which was identical in all respects with an authentic specimen derived from the bromide **4**.

The carboxylic acid **12** was reduced by lithium aluminum hydride to 4-homoisotwist-3-ylcarbinol (**14**) after esterification with diazomethane. Esters [*n*-octyl- (**18a**) and *exo*-trimethylenenorborn-2-*exo*-yl (**18b**)], amide (**16**), and *N*-alkylamides [methyl (**19a**), *n*-butyl (**19b**), cyclohexyl (**19c**), and 1-adamantyl (**19d**)] of **12** were prepared through the acyl chloride (**15**). Thionyl chloride dehydration of the amide **16** gave the corresponding nitrile (**20**), while lithium aluminum hydride reduction of **16** led to 3-aminomethyl-4-homoisotwistane (**17**) which was neutralized in ether to give the hydrochloride **21**. Novel derivatives of **3** thus prepared are listed in Table I.

Antiviral Activity. Antiviral activity of the test compounds was measured by the tube assay method employing the Miyadera strain of Newcastle disease virus and monolayer culture of chick embryo fibroblasts, as reported in the previous paper.[1] Antiviral activities and cytotoxicities are expressed by minimum inhibitory concentration (MIC, nmol/ml) and minimum cytotoxic concentration (MCC, nmol/ml), respectively. The results

Table I. Antiviral Activity and Cytotoxicity of 4-Homoisotwistane and Its Derivatives[a]

Compd	MIC,[b] nmol/ml	MCC,[c] nmol/ml	Compd	MIC,[b] nmol/ml	MCC,[c] nmol/ml
3	670	670	16	2 600	5 200
5	750	3 000	18a	330	490
6	25	200	18b	950	80
7	3 000	6 000	19a	3 000	750
9	900	1 800			
10	1 200	2 400	19b	625	300
11	750	750	19c	2 250	2 250
12	10 000	10 000	19d	7 500	2 000
13	80	80	20	570	850
14	440	870	21	45	90
			1-NH_2-Ad·HCl[d]	1 300	1 300

[a] 3-Bromo-4-homoisotwistane (4), 4-homoisotwist-2-ene (8), and 4-homoisotwist-3-ylcarbonyl chloride (15) were not tested because of their instability. [b] Minimum inhibitory concentration, as defined by that concentration of the test compounds at which the virus multiplication measured by hemagglutinating activity was supressed to 1% or less of the control experiment. [c] Minimum cytotoxic concentration. The cytotoxicity was determined by microscopic examination of host cells. [d] Amantadine hydrochloride.

are shown in Table I. Activity of amantadine hydrochloride[25] under the present assay conditions is also listed for reference.

The amine hydrochlorides **6** and **21** were found to be quite active. They were indeed 30–50 times more potent than amantadine hydrochloride. In addition, these compounds exhibited cytotoxicity (MCC) at concentrations 2–8 times larger than those effecting the virus inhibition (MIC). This is superior to amantadine hydrochloride in which the MIC and the MCC were identical.

The change of activity with substituents in 4-homoisotwistyl derivatives is similar to that in adamantyl compounds. For example, substitution by the amide group in **3** (cf. **16** and **19**) generally brought about inactivity to the compounds, as was the case for adamantyl analogs.[1] However, moderate activities of 3-acetylamino-4-homoisotwistane (**5**) and *N*-*n*-butyl-4-homoisotwistane-3-carboxamide (**19b**) seem to be exceptions throughout both series, for which we do not have any convincing interpretation at present. Hydroxy-substituted 4-homoisotwistanes (**9**, **11**, and **14**) were fairly active with MIC ≤ MCC, as found to be the case for adamantylphenols and -cyclohexanols. Inactivity of carboxylic acids (cf. **12**) was noted in both series. Activity of 4-homoisotwistane-3-carboxylic esters (**13** and **18**), similar to that of adamantyl analogs, depended on the size of their alcohol moieties, lower alkyl esters giving a high level of activity while higher esters tended to have low activity.

Experimental Section

All melting and boiling points are uncorrected. Determination of ir, ^{1}H NMR, and mass spectra, conventional and preparative VPC, and the GC–MS measurements were done on the same instruments as used in the previous study.[1] ^{13}C NMR spectra were recorded at 15.03 MHz on a JEOL JNM FX-60 Fourier transform spectrometer, using deuteriochloroform as solvent. ^{13}C NMR chemical shifts are reported in parts per million downfield from internal tetramethylsilane standard. Analyses of the elements indicated by the symbols were within ±0.4% of the calculated values for all the new compounds.

3-Bromo-4-homoisotwistane (4). A mixture of 3.0 g (0.02 mol) of 4-homoisotwistane[7,9] (**3**) and 10 ml (0.19 mol) of bromine was stirred at ambient temperature for 10 min. Most of the excess bromine was evaporated off in vacuo from the reaction mixture, and the residue was dissolved in 20 ml of carbon tetrachloride. The solution was washed repeatedly with a saturated sodium bisulfite solution until any remaining bromine had been removed and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 3.9 g (85% yield) of crude **4** which showed only one peak on conventional VPC. Purification by sublimation in vacuo gave a pure sample: mp 59.5° (sealed tube); ir (Nujol) 1210, 1110, 1050, 940, 890, 840, 750 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.6 (complex m); ^{13}C NMR (multiplicity, rel intensity) 20.2 (t, 1), 24.7 (t, 2), 26.3 (d, 1), 29.5 (t, 1), 31.3 (t, 1), 34.4 (d, 1), 42.7 (d, 1), 44.5 (t, 1), 46.1 (t, 1), 73.5 ppm (s, 1); mass spectrum *m/e* (rel intensity) 230 (0.2 M$^+$), 228 (0.3, M$^+$), 150 (23), 149 (100), 107 (18), 94 (22), 93 (21), 91 (25), 81 (27), 79 (37), 67 (40). Anal. ($C_{11}H_{17}Br$) C, H, Br.

3-Acetylamino-4-homoisotwistane (5). To a solution of 5.3 g (0.022 mol) of 3-bromo-4-homoisotwistane (**4**) and 40 ml of acetonitrile was dropped 10 ml of 95% sulfuric acid at ambient temperature in a period of 30 min. The reaction was further stirred overnight. The reaction mixture was poured onto 200 ml of ice–water and extracted with two 100-ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether and recrystallization of the residue from fresh ether gave 3.8 g (83% yield) of pure **5**: mp 125–126° (sealed tube); ir (Nujol) 3300, 1640, 1540, 1310, 740 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2–2.1 (complex m, 17 H), 2.20 (s, 3 H); mass spectrum *m/e* (rel intensity) 207 (42, M$^+$), 148 (100), 136 (25), 119 (21), 94 (41), 91 (17), 79 (19), 60 (36), 43 (19), 18 (19). Anal. ($C_{13}H_{21}NO$) C, H, N.

3-Amino-4-homoisotwistane Hydrochloride (6). A mixture of 5.22 g (0.025 mol) of 3-acetylamino-4-homoisotwistane (**5**), 8.4 g (0.21 mol) of sodium hydroxide, and 60 ml of diethylene glycol was refluxed with stirring for 5 h. The cooled reaction mixture was poured onto 200 ml of cold water and extracted with three 50-ml portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and concentrated to give 2.6 g (64% yield) of crude 3-amino-4-homoisotwistane. Since the crude amine was extremely hygroscopic, it was immediately dissolved in 50 ml of ether, and dry hydrogen chloride was bubbled into the solution. Precipitated crude **6** was filtered off and recrystallized from a methanol–acetone mixture to give a pure sample: mp 200–205° dec (sealed tube); ir (Nujol) 3200–2900 (br), 2020, 1610, 1510 cm^{-1}; mass spectrum *m/e* (rel intensity) 165 (10), 96 (10), 57 (11), 56 (100), 44 (13), 43 (14), 41 (14), 30 (16), 28 (14), 18 (82), 17 (20). Anal. ($C_{11}H_{20}NCl$) C, H, N, Cl.

3-Hydroxy-4-homoisotwistane (7). A mixture of 0.69 g (0.003 mol) of 3-bromo-4-homoisotwistane (**4**) in 30 ml of acetone and 20 ml of water was refluxed at 85° for 1 h. The reaction mixture was extracted with two 20-ml portions of petroleum ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated to give 0.49 g (98% yield) of crude **7**. Purification by sublimation gave a pure sample: mp 104.5° (sealed tube); ir (Nujol) 3260, 1350, 1340, 1310, 1300, 1210, 1100, 1080, 990, 930, 870 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.8–2.2 (complex m); ^{13}C NMR (multiplicity) 19.6 (t), 20.3 (t), 25.4 (t), 26.1 (d), 30.3 (t), 31.4 (t), 33.1 (d), 40.3 (d), 41.2 (t), 41.7 (t), 70.8 ppm (s); mass spectrum *m/e* (rel intensity) 166 (100, M$^+$), 123 (27), 110 (27), 97 (31), 96 (71), 95 (86), 84 (35), 79 (37), 55 (28), 41 (31). Anal. ($C_{11}H_{18}O$) C, H.

4-Homoisotwist-2(3)-ene (8). To a solution of 8.22 g (0.036 mol) of 3-bromo-4-homoisotwistane (**4**) in 20 ml of sodium-dried toluene was added 1.4 g (0.036 mol) of sodium amide, and the mixture was refluxed for 2 h with efficient stirring. Precipitated sodium bromide was filtered off, and the filtrate was fractionally distilled to give 2.8 g (50% yield) of **8**: bp 90–92° (19 mm); ir (neat) 3020, 1620, 1450, 840, 820, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9–2.9 (complex m, 15 H), 5.90 (d, J = 6 Hz, 1 H); mass spectrum *m/e* (rel intensity) 148 (41, M$^+$), 105 (25), 94 (100), 92 (28), 91 (51), 77 (25), 66 (33), 41 (26), 18 (39). Anal. ($C_{11}H_{16}$) C, H.

4-Homoisotwistan-2-*exo*-ol (9). A mixture consisting of 1.77 g (0.012 mol) of 4-homoisotwist-2(3)-ene (**8**), 0.14 g (0.0037 mol) of sodium borohydride, and 5 ml of sodium-dried tetrahydrofuran was kept at 20–25°, to which was dropped under nitrogen stream 0.7 g (0.0048 mol) of boron trifluoride etherate in 5 ml of tetrahydrofuran in a period of 10 min. The reaction was stirred for further 1 h. To the reaction mixture kept at 20–25° with external cooling was added 2 ml of 3 N sodium hydroxide solution and then 1.8 ml of 35% hydrogen peroxide solution. The reaction

mixture was saturated with sodium chloride and extracted with three 10-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated to give 1.5 g (77% yield) of a mixture comprising 23% of **7** and 77% of **9**, as determined on GC–MS. Fractionation of the above mixture on preparative VPC gave a pure sample of **9**: mp 92–93° (sealed tube); ir (neat) 3350, 2930, 2860, 1470, 1070, 1020, 950, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.0 (complex m, 14 H), 2.1 (s, 1 H), 2.8 (br s, 1 H), 3.4 (br s, 1 H), 3.6 (br s, 1 H); mass spectrum *m/e* (rel intensity) 166 (19, M^+), 148 (55), 135 (40), 92 (39), 91 (33), 81 (32), 79 (38), 67 (37), 41 (36), 28 (34), 18 (100). Anal. ($C_{11}H_{18}O$) C, H.

4-Homoisotwistan-2-one (10). A Jones reagent prepared from 0.35 g (0.0032 mol) of chromium trioxide, 0.5 ml of 95% sulfuric acid, and 1 ml of water was dropped in a period of 10 min to a solution of 0.7 g (0.0042 mol) of 4-homoisotwistan-2-*exo*-ol (**9**) in 5 ml of acetone kept at 5–10° by external cooling. The reaction was stirred for a further 2 h at ambient temperature. Any unreacted chromic oxide was destroyed by the addition of a saturated sodium bisulfite solution. The reaction mixture was extracted with three 30-ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether left 0.65 g (95% yield) of crude **10**. Recrystallization from *n*-hexane gave a pure material: mp 60–61° (sealed tube); ir (Nujol) 1700, 1200, 1090 cm^{-1}; mass spectrum *m/e* (rel intensity) 164 (97, M^+), 104 (72), 95 (100), 94 (63), 79 (76), 67 (71), 41 (75), 39 (54), 27 (49), 18 (73). Anal. ($C_{11}H_{16}O$) C, H.

4-Homoisotwistan-2-*endo*-ol (11). A solution of 0.6 g (0.0036 mol) of 4-homoisotwistan-2-one (**10**) in 5 ml of dry ether was dropped in a period of 15 min to a mixture of 0.1 g (0.0026 mol) of lithium aluminum hydride and 5 ml of ether kept under gentle reflux. The reaction was refluxed for further 2 h. After any unreacted lithium aluminum hydride was destroyed by methanol and then by water, the mixture was made acidic by the addition of 2% hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with three 30-ml portions of ether. The combined organic layer and ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether left 0.46 g (76% yield) of crude **11**. Recrystallization from *n*-hexane gave a pure material: mp 95–96° (sealed tube); ir (Nujol) 3350, 1150, 1070, 1040 cm^{-1}; mass spectrum *m/e* (rel intensity) 166 (5, M^+), 148 (100), 135 (51), 93 (32), 92 (54), 91 (47), 81 (54), 80 (46), 79 (64), 67 (56), 41 (57). Anal. ($C_{11}H_{18}O$) C, H.

4-Homoisotwistane-3-carboxylic Acid (12). A solution of 30 g (0.41 mol) of *tert*-butyl alcohol in 55 g (1.20 mol) of 99% formic acid was dropped in a period of 2.5 h to an efficiently stirred mixture of 15 g (0.10 mol) of 4-homoisotwistane (**3**), 100 ml of cyclohexane, and 450 g of 95% sulfuric acid kept at 10–15° with external cooling. The reaction was stirred for further 3 h at the same temperature. The reaction mixture was poured onto 1 kg of cracked ice, and the organic layer was separated. The aqueous layer was extracted with three 200-ml portions of cyclohexane. The combined organic layer and extracts were washed once with water and then shaken with three 300-ml portions of 1.5% sodium hydroxide solution. The combined sodium hydroxide extracts were made strongly acidic by the addition of 35% hydrochloric acid and extracted with three 100-ml portions of ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and fractionally distilled. Collection of the fraction boiling at 135–140° (0.9 mm) gave 12.5 g (63% yield) of crude **12**, which solidified on standing at ambient temperature overnight. Purification by sublimation in vacuo gave a pure sample: mp 95–96° (sealed tube); ir (neat) 2940, 2920, 2860, 2700–2500, 1680, 1450, 1400, 1280, 1110, 960, 900, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–2.6 (complex m, 17 H), 10.20 (s, 1 H, vanished on treatment with D_2O); mass spectrum *m/e* (rel intensity) 194 (12, M^+), 150 (13), 149 (100), 92 (12), 80 (19), 78 (15), 66 (27), 57 (12), 41 (17). Anal. ($C_{12}H_{18}O_2$) C, H.

Methyl 4-Homoisotwistane-3-carboxylate (13). 4-Homoisotwistane-3-carboxylic acid (**12**) (1.9 g, 0.01 mol) in 10 ml of ether was esterified with a diazomethane solution prepared from 2.1 g (0.002 mol) of nitrosomethylurea and 6 ml of 50% potassium hydroxide solution in 20 ml of ether.[26] The reaction mixture was fractionally distilled to give 1.6 g (76% yield) of **13**: colorless liquid; bp 87–88° (0.9 mm); $n^{24}D$ 1.4887; ir (neat) 2930, 2860, 1730, 1450, 1190, 1080 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–2.6 (complex m, 17 H), 3.64 (s, 3 H); mass spectrum *m/e* (rel intensity) 208 (10, M^+), 150 (13), 149 (100), 107 (7), 93 (9), 91 (6), 81 (14), 79 (10), 67 (21), 41 (7). Anal. ($C_{13}H_{20}O_2$) C, H.

4-Homoisotwist-3-ylcarbinol (14). A solution of 0.75 g (0.0036 mol) of methyl 4-homoisotwistane-3-carboxylate (**13**) in 5 ml of ether was dropped in a period of 20 min to a suspension of 0.16 g (0.0042 mol) of lithium aluminum hydride in 10 ml of ether kept under gentle reflux, and the mixture was refluxed for a further 1.5 h. The reaction mixture was treated in a usual manner to give an ether solution of crude **14**. Evaporation of the ether and purification of the residue on preparative VPC gave 0.33 g (51% yield) of **14**: mp 107–108° (sealed tube); ir (neat) 3640 (sh), 3340, 2920, 2860, 1450, 1370, 1120, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–2.3 (complex m, 17 H), 2.20 (s, 1 H), 3.25 (m, 2 H); mass spectrum *m/e* (rel intensity) 180 (3, M^+), 150 (14), 149 (100), 93 (11), 81 (19), 79 (13), 67 (29), 41 (11). Anal. ($C_{12}H_{20}O$) C, H.

4-Homoisotwist-3-ylcarbonyl Chloride (15). To a solution of 5.5 g (0.028 mol) of 4-homoisotwistane-3-carboxylic acid (**12**) in 20 ml of benzene was dropped at ambient temperature with stirring 12 ml of thionyl chloride and the mixture was stirred under reflux for 1 h. After most of the benzene and the excess thionyl chloride had been distilled off, the residue was fractionated to give 5.4 g (90% yield) of **15**: colorless liquid; bp 96–97° (0.9 mm); $n^{22}D$ 1.5238; ir (neat) 2930, 2860, 1790, 1470, 1450, 990, 920, 880, 750, 650 cm^{-1}; ^1H NMR (CCl_4) δ 1.2–2.4 (complex m); mass spectrum *m/e* (rel intensity) 194 (23), 150 (12), 149 (100), 93 (14), 91 (15), 81 (22), 79 (21), 67 (36), 41 (21), 39 (14), 28 (15). Anal. ($C_{12}H_{17}OCl$) C, H, Cl.

4-Homoisotwistane-3-carboxamide (16). Ammonia gas was bubbled into a solution of 5.6 g (0.026 mol) of 4-homoisotwist-3-ylcarbonyl chloride (**15**) in 30 ml of sodium-dried ether kept below 20°. Ammonia was passed through the solution for a further 1 h after heat evolution had subsided. Precipitates were filtered and triturated with two 50-ml portions of ether. The combined filtrate and ether extracts were concentrated to leave 4.8 g (96% yield) of crude **16**. Recrystallization from ether–petroleum ether gave a pure sample: mp 107–108°; ir (Nujol) 3400–3200, 1690, 1640, 1600 cm^{-1}; ^1H NMR (CCl_4) δ 1.0–2.4 (complex m, 18 H), 6.6 (br s, 1 H); mass spectrum *m/e* (rel intensity) 193 (13, M^+), 150 (13), 149 (100), 107 (86), 93 (10), 81 (18), 79 (12), 67 (29), 41 (86), 18 (10). Anal. ($C_{12}H_{19}NO$) C, H, N.

3-Aminomethyl-4-homoisotwistane (17) and Its Hydrochloride (21). A sample (1.5 g, 0.0075 mol) of 4-homoisotwistane-3-carboxamide (**16**) was reduced by 0.5 g (0.013 mol) of lithium aluminum hydride in 30 ml of refluxing tetrahydrofuran in a usual manner. Ether extraction of the reaction mixture gave crude amine **17**, which was purified by dissolution in 2% hydrochloric acid followed by alkalification and ether extraction. After being dried over potassium carbonate, the ether solution was examined on GC–MS to characterize **17**: mass spectrum *m/e* (rel intensity) 179 (9, M^+), 149 (41), 93 (9), 81 (17), 79 (11), 67 (28), 44 (14), 41 (11), 30 (25), 18 (100).

Dry hydrogen chloride was bubbled into this ether solution to precipitate 1.1 g (68% yield) of the hydrochloride (**21**) of **17**, which was purified by recrystallization from methanol–acetone: mp 255–260° dec (sealed tube); ir (Nujol) 1600, 1500 cm^{-1}; mass spectrum *m/e* (rel intensity) 179 (16), 149 (77), 93 (16), 81 (33), 79 (19), 67 (51), 41 (19), 30 (49), 18 (100), 17 (22). Anal. ($C_{12}H_{22}NCl$) C, H, N, Cl.

4-Homoisotwist-3-yl Cyanide (20). A mixture of 2.5 g (0.013 mol) of 4-homoisotwistane-3-carboxamide (**16**) and 10 ml of thionyl chloride was refluxed for 3 h. After most of the excess thionyl chloride was distilled off, the residue was chromatographed through an alumina column using ether as eluent to give 2.2 g (98% yield) of crude **20**. Sublimation in vacuo gave a pure material: mp 100–101° (sealed tube); ir (Nujol) 2230, 1110, 960 cm^{-1}; ^1H NMR (CCl_4) δ 1.2–2.2 (complex m); mass spectrum *m/e* (rel intensity) 175 (100, M^+), 160 (43), 147 (71), 146 (71), 132 (88), 131 (49), 81 (67), 79 (43), 67 (44), 41 (42). Anal. ($C_{12}H_{17}N$) C, H, N.

4-Homoisotwistane-3-carboxylic Esters (18). Reaction of 2.1 g (0.01 mol) of 4-homoisotwist-3-ylcarbonyl chloride (**15**) with 0.012 mol of an alcohol (*n*-octyl or 5,6-*exo*-trimethylenenorborn-2-*exo*-yl[27]) in the presence of 1.0 g (0.013 mol) of pyridine

in 10 ml of ether at reflux gave esters **18**. *n*-Octyl 4-homoisotwistane-3-carboxylate (**18a**): bp 130–132° (0.15 mm); $n^{22}D$ 1.4842; ir (neat) 2930, 2860, 1720, 1460, 1310, 1270, 1250, 1220, 1200, 1190, 1110, 1080, 950, 740, 720 cm^{-1}; ^1H NMR (CCl_4) δ 0.9–2.5 (complex m, 32 H), 4.0 (m, 2 H); mass spectrum *m/e* (rel intensity) 306 (2, M^+), 195 (17), 150 (14), 149 (100), 81 (14), 67 (24), 55 (10), 43 (13), 41 (18), 29 (9), 18 (13). Anal. ($C_{20}H_{34}O_2$) C, H.

5,6-*exo*-Trimethylenenorborn-2-*exo*-yl 4-homoisotwistane-3-carboxylate (**18b**): bp 201–204° (1.5 mm); $n^{24}D$ 1.5227; ir (neat) 2940, 2850, 1720, 1440, 1300, 1270, 1250, 1220, 1200, 1190, 1170, 1100, 1070, 900, 850, 740 cm^{-1}; ^1H NMR (CCl_4) δ 0.9–5.5 (complex m, 31 H), 4.5 (m, 1 H); mass spectrum *m/e* (rel intensity) 328 (1, M^+), 149 (100), 135 (57), 134 (21), 93 (15), 81 (19), 79 (18), 67 (62), 66 (30), 41 (22), 18 (24). Anal. ($C_{22}H_{32}O_2$) C, H.

***N*-Alkyl-4-homoisotwistane-3-carboxamides (19).** Methylamine gas was evolved from its 43% aqueous solution by addition of 35% sodium hydroxide and dried by passing through a potassium hydroxide column. The gas was bubbled into a solution of 2.1 g (0.01 mol) of 4-homoisotwist-3-ylcarbonyl chloride (**15**) in 20 ml of ether. The reaction mixture was treated as in the preparation of **16** to give 1.8 g (87% yield) of crude **19a**. Recrystallization from ether–petroleum ether gave a pure material: mp 110–111°; ir (Nujol) 3350, 1640, 1620, 1530, 1300, 1280 cm^{-1}; ^1H NMR (CCl_4) δ 1.0–2.6 (complex m, 17 H), 2.80 (d, J = 5 Hz, 3 H), 7.2 (br s, 1 H); mass spectrum *m/e* (rel intensity) 207 (46, M^+), 150 (16), 149 (100), 93 (17), 81 (28), 79 (19), 67 (51), 58 (20), 41 (20), 18 (23). Anal. ($C_{13}H_{21}NO$) C, H, N.

Acylation of 0.022 mol of an amine (*n*-butyl, cyclohexyl, or 1-adamantyl) with 2.1 g (0.01 mol) of **15** in refluxing ether gave the corresponding amides in 78–92% yields. *N*-*n*-Butyl-4-homoisotwistane-3-carboxamide (**19b**): bp 149–151° (0.4 mm); $n^{24}D$ 1.5107; ir (neat) 3330, 3050, 2930, 2860, 1640, 1620, 1520, 1280, cm^{-1}; mass spectrum *m/e* (rel intensity) 249 (33, M^+), 149 (100), 93 (13), 81 (22), 79 (15), 67 (38), 57 (18), 41 (25), 18 (51). Anal. ($C_{16}H_{27}NO$) C, H, N.

N-Cyclohexyl-4-homoisotwistane-3-carboxamide (**19c**): mp 143–144°; ir (Nujol) 3320, 3050, 1630, 1540, 1310, 1300, 1280 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (45, M^+), 194 (21), 150 (17), 149 (100), 81 (24), 79 (16), 67 (41), 55 (21), 41 (30), 18 (44). Anal. ($C_{18}H_{29}NO$) C, H, N.

N-(1-Adamantyl)-4-homoisotwistane-3-carboxamide (**19d**): mp 184–186° (sealed tube); ir (Nujol) 3340, 1630, 1520, 1290 cm^{-1}; mass spectrum *m/e* (rel intensity) 327 (49, M^+), 150 (30), 149 (75), 135 (51), 93 (19), 81 (22), 79 (21), 67 (35), 41 (20), 18 (100). Anal. ($C_{22}H_{33}NO$) C, H, N.

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