# Notes

## Stereochemical Analogs of a Muscarinic, Ganglionic Stimulant. 3. 2,3-Substituted Bicyclo[2.2.1]hept-5-enes and -heptanes Related to 4-[*N*-(3-Chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium Chloride (McN-A-343)[1,†]

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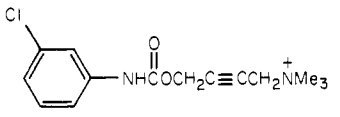
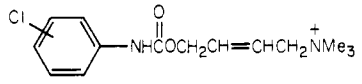
Preparation of analogs of 4-[*N*-(3-chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium chloride (1, McN-A-343), the isomeric 2-trimethylammoniomethyl-3-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene iodides (10–13), and the corresponding -bicyclo[2.2.1]heptane iodides (14–17) are reported. None of the compounds demonstrated ganglion-stimulating activity similar to 1 or antagonized the effects of 1.

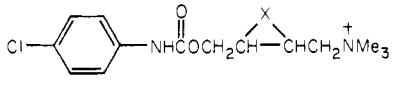
McN-A-343, 4-[*N*-(3-chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium chloride (1), has been shown to possess unique ganglion-stimulant properties through muscarinic (atropine-sensitive) mechanisms at both sympathetic and parasympathetic ganglia.[2-5] In earlier studies concerning stereochemical aspects of the action at sympathetic ganglia, we demonstrated that trans olefinic analogs with either a 3- or 4-chlorophenyl substituent on the carbamate nitrogen, compounds **2** and **4**, retained activity, but the corresponding cis olefins **3** and **5** did not.[1b,6] Also, in the analogous epoxides, this activity was retained only in trans isomer **6**, but not in cis isomer **7**. Activity was also absent in both the *trans*- and *cis*-cyclopropanes **8** and **9**. Because of these observations, we chose to prepare related stereochemical analogs of **1** incorporated in the bicyclo[2.2.1]heptane system. Specifically, these are the four isomeric 2-trimethylammoniomethyl-3-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene iodides **10–13** and saturated bicyclo[2.2.1]heptane analogs **14–17**.



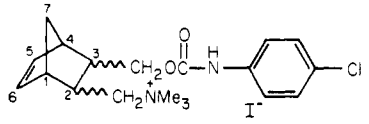
1 (McN-A-343)



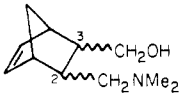
| trans | cis |
|---|---|
| **2**, 3-Cl | **3**, 3-Cl |
| **4**, 4-Cl | **5**, 4-Cl |



| trans | cis |
|---|---|
| **6**, X = O | **7**, X = O |
| **8**, X = $CH_2$ | **9**, X = $CH_2$ |



| cis | |
|---|---|
| **10**, 2-endo-3-endo | **14**, 5,6-dihydro |
| **11**, 2-exo-3-exo | **15**, 5,6-dihydro |
| trans | |
| **12**, 2-exo-3-endo | **16**, 5,6-dihydro |
| **13**, 2-endo-3-exo | **17**, 5,6-dihydro |



| cis | trans |
|---|---|
| **18**, 2-endo-3-endo | **20**, 2-exo-3-endo |
| **19**, 2-exo-3-exo | **21**, 2-endo-3-exo |

Necessary starting materials, the isomeric 2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]-hept-5-enes (**18–21**) were available by reported methods.[7] The cis tertiary amino alcohols **18** and **19** were readily obtained by $LiAlH_4$ reduction of the isomeric dimethylamine salts of *cis*-2-(*N*,*N*-dimethylcarboxamido)-3-carboxybicyclo[2.2.1]hept-5-enes. The trans amino alcohols **20** and **21** were obtained by hydride reduction [$NaH_2Al(OCH_2CH_2OCH_3)_2$] of the isomeric *trans*-2-(*N*,*N*-dimethylcarboxamido)-3-carbomethoxybicyclo-[2.2.1]hept-5-enes.[7]

The cis amino alcohols were first converted to the corresponding quaternary ammonium salts using methyl iodide and then to carbamate esters **10** and **11** with 4-chlorophenyl isocyanate. Earlier experience in the related *cis*-butene system[1b,6] dictated this sequence of steps. In *cis*-2-butene systems, decomposition of carbamate esters of the tertiary amines was noted, probably due to intramolecular attack of the amine on the carbamoyl carbon. Trans compounds **12** and **13** were prepared by the same set of reactions, except in opposite order, i.e., carbamate formation followed by conversion to the quaternary ammonium salt with methyl iodide.

The saturated analogs **14–17** of all four compounds were prepared from the olefins **10–13** by catalytic hydrogenation. The stereochemistry of compounds **10–13** was characterized and substantiated using NMR spectra spin–spin decoupling experiments performed on the respective amino alcohol percursors **18–21**.[7]

The eight compounds (**10–17**) were screened for ganglion-stimulant activity by measuring blood pressure responses in cats.[6] None of the compounds showed pressor activity like that of **1**, at any dose tested (up to 1000

† Dedicated to the memory of Edward E. Smissman.

μg/kg). No depressor effects were observed. In addition, none of the compounds antagonized the pressor response elicited by 1.

These results further demonstrate the sensitivity of the pressor response of 1 to changes or additions in its basic hydrocarbon skeleton. The observed lack of activity of compounds 10–17 is consistent with the earlier observation of a required electron-rich center between C-2 and C-3 to provide muscarinic, ganglion-stimulant activity.[1b]

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded using Varian A-60 and T-60 spectrometers using tetramethylsilane as internal standards. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England. Where analyses are indicated by the symbols of the elements, analytical results obtained for these elements were ±0.4% of theoretical values.

**2-*endo*-Trimethylammoniomethyl-3-*endo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene Iodide (10).** A solution of 360 mg (2.0 mmol) of 2-*endo*-dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (**18**)[7] in 5 ml of $Et_2O$ was treated with 1.20 g (8.5 mmol) of $CH_3I$ and the reaction allowed to stand overnight at room temperature. The white precipitate was collected by suction filtration and washed with $Et_2O$ to give 600 mg (94%) of the quaternary salt: mp 214–216° dec.

To a stirred mixture of 160 mg (0.5 mmol) of the crude quaternary ammonium salt and 1.0 ml of pyridine was added 390 mg (2.5 mmol) of 4-chlorophenyl isocyanate. The reaction was stirred at room temperature overnight. The reaction mixture was then treated with 10 ml of $Et_2O$ and the white precipitate collected by suction filtration. Crystallization from MeOH–$Et_2O$ afforded 180 mg (77%) of white crystals: mp 228–230° dec. Anal. ($C_{19}H_{26}ClIN_2O_2$) C, H, N.

**2-*exo*-Trimethylammoniomethyl-3-*exo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene Iodide (11).** Compound 11 was prepared from 2-*exo*-dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (**19**)[7] by a method similar to that used for preparation of 10. The crude quaternary salt, mp 180–182° dec, was obtained in 87% yield.

From 180 mg (0.56 mmol) of the quaternary ammonium salt and 390 mg of 4-chlorophenyl isocyanate was obtained 200 mg of 11 (76%) as light tan crystals: mp 205–206° dec. Anal. ($C_{19}H_{26}ClIN_2O_2$) C, H, N.

**2-*exo*-Trimethylammoniomethyl-3-*endo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene Iodide (12).** To a stirred solution of 350 mg (1.9 mmol) of 2-*exo*-dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]-ept-5-ene (**20**)[7] in 10 ml of anhydrous $Et_2O$ was added a solution of 470 mg (3.1 mmol) of 4-chlorophenyl isocyanate in 5 ml of $Et_2O$. The reaction was stirred at room temperature for 24 hr and then the $Et_2O$ was removed by a stream of $N_2$ at room temperature. The residue was redissolved in benzene and the insoluble *N*,*N*′-di(4-chlorophenyl)urea removed by suction filtration. The benzene was removed by rotary evaporation to yield 650 mg (~100%) of the crude amine as a colorless oil which was used without further purification.

A solution of 600 mg (1.8 mmol) of the crude amine in 10 ml of benzene was treated with 2.30 g (16.0 mmol) of $CH_3I$ and the reaction mixture allowed to stand at room temperature for 24 hr. The white precipitate was collected by suction filtration and crystallized from MeOH to afford 820 mg (96%) of white granular crystals: mp 255–257° dec. Anal. ($C_{19}H_{26}ClIN_2O_2$) C, H, N.

**2-*endo*-Trimethylammoniomethyl-3-*exo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]hept-5-ene Iodide (13).** A solution of 425 mg (2.8 mmol) of 4-chlorophenyl isocyanate in 5 ml of anhydrous $Et_2O$ was added to a solution of 300 mg (1.7 mmol) of 2-*endo*-dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (**21**)[7] in 10 ml of $Et_2O$. The reaction mixture was allowed to stand at room temperature for 48 hr and then the $Et_2O$ was removed by a stream of $N_2$ at room temperature. The residue was redissolved in benzene and the insoluble *N*,*N*′-di(4-chlorophenyl)urea removed by suction filtration. The benzene was removed by rotary evaporation to give 540 mg (98%) of the crude amine as a colorless oil which was used without further purification.

A solution of 540 mg (1.6 mmol) of the crude amine in 10 ml of benzene was treated with 2.30 g (16.0 mmol) of $CH_3I$ and the reaction allowed to stand at room temperature for 24 hr. The white precipitate was collected by suction filtration and crystallized from a MeOH–$Et_2O$ mixture to afford 640 mg (83%) of white crystals: mp 236–237° dec. Anal. ($C_{19}H_{26}ClIN_2O_2$) C, H, N.

**2-*endo*-Trimethylammoniomethyl-3-*endo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]heptane Iodide (14).** A solution of 200 mg (0.4 mmol) of olefin 10 in 30 ml of MeOH was added to a hydrogenation bottle previously charged with 50 mg of 5% Pd/C catalyst and 10 ml of MeOH. This mixture was hydrogenated at an initial $H_2$ pressure of 2.8 kg/cm$^2$ for 2 hr and then filtered through a Celite pad. The MeOH filtrate was concentrated with a stream of $N_2$ at room temperature and the product crystallized from this MeOH solution affording 180 mg (90%) of 14: mp 234–236° dec. Anal. ($C_{19}H_{28}ClIN_2O_2$) C, H, N.

**2-*exo*-Trimethylammoniomethyl-3-*exo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]heptane Iodide (15).** Compound 15 was prepared from 11 in 77% yield by the method described for preparation of 14: mp 190–192° dec. Anal. ($C_{19}H_{28}ClIN_2O_2$) C, H, N.

**2-*exo*-Trimethylammoniomethyl-3-*endo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]heptane Iodide (16).** Compound 16 was prepared from 12 in 85% yield by the method described for preparation of 14: mp 259–260.5° dec. Anal. ($C_{19}H_{28}ClIN_2O_2$) C, H, N.

**2-*endo*-Trimethylammoniomethyl-3-*exo*-[*N*-(4-chlorophenyl)carbamoyloxymethyl]bicyclo[2.2.1]heptane Iodide (17).** Compound 17 was prepared from 13 in 82% yield by the method described for preparation of 14: mp 239–240° dec. Anal. ($C_{19}H_{28}ClIN_2O_2$) C, H, N.

**Pharmacological Testing.** The compounds were screened for effects on blood pressure in anesthetized cats as previously described.[6]

## References and Notes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