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(32) When L-Pya was treated under regular hydrolytic conditions for peptides, 20% of D-Pya resulted. If the percent of racemization of the peptide is expressed as two times the percent of D isomer found in the reaction product, no racemization occurs when no D isomer is found, and total racemization occurs when the reaction product gives 50% D and 50% L isomer. When 43.5% D-Pya was found in the hydrolysate of Boc-Pya-Pro-Phe-polymer as the sum of the racemization during DCC coupling and acid hydrolysis, $43.5\% = (1 - 0.2)D + 0.2L$. D and L represent the percent of the D- and L-Pya-containing tripeptide resulting from the coupling. Therefore, D and L total 100% of the product tripeptide, and 20% of either D or L is converted to the opposite isomer by acid hydrolysis. The amount of D-Pya-containing tripeptide can be calculated from $43.5\% = (1 - 0.2)D + 0.2(1 - D)$, where $0.6D = 0.235$. The amount of D-Pya-containing peptide was $0.235/0.6 = 39\%$ of the total tripeptide; thus, DCC coupling caused 78% of the Boc-L-Pya to racemize.
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Biologically Active Polycycloalkanes. 6.[1] Antiviral 1-Tricyclo[4.3.1.1^{2,5}]undecyl Derivatives

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Functionalization reactions via cationic intermediates of tricyclo[4.3.1.1^{2,5}]undecane (**2**) were investigated to prepare derivatives with potential antiviral activities. Bromination of **2** took place regiospecifically at C-1, and the resulted bromide **5** was converted into the hydroxide **9**, the carboxylic acid **12**, and the amine **22**, from which were synthesized a variety of secondary derivatives, including homologous esters **10** and **20**, amides 14 and **19**, carbamates **24**, and ureas **17** and **25**. The hydroxide **9**, the acid **12**, and the acetamide **21** were also obtainable directly from tricyclo[5.2.1.0^{2,6}]dec-*endo*-2-ylcarbinol (**1**), the precursor for the synthesis of the hydrocarbon **2**. Success in these functionalization–rearrangements was attributed to the inability of the intermediate **2**-1-yl cation (**2**$^+$) for further skeletal isomerizations. Among the 1-substituted derivatives of **2** prepared, the amine hydrochlorides (**16** and **23**), a few esters (**20b** and **20d**), and some *N*-alkylamides (**19c**, **19d**, and **19e**) exhibited marked antiviral activities as compared to amantadine hydrochloride, when tested in vitro on a monolayer culture of chick embryo fibroblasts against Newcastle disease virus.

Since the discovery in 1964 of the antiviral activity of amantadine (1-aminoadamantane)[2] which has a characteristic bridged tricyclic structure, a number of efforts have been devoted for the synthesis of a wide variety of its analogues having larger activities with broader antiviral spectra and less CNS effects. While the modifications of the 1-amino group to form substituted amines mainly effected variations in specificity to individual virus, as well as extent of side effects,[3] entire replacements of the amino by other functional groups only slightly modified the activity, as measured in vitro on chick embryo cells against NDV.[4] In contrast to this, a change in the tricyclic alkyl residue from 1-adamantyl to 4-homoisotwistyl (tricyclo-[5.3.1.0^{3,8}]undecyl) resulted in a drastic enhancement of the activity for amino derivatives.[5] The evidence suggested the possibility of access to still more potent compounds by appropriate choice of the bridged polycyclic structure. Tricyclo[4.3.1.1^{2,5}]undecane (**2**), another tricycloalkane recently prepared by us,[6] was now functionalized, and the resulting derivatives, as well as their secondary derivatives,

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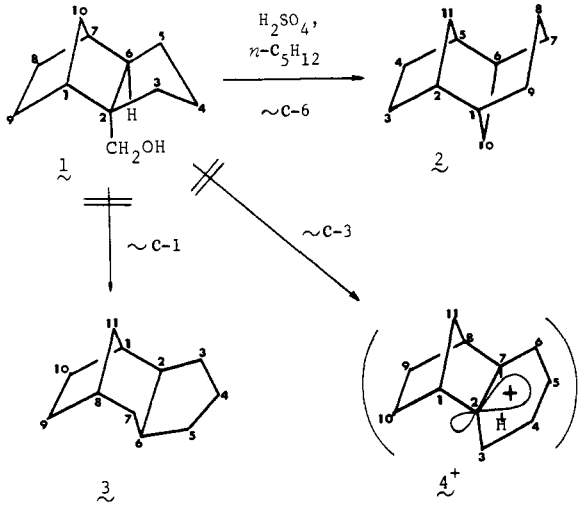
Scheme I



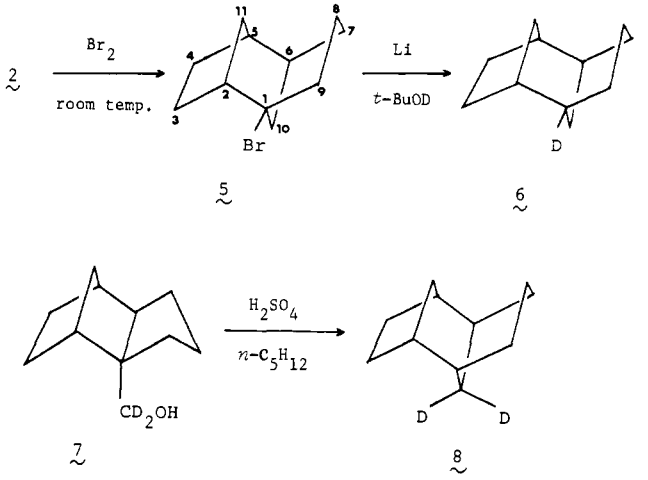
were examined for antiviral activity.

Chemistry. The acid-catalyzed multistep skeletal isomerization of tricycloundecanes, which gives methyladamantanes as the ultimate products, has been shown in a series of theoretical[7] as well as experimental[8] studies to consist of a complex network of competitive and consecutive reactions involving a number of intermediates with varing thermodynamic stabilities. Some of the intermediates, which would be best exemplified by 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane),[5,7,8] are stable enough to accumulate during the reaction, although further reaction led them to a complete conversion into methyladamantanes in the end. Other intermediates, in spite of their relative low thermodynamic stabilities, may also be isolated, if all of their possible rearrangement routes are associated with high activation energies. Tricyclo[4.3.1.$1^{2,5}$]undecane (**2**, Scheme I) is one of the typical isomers having stability in the latter sense.[7]

The tricycloundecane **2** was prepared[6] from *cis-exo*-2,3-trimethylenenorborn-*endo*-2-ylcarbinol (tricyclo[5.2.1.$0^{2,6}$]dec-*endo*-2-ylcarbinol, 1) via the route shown in Scheme I. The precursor carbinol 1 was found to give exclusively **2**. The other two possible ring-enlargement products, tricyclo[6.2.1.$0^{2,6}$]undecane (**3**)[9] and 2,3-tetramethylenenorbornane (**4**),[7] were not detected among the products. Preferable migration of C-6 over that of C-1 in **1** had been explained[10] in terms of the relative instability of the transition state for C-1 migration as compared to that for C-6 due to steric repulsion around the cationic center. On the other hand, retardation of the migration of C-3 may be attributed to the increased tortional strain in tricyclo[6.2.1.$0^{2,7}$]undec-1-yl cation $\mathbf{4}^+$ to be formed in this process. The strain in 4^+ is considered to arise as a result of the unsymmetrical distribution of the vacant p orbital on the C-2 cationic center in which the orbital lobe extends to the exo side under the influence of the C-11 methano bridge[11] to give a hybridization more like sp^3, as in the case of the bridgehead cationic center in the protonated anti-Bredt olefin.[12] This electronic configuration of C-2 necessarily requires $\mathbf{4}^+$ to assume a similar skeletal configuration to that of the trans-endo-2-exo-7 isomer ($\mathbf{4}^+$-H) of tricyclo[6.2.1.$0^{2,7}$]undecane, which is much strained (the calculated standard heat of formation $\Delta H°_f$,[7] -17.73 kcal/mol) as compared to **2** ($\Delta H°_f$ -20.66) or **3** ($\Delta H°_f$ -25.54).

Bromination of **2** in excess bromine at room temperature occurred regiospecifically at the C-1 bridgehead (Scheme II).[13] This orientation of the bromine substituent was determined unequivocally with the use of deuterium

Scheme II



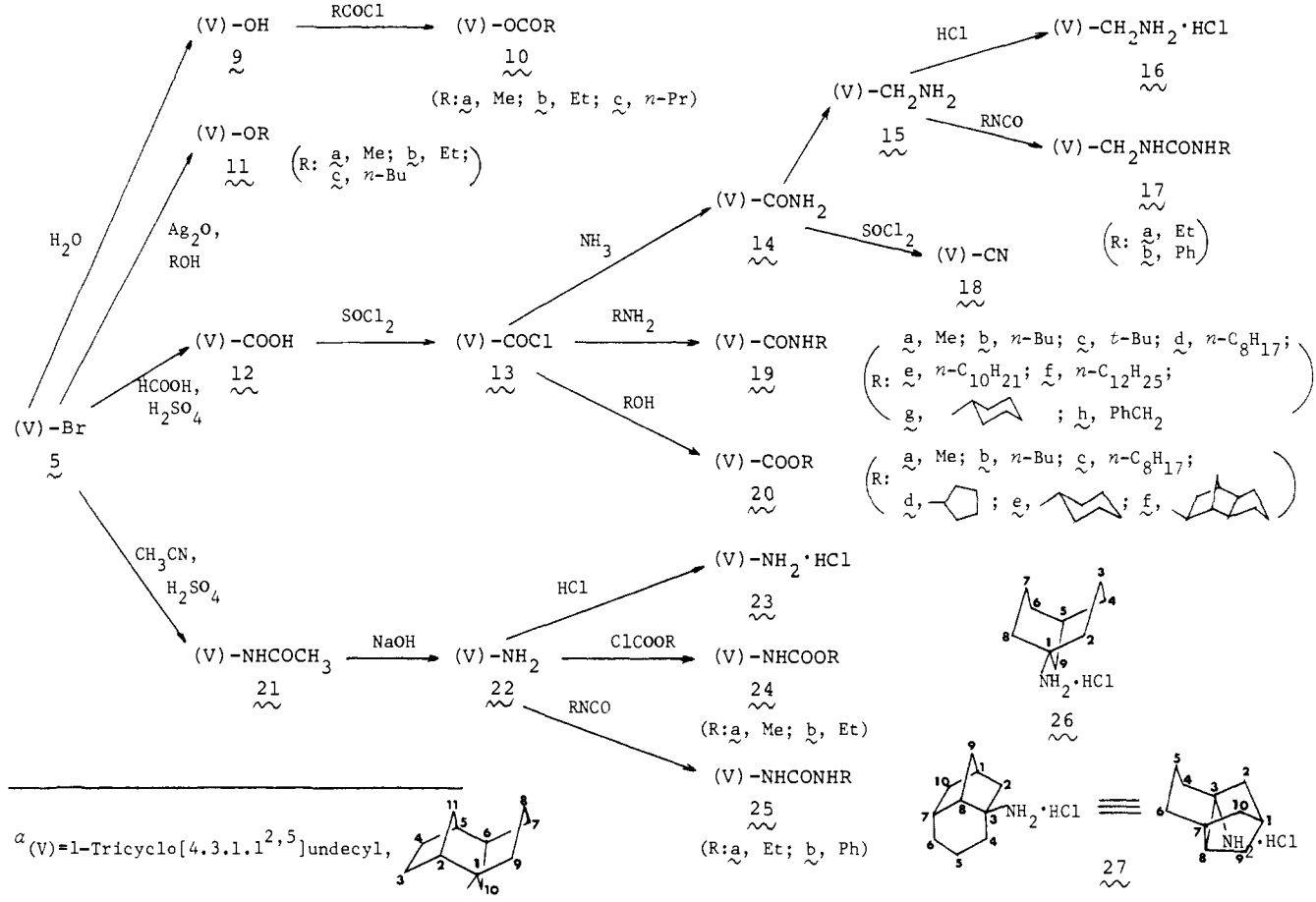
isotope effects on ^{13}C NMR spectra.[13,14] While the undeuterated compound **2** showed seven (three single intensity and four double intensity) signals in the total proton-decoupled spectrum, off-resonance proton decoupling indicated them to be three single-intensity triplets, two double-intensity triplets, and two double-intensity doublets. The result is in complete agreement with the molecular structure of **2** with C_s symmetry. 10,10-Dideuterio-substituted **2** (**8**) was then synthesized from the corresponding dideuterated carbinol **7**, and its total proton-decoupled spectrum was measured. One of the three single-intensity triplet signals of **2**, the signal at δ_C 26.41, vanished in the spectrum of the dideuterated analogue **8** and, therefore, should be assigned to C-10. This is caused by the splitting of the signal into quintet on coupling with the two deuterium atoms, by which the signal heights were decreased to a level as low as that of the noise signals.

The signal of **8** (δ_C 32.90) corresponding to one of the two double-intensity doublets of **2** (for the C-1 and C-2 bridgeheads) exhibited a marked geminal deuterium isotope effect, i.e., band broadening with a little (~0.2 ppm) upfield shift, while the other bridgehead signal (δ_C 41.09) showed a clear vicinal effect ("N" form coupling with the *anti*-10-^{2}H to split into a small triplet, $J \approx 1$ Hz). Therefore, the former signal should be assigned to the C-1 bridgehead which is geminal to 10-^{2}H on C-10, and the latter to the C-2.

The bromo derivative **5** obtained above was then reduced with lithium in *O*-deuterio-*tert*-butyl alcohol to the corresponding monodeuterio compound **6**. The signal (δ_C 32.52) which had been assigned to C-1 in the above appeared as a large triplet ($J \approx 20$ Hz) in the spectrum of **6**, indicating deuterium substitution at C-1. Identity, except for the deuterium isotope effects, of the spectrum of **6** with that of **2** also proved the intactness of the tricycloundecane skeleton during the bromination. Thus, the results clearly demonstrated that the bromine substitution took place at the C-1 bridgehead.

Bromination of polycycloalkanes by bromine has been shown to be an ionic process involving the rate-determining formation of bridgehead cations.[3,4] In accordance with this, the relative bromination rates have been found to be parallel with the relative stabilities of the corresponding bridgehead cations, and the relationship holds true when the comparison is made between the bridgeheads of different molecules as well as among the different kinds of bridgeheads within the same molecule.[13,15] The relative stabilities of the C-1 and the C-2 cations of **2** may be approximated to those of 1-bicyclo[3.3.1]nonyl and 1-

Scheme III[a]



bicyclo[3.2.1]octyl cations, since the attachment of an *exo*-2,4-ethano bridge to the former bicyclic cation and that of an *exo*-2,4-trimethylene bridge to the latter, hypothetical processes giving **2**-1- and **2**-2-yl cations, respectively, do not appear to alter the strains and, hence, the relative stabilities of the bicyclic cations. 1-Bicyclo[3.3.1]nonyl cation was known[16] to be 3×10^5 times more stable than the 1-bicyclo[3.2.1]octyl. The stability difference tells us that **2**-2-yl bromide is to be formed only to the extent of 0.0003% of **2**-1-yl bromide (**5**), and this is well below the range of detection by VPC (0.2%).

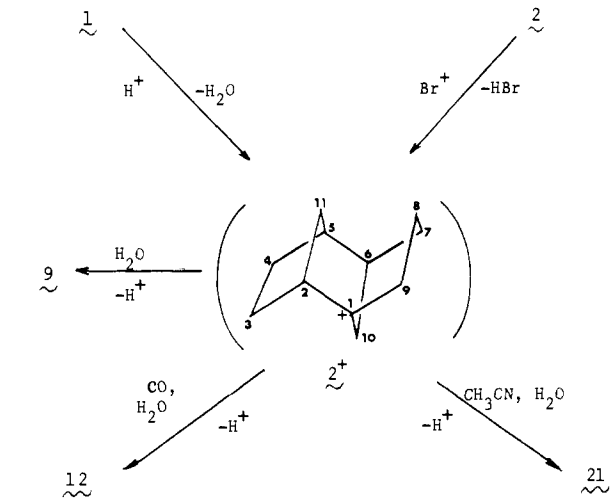
The 1-bromo derivative **5** thus obtained was hydrolyzed in acetone–water at reflux to give the 1-ol **9** (Scheme III). The esters **10** of the 1-ol were prepared by the reaction with the corresponding acyl chlorides. On the other hand, silver ion catalyzed alcoholysis of **5** led to the ethers **11**.

The Koch carboxylation[3-5] of the bromide **5** in the usual manner gave the 1-carboxylic acid **12**. The structure of the acid was determined unequivocally by lead tetraacetate decarboxylation in acetic acid[10,17] to form the same 1-acetoxy derivative **10a** as from the 1-ol **9** by acetylation. From the acid **12** were derived, via the acyl chloride **13**, the amide **14**, the *N*-alkylamides **19**, and the esters **20**. The amide **14** was converted into the methylamine **15** and the cyanide **18**. The amine **15** was further transformed into its hydrochloride **16** and the urea derivatives **17**.

The Ritter amidation reaction[3-5] was applied to the bromide **5** to afford the corresponding acetamide **21**, which was hydrolyzed to the amine **22**. The amine **22** was converted into the hydrochloride **23**, the carbamates **24**, and the ureas **25** in the usual manner.

The 1-ol **9**, the acid **12**, and the acetamide **21** were also obtainable in one step from the precursor carbinol **1** (Scheme IV). The carbinol **1** dissolved in carbon tetrachloride was stirred at room temperature with 50% sulfuric acid to give the 1-ol **9** in 98% yield. Similarly, the Koch carboxylation and the Ritter amidation of **1** under the usual reaction conditions[3-5] afforded in good yields the acid **12** and the acetamide **21**, respectively. The direct acetamidation method recently discovered by us[15] was also successfully applicable to the hydrocarbon **2** to give **21**.

Scheme IV



The one-step formation of the functionalized **2** from the precursor carbinol **1** is a manifestation of the stability of the hydrocarbon **2** in the acid-catalyzed isomerizations. The "stability" here is considered[7,8] to arise from the difficulty with which the cation 2^+ (Scheme IV) undergoes 1,2-alkyl shifts and intramolecular 1,2- and 1,3-hydride transfers. All the 1,2 shifts of the β-alkyls (C-3, -6, -8, and

Table I. Antiviral Activity and Cytotoxicity of Tricyclo[4.3.1.1^{2,5}]undecane and Its Derivatives[a]

no.	MIC,[b] nmol/mL	MCC,[c] nmol/mL
2	1100	1100
9	1400	2900
10a	>4800	>4800
10b	>4500	>4500
10c	>4200	>4200
11a	1100	1100
11b	1000	1000
11c	900	900
12	5200	5200
14	5200	5200
16	190	190
17a	800	800
17b	>3500	>3500
18	1100	1100
19a	4800	>4800
19b	4000	>4000
19c	>4000	>4000
19d	210	420
19e	380	380
19f	350	1400
19g	>3600	>3600
19h	>3500	>3500
20a	960	960
20b	160	800
20c	650	3300
20d	150	760
20e	720	720
20f	610	3000
21	540	1100
23	430	430
24a	4500	4500
24b	840	4200
25a	4200	4200
25b	>3500	>3500
26	230	230
27	1100	1100

[a] 1-(Chlorocarbonyl)tricyclo[4.3.1.1^{2,5}]undecane (13) was not tested because of the instability. [b] Minimum inhibitory concentration, as defined by that concentration of the test compound at which the virus multiplication measured by hemagglutinating activity was suppressed to 1% or less of the control experiment. [c] Minimum cytotoxic concentration. The cytotoxicity was determined by microscopic examination of the host cells.

-11) produce structures appreciably more strained than 2^+ itself, thus rendering these shifts impracticable. There is left the possibility for 2^+ to undergo intramolecular hydride transfers forming cations of **2** other than 2^+ in which 1,2-alkyl shifts may give rise to more stable skeletal structures. However, these hydride-transfer processes seem less likely to occur because[7,8] of poor overlaps between the vacant p orbital on the C-1 cationic center and the relevant σ orbitals of the α and β hydrogens (2-H and 9-, 10-, 3-, 8-, and 11-H's). Thus, the cation 2^+, although the thermodynamic stability of its skeleton is not quite large,[7] is required to overcome high activation energies for further isomerizations to take place.

Some bridgehead amines having a skeleton other than tricyclo[4.3.1.1^{2,5}]undecane were also needed, as described below, for a survey of skeletal structure–antiviral activity relationships. 1-Aminobicyclo[3.3.1]nonane and 3-amino-4-homobrendane (3-aminotricyclo[5.2.1.0^{3,8}]decane) hydrochlorides (**26** and **27**, respectively) were readily prepared from the corresponding acetamides which had been obtained by our one-step acetamidation method.[15]

Antiviral Activity. The tube assay method utilizing the Miyadera strain of Newcastle disease virus on a monolayer culture of chick embryo fibroblasts[1,4,5] was also employed in this study. Antiviral activities are expressed in terms of minimum inhibitory concentration (MIC, nmol/mL), while cytotoxicities are expressed in terms of minimum cytotoxic concentration (MCC, nmol/mL), as in the previous studies.[1,4,5] The results are listed in Tables I and II.

Table II. Antiviral Activity of 1-Bicyclo[3.3.1]nonylamine and Its Methano- and Ethano-Bridged Derivatives

compound no.	compound bridge[b]	MIC,[a] nmol/mL	ref
26		230	*c*
27	3,9-methano	1100	*c*
Ad[d]	3,7-methano	1300	*e*
23	2,4-ethano	430	*c*
HIT[f]	3,9-ethano	25	*g*

[a] Minimum inhibitory concentration, as defined in footnote *b*, Table I. [b] The bridge to be added to 1-bicyclo[3.3.1]nonylamine hydrochloride to construct the compound. [c] The present study (Table I). [d] 1-Adamantylamine (amantadine) hydrochloride. [e] Reference 4. [f] 4-Homoisotwist-3-ylamine hydrochloride. [g] Reference 5.

The amine hydrochlorides **16** and **23** exhibited the highest level of activity among the various kinds of functional derivatives, as was the case for the adamantane and 4-homoisotwistane series.[4,5] The present amines were appreciably more active than amantadine but were not so potent as the 4-homoisotwistylamines.

It may be recalled that *N*-alkyl-4-homoisotwistane-3-carboxamides and *N*-alkyladamantane-1-carboxamides were mostly inactive, with the exception of *N*-*n*-butyl-4-homoisotwistane-3-carboxamide.[4,5] In contrast to this, homologous alkylamides **19** with the tricyclo[4.3.1.1^{2,5}]-undecane skeleton were found fairly active when the alkyl groups were of C_8 through C_{12} carbon chain lengths. The *N*-*n*-butyl group which brought a fair activity to 4-homoisotwistane-3-carboxamide was ineffective for the present amide (**19b**).

A maximum in the activity appears to exist for a series of alkyl esters **20** with the change in the size of the alkyl groups. The activity increases from the methyl (**20a**) to the *n*-butyl (**20b**) and the cyclopentyl (**20e**) and then decreases as the size of the alkyl group increases. In a series of alkyl 4-homoisotwistane-3-carboxylates, the methyl ester was the most active of all.[5] Thus, the maximum in the activity of a series of alkyl esters seems to be shifted by three to four carbon atoms toward the larger side in the tricyclo[4.3.1.1^{2,5}]undecane series than in the 4-homoisotwistane one. The same thing appears to be true for *N*-alkylcarboxamides of both series mentioned above.

1-Tricyclo[4.3.1.1^{2,5}]undecylamine (**23**) and 4-homoisotwist-3-ylamine have the 1-bicyclo[3.3.1]nonyl partial structure. Thus, **23** may be regarded as the *exo*-2,4-ethano, while 4-homoisotwist-3-ylamine as the 3,9-ethano, derivative of 1-bicyclo[3.3.1]nonylamine (**26**). This suggested to us that the 1-bicyclo[3.3.1]nonyl structure might be associated with the antiviral activity. In order to examine this postulate, the MIC's and the MCC's of **26** and 4-homobrend-3-ylamine hydrochloride (**27**), which was the 3,9-methano derivative of **26**, were also measured (Table II). In Table II were also listed the results for 4-homoisotwist-3-ylamine and 1-adamantylamine (3,7-methano-1-bicyclo[3.3.1]nonylamine) hydrochlorides tested before.[4,5,18]

1-Bicyclo[3.3.1]nonylamine hydrochloride (**26**) itself was indeed found to be fairly active. However, no simple relationship seems to exist between the skeletal structure

and activity. Thus, the activity does not correlate with the total carbon number of the compounds, i.e., C_9 for **26**, C_{10} for **27** and 1-adamantyl, and C_{11} for **23** and 4-homoisotwistyl, nor is it dependent upon the conformation of the bicyclo[3.3.1]nonyl moiety: **23**, **26**, and 1-adamantyl have the chair–chair (*E*),[19] whereas 4-homobrendyl (**27**) and 4-homoisotwistyl have the more strained chair–boat (*Z*) form.

Experimental Section

All melting and boiling points are uncorrected. Determination of IR, ^{1}H NMR, ^{13}C NMR, and mass spectra, conventional and preparative VPC, and the GC–MS measurements were done on the same instruments as in the previous works.[1,4,5] *cis-exo*-2,3-Trimethylenenorborn-*endo*-2-ylcarbinol (**1**) and tricyclo[4.3.1.1^{2,5}]undecane (**2**) were prepared before.[6] Analyses of the elements indicated by the symbols were within ±0.4% of the calculated values for all the new compounds.

1-Bromotricyclo[4.3.1.1^{2,5}]undecane (5). To 2 mL (0.039 mol) of bromine was added 1.0 g (0.0067 mol) of tricyclo[4.3.1.1^{2,5}]undecane (**2**), and the reaction was stirred at room temperature for 17 h. The mixture was poured onto 120 mL of a saturated sodium bisulfite solution at 0 °C and stirred until the mixture became colorless. The mixture was extracted with two 20-mL portions of carbon tetrachloride, and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off, and the residue was fractionally distilled to give 1.04 g (68% yield) of 1-bromotricyclo[4.3.1.1^{2,5}]undecane (**5**): bp 96–98 °C (2 mm); mp 57.5–58.5 °C; IR (Nujol) 3030,[20] 1300, 1240, 1200, 160, 1120, 1090, 1060, 1000, 960, 880, 790, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8–2.6 (complex m); ^{13}C NMR ($CDCl_3$) δ_C 22.46 (t), 26.52 (t), 27.98 (t and t), 34.27 (t), 37.77 (d), 39.35 (t), 39.80 (d), 41.18 (t), 51.41 (d), 75.08 (s); MS *m/e* (relative intensity) 230 (1, M$^+$), 228 (2, M$^+$), 149 (100), 93 (18), 91 (15), 83 (18), 81 (44), 79 (23), 67 (82), 41 (24), 39 (18). The sample gave only one major peak (98% of the combined peak areas) upon examination on Golay column VPC. Anal. ($C_{11}H_{17}Br$) C, H, Br.

1-Hydroxytricyclo[4.3.1.1^{2,5}]undecane (9). (a) Hydrolysis of 1-Bromotricyclo[4.3.1.1^{2,5}]undecane (5). The bromide **5** (1.5 g, 0.0044 mol) was dissolved in a mixture comprising 145 mL of acetone and 95 mL of water, and the solution was heated under reflux for 1 h. The mixture was cooled and extracted with five 30-mL portions of petroleum ether. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent and sublimation of the residue gave 0.63 g (95% yield) of 1-hydroxytricyclo[4.3.1.1^{2,5}]undecane (**9**): colorless solid, mp 79–80 °C; IR (KBr) 3300 (br), 2950, 2870, 1490, 1470, 1450, 1350, 1280, 1190, 1100, 1080, 1040, 1000, 970, 950, 920, 810 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ_C 20.55 (t), 25.18 (t), 26.80 (t), 28.63 (t), 32.65 (t), 35.33 (t), 36.06 (d), 37.81 (t), 39.92 (d), 47.67 (d), 71.92 (s); MS *m/e* (relative intensity) 166 (0.3, M$^+$), 123 (57), 98 (7), 97 (100), 95 (23), 81 (5), 79 (9), 77 (5), 67 (10), 55 (10), 41 (11). Anal. ($C_{11}H_{18}O$) C, H.

(b) Functionalization–Rearrangement of *cis-exo*-2,3-Trimethylenenorborn-*endo*-2-ylcarbinol (1). A solution of 4.0 g (0.024 mol) of the carbinol **1** in 10 mL of carbon tetrachloride was mixed with 40 mL of 50% sulfuric acid, and the reaction was stirred at ambient temperature for 35 h. The organic layer was separated, and the aqueous layer was extracted with three 20-mL portions of ether. The combined organic layer and ether extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated off, and the residue was purified by sublimation to give 3.9 g (98% yield) of the alcohol **9**. Melting point, mixture melting point, and IR and ^{13}C NMR spectra were identical with those described in the preceding paragraph.

1-Acetoxytricyclo[4.3.1.1^{2,5}]undecane (10a). A mixture comprising 0.17 g (0.001 mol) of the alcohol **9**, 0.094 g (0.0012 mol) of acetyl chloride, 0.1 g (0.0013 mol) of pyridine, and 5 mL of ether was heated under reflux for 30 min. The mixture was diluted with 5 mL of water, and the organic layer was separated. The aqueous layer was extracted with three 5-mL portions of ether. The combined organic layer and ether extracts were washed with 2% hydrochloric acid and then with water and dried over anhydrous sodium sulfate. After the solvent was evaporated off, the residue was distilled in vacuo to give a fraction boiling at 91–92 °C (1.5 mm). Purification of the fraction on preparative VPC afforded 0.13 g (61% yield) of a pure sample of 1-acetoxytricyclo[4.3.1.1^{2,5}]undecane (**10a**): IR (neat) 3030, 2920, 2860, 1720, 1470, 1360, 1240, 1180, 1150, 1060, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9–2.8 (complex m) with 1.93 (s, $OCOCH_3$); MS *m/e* (relative intensity) 208 (1, M$^+$), 166 (15), 148 (22), 139 (15), 123 (37), 97 (100), 95 (11), 67 (19), 66 (11), 43 (28), 41 (17). Anal. ($C_{13}H_{20}O_2$) C, H.

1-(Propionyloxy)tricyclo[4.3.1.1^{2,5}]undecane (10b). A mixture comprising 1.66 g (0.01 mol) of the alcohol **9**, 1.39 g (0.015 mol) of propionyl chloride, 1.5 g (0.02 mol) of pyridine, and 50 mL of ether was heated under reflux for 1 h. The reaction mixture was treated similarly as for the 1-acetoxy derivative **10a** to give 1.44 g (65% yield) of 1-(propionyloxy)tricyclo[4.3.1.1^{2,5}]undecane (**10b**): bp 93–94 °C (0.8 mm); IR (neat) 3030, 2940, 2880, 1730, 1360, 1270, 1200, 1180, 1150, 1060, 1020, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8–2.7 (complex m) with 1.04 (t, J = 8 Hz, $OCOCH_2CH_3$) and 2.17 (q, J = 8 Hz, $OCOCH_2CH_3$); MS *m/e* (relative intensity) 222 (3, M$^+$), 166 (20), 153 (33), 148 (39), 123 (55), 120 (22), 97 (100), 67 (27), 57 (50), 41 (21). Anal. ($C_{14}H_{22}O_2$) C, H.

1-(*n*-Butyryloxy)tricyclo[4.3.1.1^{2,5}]undecane (10c). The alcohol **9** (1.66 g, 0.01 mol), 1.60 g (0.015 mol) of *n*-butyryl chloride, and 1.5 g (0.02 mol) of pyridine in 50 mL of ether were allowed to react, and the product was isolated in a similar way as for the homologous esters **10a** and **10b**. VPC purification afforded 1.37 g (58% yield) of pure 1-(*n*-butyryloxy)tricyclo[4.3.1.1^{2,5}]undecane (**10c**): bp 105–106 °C (0.8 mm); IR (neat) 3030, 2960, 2930, 2870, 1730, 1470, 1360, 1310, 1260, 1190, 1180, 1150, 1090, 1060, 1020, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8–2.8 (complex m) with 0.92 (t, J = 7 Hz, CH_3); MS *m/e* (relative intensity) 236 (5, M$^+$), 167 (40), 166 (29), 149 (25), 148 (50), 123 (61), 120 (31), 97 (100), 91 (21), 79 (23), 71 (73), 67 (32), 43 (51), 41 (33). Anal. ($C_{15}H_{24}O_2$) C, H.

1-Methoxytricyclo[4.3.1.1^{2,5}]undecane (11a). A mixture of 1.14 g (0.005 mol) of 1-bromotricyclo[4.3.1.1^{2,5}]undecane (**5**), 10 mL of methanol, and 1.0 g of silver oxide was heated under reflux for 30 min. The reaction mixture was filtered, and the filtrate was concentrated. The residue was fractionally distilled to give 0.71 g (79% yield) of 1-methoxytricyclo[4.3.1.1^{2,5}]undecane (**11a**): bp 89–90 °C (4 mm); IR (neat) 3030, 2930, 2870, 2820, 1470, 1370, 1200, 1160, 1110, 1060, 1030, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9–2.4 (complex m, 17 H), 3.15 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ_C 20.01 (t), 24.64 (t), 26.64 (t), 28.55 (t), 31.51 (t and t), 32.04 (t), 35.29 (t), 40.49 (d), 43.05 (d), 47.80 (q), 74.02 (s); MS *m/e* (relative intensity) 180 (11, M$^+$), 138 (18), 137 (100), 112 (31), 111 (99), 109 (46), 91 (14), 81 (18), 79 (33), 77 (16), 67 (29), 55 (14), 53 (14), 45 (18), 43 (10), 41 (47), 39 (24). Anal. ($C_{12}H_{20}O$) C, H.

1-Ethoxytricyclo[4.3.1.1^{2,5}]undecane (11b). Ethanolysis of 1.14 g (0.005 mol) of the bromide **5** with 10 mL of ethanol in the presence of 1.0 g of silver oxide gave 0.80 g (83% yield) of 1-ethoxytricyclo[4.3.1.1^{2,5}]undecane (**11b**): bp 97–98 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 1.0–2.4 (complex m, 20 H) with 1.13 (t, J = 8 Hz, 3 H, OCH_2CH_3), 3.40 (q, J = 8 Hz, 2 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ_C 16.40 (q), 20.06 (t), 24.69 (t), 26.72 (t), 28.55 (t), 32.00 (t and t), 32.49 (t), 35.29 (d), 40.57 (d), 43.49 (d), 55.10 (t), 75.90 (s); MS *m/e* (relative intensity) 194 (4, M$^+$), 151 (48), 126 (9), 125 (100), 123 (12), 97 (40), 95 (11), 67 (12), 55 (9), 44 (15), 41 (17). Anal. ($C_{13}H_{22}O$) C, H.

1-*n*-Butoxytricyclo[4.3.1.1^{2,5}]undecane (11c). Reaction of 1.14 g (0.005 mol) of the bromide **5** and 5 mL of *n*-butyl alcohol catalyzed by 1.0 g of silver oxide gave 0.72 g (65% yield) of 1-*n*-butoxytricyclo[4.3.1.1^{2,5}]undecane (**11c**): bp 97–98 °C (4 mm); IR (neat) 3030, 2940, 2870, 1480, 1380, 1170, 1110, 1080, 990, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 3 H, $-CH_3$), 1.1–2.4 (complex m, 21 H), 3.30 (t, J = 6 Hz, 2 H, $-OCH_2-$); ^{13}C NMR ($CDCl_3$) δ_C 14.10 (q), 19.47 (t), 20.06 (t), 24.69 (t), 26.76 (t), 28.54 (t), 32.08 (t and t), 32.41 (t), 32.97 (t), 35.33 (d), 40.53 (d), 43.41 (d), 59.53 (t), 75.69 (s); MS *m/e* (relative intensity) 222 (4, M$^+$), 179 (49), 154 (11), 153 (93), 123 (44), 120 (13), 119 (11), 97 (100), 95 (15), 91 (10), 81 (11), 79 (18), 67 (20), 55 (12), 41 (29), 39 (11). Anal. ($C_{15}H_{26}O$) C, H.

Tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylic Acid (12). (a) Koch Carboxylation of 1-Bromotricyclo[4.3.1.1^{2,5}]undecane (5). A solution of 6.8 g (0.03 mol) of the bromide **5** in 20 mL (0.5 mol) of 99% formic acid was added dropwise with efficient stirring

in a period of 1.5 h to 40 mL of 98% sulfuric acid kept at 0–10 °C. The reaction was stirred for an additional 1 h at the same temperature. The solids separated were filtered, washed with water, and dried in vacuo at ambient temperature. Recrystallization of the solids from *n*-hexane gave 5.6 g (96% yield) of tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylic acid (**12**): mp 158.5–159.5 °C; IR (KBr) 3300–2500, 1690, 1470, 1410, 1290, 1270, 1210, 1150, 1070, 950 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ_C 18.19 (t), 26.25 (t), 26.70 (t and t), 28.13 (t), 30.93 (t), 31.38 (t), 32.36 (d), 40.35 (d), 42.95 (d), 44.90 (s), 185.63 (s); MS *m/e* (relative intensity) 194 (21, M$^+$), 149 (36), 127 (40), 93 (29), 81 (73), 80 (29), 79 (38), 67 (89), 60 (26), 57 (29), 55 (39), 44 (100), 43 (29), 41 (65), 39 (32). Anal. ($C_{12}H_{18}O_2$) C, H.

(b) **Functionalization–Rearrangement of *cis-exo*-2,3-Trimethylenenorborn-*endo*-2-ylcarbinol (1).** A solution of 5.0 g (0.030 mol) of the carbinol 1 in 20 mL (0.5 mol) of 99% formic acid was added dropwise with vigorous stirring in a period of 2.5 h to 40 mL of 98% sulfuric acid kept at 0–5 °C. The precipitates formed were filtered, washed with water, dried, and recrystallized from *n*-hexane to give 5.3 g (91% yield) of tricyclo[4.3.1.1^{2,5}]-undecane-1-carboxylic acid (**12**). Melting point, mixture melting point, and IR and mass spectra were identical with those of the sample obtained in the preceding paragraph.

Decarboxylation of the acid **12** was effected in the following manner. A mixture of 0.19 g (0.001 mol) of the acid **12**, 0.72 g (0.0016 mol) of lead tetraacetate, 0.84 g (0.0086 mol) of potassium acetate, and 10 mL of acetic acid was heated under reflux with stirring overnight. The mixture was poured onto 20 mL of water, and extracted with five 10-mL portions of ether. The combined extracts were washed with a saturated sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. The ether was evaporated off, and the residue was purified through preparative VPC to give 0.10 g (48% yield) of 1-acetoxytricyclo[4.3.1.1^{2,5}]undecane (**10a**). IR, ^{1}H NMR, and mass spectra of this sample were identical with those of **10a** obtained by acetylation of the alcohol **9** as described above.

Tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl Chloride (13). To a solution of 46.0 g (0.24 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylic acid (**12**) in 200 mL of benzene was added dropwise 68 mL (0.96 mol) of thionyl chloride at ambient temperature, and the resulting mixture was heated under reflux for 1.5 h. The excess thionyl chloride and the benzene were evaporated off under diminished pressure, and the residue was fractionally distilled in vacuo to give 47.0 g (92% yield) of tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl chloride (**13**): bp 101 °C (1 mm); IR (neat) 3030, 2930, 2880, 1790, 1750, 1480, 990, 860, 840, 740 cm^{-1}. Anal. ($C_{12}H_{17}OCl$) C, H, Cl.

1-(Aminocarbonyl)tricyclo[4.3.1.1^{2,5}]undecane (14). Ammonia gas was bubbled for 15 min at a rate of ca. 200 mL/min through a solution of 10.0 g (0.047 mol) of tricyclo[4.3.1.1^{2,5}]-undecane-1-carbonyl chloride (**13**) in 80 mL of ether kept at 0–5 °C. The precipitates formed were filtered, washed with ether, and tritulated with water. Undissolved materials were filtered, washed throughly with water, and dried in vacuo at ambient temperature. Recrystallization of the solids from benzene–methanol (1:1) afforded 9.7 g (96% yield) of 1-(aminocarbonyl)tricyclo[4.3.1.1^{2,5}]undecane (**14**): mp 173–174 °C; IR (KBr) 3450, 3350, 3300, 3220, 3030, 2980, 2860, 1650, 1640 (sh), 1610, 1480, 1360, 1200, 1120, 1090, 920, 870 cm^{-1}; MS *m/e* (relative intensity) 193 (72, M$^+$), 149 (71), 127 (18), 126 (31), 107 (19), 93 (29), 91 (17), 83 (27), 81 (51), 79 (30), 77 (17), 67 (100), 55 (20), 41 (34), 39 (18). Anal. ($C_{12}H_{19}ON$) C, H, N.

1-(Aminomethyl)tricyclo[4.3.1.1^{2,5}]undecane (15) and Its Hydrochloride 16. A solution of 4.5 g (0.023 mol) of 1-(aminocarbonyl)tricyclo[4.3.1.1^{2,5}]undecane (**14**) in 60 mL of tetrahydrofuran (THF) was added dropwise at ambient temperature to a suspension of 1.5 g (0.04 mol) of lithium aluminum hydride in 90 mL of THF, and the resulting mixture was heated under reflux with efficient stirring for 1.5 h. To the cooled mixture were added successively 1.5 mL of water, 1.5 mL of 3 N sodium hydroxide solution, and 4.5 mL of water. The precipitates were filtered off, and the filtrate was concentrated in vacuo. The residue was fractionally distilled to give 3.2 g (78% yield) of 1-(aminomethyl)tricyclo[4.3.1.1^{2,5}]undecane (**15**): bp 94 °C (0.6 mm); IR (neat) 3390, 3300, 3030, 2900 (br), 1600, 1460, 1370, 1310, 1190, 1050, 980 cm^{-1}; MS *m/e* (relative intensity) 179 (32, M$^+$), 162 (19), 149 (78), 107 (18), 95 (57), 94 (22), 93 (41), 83 (32), 81 (60), 79 (31), 67 (100), 55 (20), 44 (46), 41 (33), 30 (93).

Through a solution of 3.2 g (0.018 mol) of 1-(aminomethyl)-tricyclo[4.3.1.1^{2,5}]undecane (**15**) in 50 mL of ether was bubbled dry hydrogen chloride gas until no more precipitate was formed. The solids were collected by filtration and recrystallized from acetone–methanol (1:1) to give 3.0 g (80% yield) of 1-(aminomethyl)tricyclo[4.3.1.1^{2,5}]undecane hydrochloride (**16**): mp 175.2–176.5 °C; IR (KBr) 3500 (br), 2900 (br), 1600, 1510, 1460, 1380, 990 cm^{-1}; MS *m/e* (relative intensity) 179 (19), 162 (13), 149 (73), 107 (14), 95 (40), 94 (15), 93 (31), 83 (24), 81 (47), 79 (25), 67 (100). Anal. ($C_{12}H_{22}NCl$) C, H, N, Cl.

***N*-Ethyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylmethylurea (17a).** A solution of 0.5 g (0.0028 mol) of 1-(aminomethyl)tricyclo-[4.3.1.1^{2,5}]undecane (**15**) and 0.22 g (0.0031 mol) of ethyl isocyanate in 10 mL of benzene was stirred at ambient temperature for 3 h. The benzene was evaporated off, and the residue was recrystallized from benzene–methanol (2:1) to give 0.58 g (83% yield) of *N*-ethyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylmethylurea (**17a**): mp 120–121 °C; IR (KBr) 3550 (br), 3030, 2920, 2860, 1630, 1580, 1470, 1370, 1260, 1160, 980, 900, 770 cm^{-1}; MS *m/e* (relative intensity) 250 (6, M$^+$), 149 (100), 93 (22), 83 (20), 81 (38), 79 (19), 71 (29), 67 (87), 56 (45), 44 (21), 41 (26), 30 (63). Anal. ($C_{15}H_{26}ON_2$) C, H, N.

***N*-Phenyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylmethylurea (17b).** 1-(Aminomethyl)tricyclo[4.3.1.1^{2,5}]undecane (**15**; 0.5 g, 0.0028 mol) was treated with 0.37 g (0.0031 mol) of phenyl isocyanate in 10 mL of benzene using the same procedure as that for the *N*-ethyl derivative **17a**. The crude product was recrystallized from benzene–methanol (1:1) to give 0.66 g (79% yield) of *N*-phenyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylmethylurea (**17b**): mp 188–189 °C; IR (KBr) 3330, 3030, 2920, 2860, 1640, 1590, 1560, 1500, 1440, 1310, 1240, 1040 980, 900, 760, 720, 690 cm^{-1}; MS *m/e* (relative intensity) 179 (16), 149 (62), 119 (100), 95 (31), 93 (47), 91 (58), 83 (21), 81 (37), 79 (21), 67 (83), 64 (30), 41 (26), 39 (23), 30 (38). Anal. ($C_{19}H_{26}ON_2$) C, H, N.

1-Cyanotricyclo[4.3.1.1^{2,5}]undecane (18). A mixture of 3.0 g (0.016 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (**14**) and 12 mL (0.16 mol) of thionyl chloride was heated under reflux for 4 h. After most of the excess thionyl chloride had been distilled off, the trace amount of thionyl chloride left was removed by azeotropic distillation using 20 mL of benzene. The distillation residue was purified by sublimation under slightly diminished pressure to give 2.3 g (84% yield) of 1-cyanotricyclo[4.3.1.1^{2,5}]-undecane (**18**): mp 109–110 °C; IR (KBr) 3030, 2930, 2860, 2230, 1470, 1290, 1190, 1150, 1120, 980, 910, 860, 800 cm^{-1}; MS *m/e* (relative intensity) 175 (31, M$^+$), 149 (16), 147 (72), 146 (49), 108 (17), 107 (79), 95 (25), 93 (15), 81 (23), 79 (22), 77 (18), 67 (100), 66 (18), 55 (15), 53 (19), 41 (59), 39 (37). Anal. ($C_{12}H_{17}N$) C, H, N.

***N*-Methyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19a).** To 50 mL of a 40% aqueous solution of methylamine kept at 0–10 °C was added dropwise with efficient stirring a solution of 2.5 g (0.012 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl chloride (**13**) in 30 mL of chloroform in a period of 30 min, and the reaction was stirred for another 3 h at the same temperature. The organic layer was separated, and the aqueous layer was extracted once with 20 mL of chloroform. The combined organic layer and extract were washed with 2% hydrochloric acid and then with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from acetone–*n*-hexane (1:1) gave 2.2 g (89% yield) of *N*-methyltricyclo[4.3.1.1^{2,5}]-undecane-1-carboxamide (**19a**): mp 149–150 °C; IR (KBr) 3300, 3050 (sh), 3030, 2930, 2860, 1630, 1530, 1480, 1400, 1290, 1150, 980, 920 cm^{-1}; MS *m/e* (relative intensity) 207 (100, M$^+$), 149 (39), 141 (32), 93 (26), 86 (50), 83 (30), 81 (46), 79 (28), 73 (30), 67 (97), 58 (35), 41 (35). Anal. ($C_{13}H_{21}ON$) C, H, N.

***N*-*n*-Butyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19b).** To a solution of 0.44 g (0.006 mol) of *n*-butylamine in 15 mL of ether was added dropwise with vigorous stirring 0.5 g (0.0024 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl chloride (**13**) dissolved in 5 mL of ether. The reaction was heated under reflux for 1 h. The reaction mixture was poured onto 20 mL of water, and the organic layer was separated. The aqueous layer was extracted with 20 mL of chloroform. The combined organic layer and chloroform extract were washed with 2% hydrochloric acid

and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization of the residue from acetone–*n*-hexane (1:1) gave 0.56 g (93% yield) of *N*-*n*-butyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (**19b**): mp 92–93 °C; IR (KBr) 3350, 3030, 2940 (sh), 2920, 2860, 1630, 1520, 1460, 1420, 1280, 1220, 1150, 1010, 980, 950 cm^{-1}; MS *m/e* (relative intensity) 249 (86, M$^+$), 183 (24), 149 (49), 128 (46), 92 (24), 83 (26), 81 (46), 79 (29), 67 (100), 57 (24), 55 (24), 41 (48). Anal. ($C_{16}H_{27}ON$) C, H, N.

By a similar procedure using 0.5 g (0.0024 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl chloride (**13**) and 0.006 mol of alkylamine were prepared the following *N*-alkylamides.

***N*-*tert*-Butyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19c)**: 90% yield; mp 127–128 °C; IR (KBr) 3330, 3030, 2970 (sh), 2940, (sh), 2920, 2860, 1630, 1530, 1470, 1440, 1380, 1350, 1290, 1230, 1150, 980, 930 cm^{-1}; MS *m/e* (relative intensity) 249 (100, M$^+$), 183 (26), 149 (62), 128 (33), 93 (23), 83 (25), 81 (45), 79 (28), 67 (98), 58 (21), 55 (20), 41 (49). Anal. ($C_{16}H_{27}ON$) C, H, N.

***N*-*n*-Octyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19d)**: 88% yield; mp 69–70 °C; IR (KBr) 3350, 3030, 2950 (sh), 2920, 2850, 1630, 1530, 1460, 1370, 1290, 1270, 1160, 980, 920, 870, 800 cm^{-1}; MS *m/e* (relative intensity) 305 (100, M$^+$), 239 (17), 184 (25), 149 (44), 93 (17), 83 (19), 81 (36), 79 (19), 67 (76), 55 (21), 43 (24), 41 (36). Anal. ($C_{20}H_{35}ON$) C, H, N.

***N*-*n*-Decyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19e)**: 83% yield; mp 58–58.5 °C; IR (KBr) 3330, 3030, 2950 (sh), 2930, 2840, 1630, 1530, 1460, 1380, 1290, 1220, 1160, 990, 930, 870, 800 cm^{-1}; MS *m/e* (relative intensity) 333 (100, M$^+$), 267 (20), 266 (10), 212 (32), 149 (52), 141 (10), 107 (12), 93 (15), 83 (17), 81 (29), 79 (14), 67 (49), 55 (14), 43 (13), 41 (14). Anal. ($C_{22}H_{39}ON$) C, H, N.

***N*-*n*-Dodecyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19f)**: 77% yield; mp 72–73 °C; IR (KBr) 3330, 3030 (sh), 2960, 2930, 2850, 1630, 1530, 1460, 1370, 1290, 1160, 720 cm^{-1}; MS *m/e* (relative intensity) 361 (100, M$^+$), 295 (18), 292 (15), 240 (28), 149 (47), 107 (10), 93 (14), 83 (17), 81 (26), 79 (13), 69 (11), 67 (49), 57 (11), 55 (19), 43 (20), 41 (20). Anal. ($C_{24}H_{43}ON$) C, H, N.

***N*-Cyclohexyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19g)**: mp 161–162 °C; IR (KBr) 3330, 3030, 2980 (sh), 2930, 2840, 1620, 1520, 1480, 1320, 1250, 1140, 980, 890, 840 cm^{-1}; MS *m/e* (relative intensity) 275 (100, M$^+$), 194 (25), 154 (28), 149 (41), 128 (29), 83 (30), 81 (41), 79 (25), 67 (87), 55 (39), 41 (49). Anal. ($C_{18}H_{29}ON$) C, H, N.

***N*-Benzyltricyclo[4.3.1.1^{2,5}]undecane-1-carboxamide (19h)**: mp 153–154 °C; IR (KBr) 3330, 3080 (sh), 3050, 3030, 2920, 2860, 1630, 1600 (sh), 1520, 1490, 1470, 1450, 1410, 1350, 1300, 1280, 1250, 1020, 990, 710, 690 cm^{-1}; MS *m/e* (relative intensity) 283 (100, M$^+$), 217 (32), 162 (20), 149 (40), 93 (21), 91 (86), 83 (22), 81 (41), 79 (26), 67 (83), 55 (19), 41 (34). Anal. ($C_{19}H_{25}ON$) C, H, N.

Methyl Tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20a). A solution of 1.0 g (0.0048 mol) of tricyclo[4.3.1.1^{2,5}]undecane-1-carbonyl chloride (**13**) in 5 mL of ether was added dropwise with stirring to a solution of 0.5 mL (0.012 mol) of methanol and 0.5 g (0.0063 mol) of pyridine in 5 mL of ether, and the reaction was heated under reflux with stirring for 2 h. The reaction mixture was poured onto 10 mL of 5% hydrochloric acid, and the ether layer was separated. The aqueous layer was extracted with two 5-mL portions of ether. The combined ether layer and extracts were washed with a saturated sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent and fractional distillation of the residue afforded 0.91 g (91% yield) of methyl tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (**20a**): bp 115 °C (2 mm); IR (neat) 3030, 2980, 2940, 2010 (sh), 2870, 1730, 1480, 1430, 1340, 1320, 1290, 1250, 1210, 1180, 1150, 1120, 1090, 1070, 1040, 990, 900, 830 cm^{-1}; MS *m/e* (relative intensity) 208 (22, M$^+$), 149 (81), 148 (22), 141 (72), 109 (16), 107 (18), 93 (29), 91 (18), 83 (19), 81 (61), 79 (33), 77 (17), 67 (100), 55 (16), 53 (15), 41 (38), 39 (19). Anal. ($C_{13}H_{20}O_2$) C, H.

The following esters (**20b–f**) of tricyclo[4.3.1.1^{2,5}]undecane-1-carboxlyic acid were prepared in the same way as for the methyl ester **20a**, except that the alcohols corresponding to the esters were used in place of methanol.

***n*-Butyl tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20b)**: 93% yield; bp 142–143 °C (3 mm); IR (neat) 3030, 2960 (sh), 2930, 2880, 1730, 1470, 1380, 1320, 1290, 1260, 1220, 1180, 1150, 1080, 1040, 990 cm^{-1}; MS *m/e* (relative intensity) 250 (22, M$^+$), 183 (26), 149 (90), 127 (30) 93 (23), 83 (20), 81 (47), 79 (25), 67 (100), 41 (42). Anal. ($C_{16}H_{26}O_2$) C, H.

***n*-Octyl tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20c)**: 89% yield; bp 167 °C (2 mm); IR (neat) 3030, 2960 (sh), 2930, 2860, 1730, 1470, 1380, 1290, 1250, 1220, 1180, 1150, 1070, 1040, 990 cm^{-1}; MS *m/e* (relative intensity) 306 (20, M$^+$), 195 (36), 194 (21), 149 (91), 127 (40), 93 (20), 83 (20), 81 (42), 79 (21), 67 (100), 55 (26), 43 (31), 41 (45). Anal. ($C_{20}H_{34}O_2$) C, H.

Cyclopentyl tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20d): 88% yield; 135 °C (1 mm); IR (neat) 3030, 2960 (sh), 2930, 2870, 1730, 1480, 1450, 1350, 1320, 1290, 1250, 1170, 1150, 1090, 1070, 1040, 990, 960 cm^{-1}; MS *m/e* (relative intensity) 262 (3, M$^+$), 195 (37), 194 (55), 149 (100), 127 (29), 93 (19), 83 (18), 81 (38), 79 (21), 69 (19), 67 (97), 41 (47). Anal. ($C_{17}H_{26}O_2$) C, H.

Cyclohexyl tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20e): 95% yield; bp 158–159 °C (1 mm); IR (neat) 3030, 2070 (sh), 2930, 2860, 1720, 1460, 1440, 1340, 1310, 1280, 1250, 1180, 1150, 1090, 1070, 1040, 1020, 980, 920 cm^{-1}; MS *m/e* (relative intensity) 276 (6, M$^+$), 195 (70), 194 (61), 149 (78), 127 (28), 93 (18), 83 (37), 82 (14), 81 (41), 79 (20), 67 (100), 55 (39), 41 (41). Anal. ($C_{18}H_{28}O_2$) C, H.

***cis-exo*-5,6-Trimethylenenorborn-*exo*-2-yl (*exo*-tricyclo[5.2.1.0^{2,6}]dec-*exo*-8-yl) tricyclo[4.3.1.1^{2,5}]undecane-1-carboxylate (20f)**: 96% yield; bp 162–163 °C (1 mm); IR (neat) 3030, 2930, 2860, 1720, 1470, 1440, 1250, 1180, 1150, 1130, 1090, 1070, 980 cm^{-1}; MS *m/e* (relative intensity) 328 (3, M$^+$), 195 (20), 150 (13), 149 (100), 135 (69), 134 (16), 93 (16), 83 (10), 81 (25), 79 (19), 67 (86), 66 (24), 55 (12), 41 (23). Anal. ($C_{22}H_{32}O_2$) C, H.

1-Acetamidotricyclo[4.3.1.1^{2,5}]undecane (21). (a) Ritter Reaction of 1-Bromotricyclo[4.3.1.1^{2,5}]undecane (5). To a solution of 1.18 g (0.0051 mol) of the bromide **5** in 10 mL (0.19 mol) of acetonitrile kept at 0–5 °C was added dropwise with stirring 2.5 mL of 95% sulfuric acid in a period of 30 min. The reaction was further stirred at ambient temperature overnight. The reaction mixture was poured onto 20 g of ice–water and extracted with three 10-mL portions of ether. The combined ether extracts were washed with a saturated sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. Evaporation of the ether and recrystallization of the residue from acetone–*n*-hexane (1:1) gave 0.98 g (92% yield) of 1-acetamidotricyclo[4.3.1.1^{2,5}]undecane (**21**): mp 138–139 °C; IR (KBr) 3330, 3070, 3030, 2990 (sh), 2960, 2940, 2870, 1650, 1550, 1470, 1370, 1350, 1300, 1130, 1110, 1050, 990, 960 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ_C 18.92 (t), 24.30 (q), 25.34 (t), 26.25 (t), 28.46 (t), 31.06 (t), 31.58 (t), 33.92 (t and d), 40.15 (d), 43.79 (d), 55.23 (s), 169.19 (s); MS *m/e* (relative intensity) 207 (14, M$^+$), 164 (45), 139 (12), 138 (100), 122 (39), 96 (81), 94 (10), 79 (10), 67 (12), 43 (25), 41 (19). Anal. ($C_{13}H_{21}ON$) C, H, N.

(b) Functionalization–Rearrangement of *cis-exo*-2,3-Trimethylenenorborn-*endo*-2-ylcarbinol (1). To a solution of 10.0 g (0.060 mol) of the carbinol **1** in 120 mL (2.2 mol) of acetonitrile kept at 0–5 °C was added with efficient stirring 25 mL of 95% sulfuric acid in a period of 45 min. After being stirred for an additional 5 h at ambient temperature, the reaction mixture was poured onto 200 g of ice–water and extracted with three 100-mL portions of ether. The combined extracts were washed with a saturated sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization of the residue from acetone–*n*-hexane (1:1) gave 12.2 g (98% yield) of 1-acetamidotricyclo[4.3.1.1^{2,5}]undecane (**21**): mp 138–139 °C. The melting point was not depressed on admixture with the sample of **21** obtained in the preceding paragraph. The IR, ^{13}C NMR, and mass spectra of both samples were also identical.

(c) Acetamidation through Bromine–Sulfuric Acid Oxidation of Tricyclo[4.3.1.1^{2,5}]undecane (2). A solution of 2.5 g (0.017 mol) of the hydrocarbon **2** in 50 mL (0.92 mol) of acetonitrile kept below 10 °C was mixed with 13 mL of 95% sulfuric acid. To the resulting solution kept at 10–15 °C was added dropwise 13.6 g (0.085 mol) of bromine in a period of 10 min, and the reaction was stirred at ambient temperature for an additional 24 h. The reaction mixture was poured onto 300 mL of a saturated sodium thiosulfate solution cooled to 5 °C and extracted with four 50-mL portions of ether. The combined ether extracts were

treated similarly as in the preceding paragraphs to give 2.64 g (75% yield) of the acetamide **21**. The sample was in all respects identical with those obtained by the methods described above.

1-Aminotricyclo[4.3.1.1^{2,5}]undecane (22). A solution of 13.0 g (0.063 mol) of 1-acetamidotricyclo[4.3.1.1^{2,5}]undecane (**21**) and 8.4 g (0.21 mol) of sodium hydroxide in 160 mL of diethylene glycol was heated under reflux for 16 h. The mixture was poured onto 500 mL of water and extracted with three 200-mL portions of ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated off, and the residue was fractionally distilled. Collection of the fraction boiling at 65–66 °C (1 mm) afforded 9.4 g (90% yield) of 1-aminotricyclo[4.3.1.1^{2,5}]undecane (**22**): colorless crystals; mp 113–114 °C; IR (KBr) 3340, 3250, 3030, 2920, 2860, 1580, 1460, 1360, 1310, 1150, 1120, 910, 810 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ_C 20.14 (t), 25.46 (t), 26.96 (t), 28.67 (t), 32.65 (t), 35.17 (d), 36.02 (t), 38.17 (t), 39.84 (d), 48.49 (d), 50.80 (s); MS *m/e* (relative intensity) 122 (19), 97 (8), 96 (100), 94 (7), 79 (5), 69 (3), 67 (6), 57 (6), 42 (5), 41 (8), 39 (5), 28 (3). Anal. ($C_{11}H_{19}N$) C, H, N.

1-Aminotricyclo[4.3.1.1^{2,5}]undecane Hydrochloride (23). Dry hydrogen chloride was bubbled through a solution of 1.0 g (0.0067 mol) of 1-aminotricyclo[4.3.1.1^{2,5}]undecane (**22**) in 15 mL of ether until no more precipitate was formed. The solids were filtered and recrystallized from acetone–methanol (2:1) to give 1.1 g (91% yield) of 1-aminotricyclo[4.3.1.1^{2,5}]undecane hydrochloride (**23**): mp >300 °C; IR (KBr) 3300–3050 (br), 2940, 2870, 1620, 1600, 1590, 1510, 1470, 1380, 1330 cm^{-1}. Anal. ($C_{11}H_{20}NCl$) C, H, N, Cl.

Methyl *N*-1-Tricyclo[4.3.1.1^{2,5}]undecylcarbamate (24a). To a solution of 1.0 g (0.0061 mol) of 1-aminotricyclo[4.3.1.1^{2,5}]-undecane (**22**) and 0.65 g (0.0064 mol) of triethylamine in 10 mL of benzene was added dropwise with stirring 0.60 g (0.0063 mol) of methyl chloroformate in 2 mL of benzene. The reaction was stirred overnight at ambient temperature. The reaction mixture was washed with two 10-mL portions of water and dried over anhydrous sodium sulfate. The benzene was evaporated off, and the residue was recrystallized from *n*-hexane to give 1.1 g (81% yield) of methyl *N*-1-tricyclo[4.3.1.1^{2,5}]undecylcarbamate (**24a**): mp 305–306 °C; IR (KBr) 3300, 3030, 2950, 2930, 2870, 1630, 1550, 1460, 1300 cm^{-1}; MS *m/e* (relative intensity) 148 (29), 123 (13), 122 (62), 120 (15), 97 (13), 96 (100), 81 (12), 79 (20), 67 (27), 41 (31), 39 (18), 28 (17). Anal. ($C_{13}H_{21}O_2N$) C, H, N.

Ethyl *N*-1-Tricyclo[4.3.1.1^{2,5}]undecylcarbamate (24b). 1-Aminotricyclo[4.3.1.1^{2,5}]undecane (**22**; 1.0 g, 0.0061 mol) was allowed to react in a similar procedure as for the methyl carbamate **24a** with 0.68 g (0.0063 mol) of ethyl chloroformate in the presence of 0.65 g (0.0064 mol) of triethylamine to give 1.27 g (88% yield) of ethyl *N*-1-tricyclo[4.3.1.1^{2,5}]undecylcarbamate (**24b**): mp 285–285.5 °C; IR (KBr) 3350, 3030, 2930, 2860, 1630, 1550, 1510, 1470, 1290, 1120, 990 cm^{-1}; MS *m/e* (relative intensity) 122 (54), 97 (21), 96 (100), 94 (18), 79 (13), 67 (16), 57 (15), 42 (13), 41 (23), 39 (13), 30 (12). Anal. ($C_{14}H_{23}O_2N$) C, H, N.

***N*-Ethyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylurea (25a).** Reaction of 0.5 g (0.0033 mol) of 1-aminotricyclo[4.3.1.1^{2,5}]undecane (**22**) with 0.3 g (0.0042 mol) of ethyl isocyanate in 10 mL of benzene at ambient temperature overnight and recrystallization of the crude product from benzene–*n*-hexane (1:1) afforded 0.71 g (91% yield) of *N*-ethyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylurea (**25a**): mp 155–156 °C; IR (KBr) 3360 (br), 3030, 2980 (sh), 2940, 2900 (sh), 2870, 1640, 1560, 1470, 1310, 1260, 1220, 1200, 1160 cm^{-1}; MS *m/e* (relative intensity) 148 (27), 122 (94), 96 (100), 79 (18), 78 (17), 71 (22), 67 (40), 56 (35), 42 (15), 41 (28), 39 (17), 30 (42). Anal. ($C_{14}H_{24}ON_2$) C, H, N.

***N*-Phenyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylurea (25b).** Use of 0.5 g (0.0042 mol) of phenyl isocyanate in place of the ethyl isocyanate in the above procedure gave 0.91 g (97% yield) of *N*-phenyl-*N'*-1-tricyclo[4.3.1.1^{2,5}]undecylurea (**25b**): mp 206–207 °C; IR (KBr) 3350, 3030, 2980, 2950, 2920, 2870, 1650, 1600, 1550, 1500, 1440, 1320, 1280, 1250, 1040, 760, 690 cm^{-1}; MS *m/e* (relative intensity) 122 (49), 119 (65), 96 (100), 94 (12), 93 (26), 91 (33), 79 (11), 67 (20), 65 (11), 64 (20), 41 (19), 39 (18). Anal. ($C_{18}H_{24}ON_2$) C, H, N.

1-Aminobicyclo[3.3.1]nonane Hydrochloride (26). Hydrolysis of 1.81 g (0.01 mol) of 1-acetamidobicyclo[3.3.1]nonane[15] with 4.0 g (0.05 mol) of sodium hydroxide in 20 mL of diethylene glycol at reflux overnight gave 1.1 g (79% yield) of 1-aminobicyclo[3.3.1]nonane: mp 123–124 °C; IR (KBr) 3300 (br), 2920, 2850, 1490, 1450, 1440 (sh), 1360, 1310, 1130, 1110, 960, 950, 900, 860, 820 cm^{-1}; MS *m/e* (relative intensity) 139 (11, M$^+$), 97 (21), 96 (100), 82 (11), 79 (10), 69 (13), 57 (46), 42 (15), 41 (18), 39 (11). Anal. ($C_9H_{17}N$) C, H, N.

Neutralization of the amine with hydrogen chloride gas in ether gave the corresponding hydrochloride **26**: IR (KBr) 3300 (br), 2960, 2930, 2860, 2700–2500, 2050, 1720, 1610, 1540, 1530, 1490, 14708 1360, 1320, 1220, 1080, 980 cm^{-1}. Anal. ($C_9H_{18}NCl$) C, H, N, Cl.

3-Amino-4-homobrendane (3-Aminotricyclo[5.2.1.0^{3,8}]decane) Hydrochloride (27). 3-Acetamido-4-homobrendane[15] (1.93 g, 0.01 mol) was hydrolyzed by the same procedure as in the preceding paragraph to give 1.6 g (85% yield) of 3-amino-4-homobrendane: mp 119–120 °C; IR (KBr) 3350, 3300, 2930, 2850, 2840 (sh), 1590, 1470, 1440, 1350, 1300, 1260, 1200, 1140, 1110, 1090, 1010, 900, 880, 840, 820, 760 cm^{-1}. Anal. ($C_{10}H_{17}N$) C, H, N.

Addition of hydrogen chloride to the amine in ether solvent afforded 3-amino-4-homobrendane hydrochloride (**27**), mp 229–230 °C. Anal. ($C_{10}H_{18}NCl$) C, H, N, Cl.

1-Deuteriotricyclo[4.3.1.1^{2,5}]undecane (6). To a mixture comprising 3.4 g (0.015 mol) of 1-bromotricyclo[4.3.1.1^{2,5}]undecane (**5**), 25 mL of *O*-deuterio-*tert*-butyl alcohol, and 20 mL of tetrahydrofuran was added 1.2 g (0.17 mol) of lithium in small portions, and the reaction was heated under reflux for 5 h. The mixture was diluted successively with 10 mL of methanol and 50 mL of water and extracted with five 50-mL portions of *n*-hexane. The combined hexane extracts were washed with 2% hydrochloric acid and water and dried over anhydrous magnesium sulfate. The solvent was evaporated off, and the residue was purified by sublimation under slightly diminished pressure to give 1.8 g (81% yield) of 1-deuteriotricyclo[4.3.1.1^{2,5}]undecane (**6**): mp 58–59 °C; IR (KBr) 3030, 2960, 2870, 2170, 2140, 2130 (ν_{C-D}), 1490, 1450, 1310, 1200, 1160, 1120, 1090, 1060, 980, 790 cm^{-1}; ^{13}C NMR ($CDCl_3$) total proton-decoupled spectrum δ_C 18.41, 26.28, 27.94 and 27.89, 28.39, 31.76, 33.15 and 35.52 (t, J = 20 Hz, C-1), 41.21 and 41.15; MS *m/e* (relative intensity) 151 (66, M$^+$), 123 (100), 122 (42), 109 (33), 83 (33), 82 (42), 81 (81), 80 (62), 79 (36), 68 (55), 67 (78), 41 (45).

***cis-exo*-2,3-Trimethylenenorborn-*endo*-2-yldideuteriocarbinol (7).** Methyl *cis-exo*-2,3-trimethylenenorbornane-*endo*-2-carboxylate[6,21] (3.9 g, 0.02 mol) was reduced with 0.84 g (0.02 mol) of lithium aluminum deuteride in 15 mL of ether under reflux for 8 h. The reaction mixture was treated in the usual manner[4–6] to afford 3.3 g (97% yield) of *cis-exo*-2,3-trimethylenenorborn-*endo*-2-yldideuteriocarbinol (**7**): mp 76–77 °C; IR (KBr) 3380 (br), 2980 (sh), 2950, 2890, 2870, 2220, 2190, 2090, 2070 (ν_{C-D}), 1490, 1470, 1450, 1370, 1290, 1260 1230, 1140, 1130, 1110, 1060, 1040, 990, 980, 970, 860, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8–2.2 (complex m); ^{13}C NMR ($CDCl_3$) total proton-decoupled spectrum δ_C 23.84, 25.30, 28.18, 32.64, 34.56, 34.76, 41.42, 51.78, 55.39, 66.18 (quintet, J = 22 Hz, methylene C); MS *m/e* (relative intensity) 150 (50), 136 (12), 135 (100), 107 (12), 98 (10), 93 (17), 91 (11), 81 (14), 79 (20), 77 (10), 67 (36), 66 (10), 41 (10).

10,10-Dideuteriotricyclo[4.3.1.1^{2,5}]undecane (8). A mixture of 1.0 g (0.0060 mol) of *cis-exo*-2,3-trimethylenenorborn-*endo*-2-yldideuteriocarbinol (**6**), 30 mL of *n*-pentane, and 10 mL of 95% sulfuric acid was stirred vigorously at ambient temperature for 1 h. The pentane layer was separated, washed with a saturated sodium bicarbonate solution and water, and dried over anhydrous calcium chloride. Evaporation of the solvent and purification of the residue by sublimation under slightly diminished pressure gave 0.24 g (26% yield) of 10,10-dideuteriotricyclo[4.3.1.1^{2,5}]-undecane (**8**): mp 57.5–58.5 °C; IR (neat) 3030, 2980 (sh), 2930, 2870, 2220, 2190, 2120 (ν_{C-D}), 1490, 1470, 1350, 1310, 1250, 1200, 1170, 1090, 1040, 970, 940, 880 cm^{-1}; ^{13}C NMR ($CDCl_3$) total proton-decoupled spectrum δ_C 18.41, 27.89, 28.39, 31.77, 32.90, 41.09 (t, J = 1 Hz, C-2 and C-5);[22] MS *m/e* (relative intensity) 152 (42, M$^+$), 124 (100), 109 (25), 95 (29), 83 (32), 82 (39), 81 (71), 80 (58), 79 (27), 69 (31), 68 (48), 67 (65), 66 (27), 41 (39).

References and Notes

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(22) The signal for C-10 was hidden in the background noise because it was split into a quintet, so that the peak heights became as low as those of noise signals.

3-[(1,2,3-Thiadiazol-5-ylthio)methyl]cephalosporins[1]

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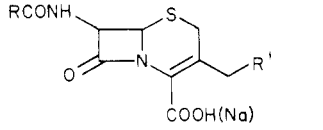
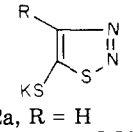
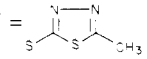
The syntheses of ten 3-[(1,2,3-thiadiazol-5-ylthio)methyl]cephalosporins, made by displacement of the 3′-acetoxy group by the novel thiol derivatives, potassium 1,2,3-thiadiazole-5-thiolate and dipotassium 1,2,3-thiadiazole-4-carboxylate-5-thiolate, are described. Several of the compounds showed good in vitro antibacterial activity against both Gram-positive and Gram-negative organisms. The subcutaneous in vivo activities against *Staphylococcus aureus* were generally less than that of cefazolin. Four of the compounds were administered orally and all were active; the 7β-(thiophen-2-acetamido) and 7β-(D-2-amino-2-phenylacetamido)-3-[(1,2,3-thiadiazol-5-ylthio)methyl] compounds were equally active by either route, with a PD_{50} of ca. 1 mg/kg.

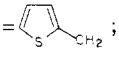
One of the more important reactions in the preparation of cephalosporin antibiotics is the displacement, by nucleophiles, of the allylic acetoxy group at C_3. A wide range of heteroaromatic thiols have been used in the reaction, and some of the products have shown enhanced activity against Gram-negative bacteria,[2] depending on the nature of the heterocycle and the substituent at C_7. Among those compounds which have reached advanced testing or clinical use are compounds derived from displacement of the acetoxy group with 5-methyl-1,3,4-thiadiazole-2-thiol [e.g., cefazolin (**1a**)[3]], 1-methyl-1,2,3,4-tetrazole-5-thiol,[4] and 1,2,3-triazole-5-thiol.[5] Recent work in these laboratories[6] has led to the synthesis of the novel 1,2,3-thiadiazole-5-thiol derivatives **2a** and **2b**. It was of interest to determine the antibacterial activities of cephalosporins incorporating these previously inaccessible groups at the 3 position.





2a, R = H
b, R = COOK

1a, R =  ; R′ = 

b, R =  ; R′ = $OCOCH_3$

c, R = $C_6H_5CH(NH_2)$; R′ = $OCOCH_3$

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