# A Comparison of the Antiserotonin, Antihistamine, and Anticholinergic Activity of Cyproheptadine with Analogues Having Furan Nuclei Fused to the 10,11-Vinylene Bridge

David C. Remy,* Andrew W. Raab, Kenneth E. Rittle, Edward L. Engelhardt,

*Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486*

Alexander Scriabine, and Victor J. Lotti

*Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486.* *Received November 18, 1976*

A series of cyproheptadine derivatives having furan nuclei fused to the 10,11-vinylene bridge has been prepared. None of the compounds retain the potent antiserotonin and antihistaminic actions of cyproheptadine. 1-Methyl-4-(1-methyl-8*H*-dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)piperidine (**7**), 1-methyl-4-(1,3-dihydro-1-oxo-8*H*-[3,4:6,7]cyclohepta[1,2-*c*]furan-8-ylidene)piperidine (**10**), and its reduction product **11** retained the peripheral anticholinergic activity of cyproheptadine.

The drug cyproheptadine (**1**) is a potent serotonin and histamine antagonist with anticholinergic properties. Structure–activity relationships for a series of compounds related to cyproheptadine have been studied by Engelhardt et al.[1] Structural variations in this series included replacement of the 10,11-vinylene bridge by oxygen, sulfur, an ethane bridge, or by joining the benzene rings together directly in a fluorene system. The present report deals with a continuation of this study and, in particular, describes the synthesis and pharmacological evaluation of cyproheptadine derivatives having furan nuclei condensed on the 10,11-vinylene bridge.

Using the general procedures developed by Tochtermann for the addition of substituted furans to dibenzocycloalkynes[2] and for retro-Diels–Alder reactions on the resulting adducts,[3] 10-bromocyproheptadine[4] (**2**) was found to condense with furan and 2-methylfuran to give **3** (64%) and **4** (43%), respectively. Each of these compounds undergoes a retro-Diels–Alder reaction when treated with tetraphenylcyclopentadienone in refluxing xylene affording **6** (97%) and **7** (62%), respectively.

The dimethoxydihydrofuran **9** was prepared by methanolysis of the product arising from 1,4 addition of bromine to **6**.[5] Suprisingly, acid hydrolysis of this cyclic acetal did not give the expected dialdehyde but rather gave the furanone **10** in 86% yield. The intermediate **9** apparently undergoes a preferential acid-catalyzed methanol elimination followed by acid hydrolysis of the resulting enol ether.[6]

The antiserotonin, antihistaminic, and anticholinergic properties of the compounds reported in Table I were compared to those of cyproheptadine (**1**). None of these compounds retained any appreciable antiserotonin activity. At the highest dose tested (10 mg/kg sc), all of the compounds were at least 500 times less active than **1** (**1**, antiserotonin $ED_{50}$ 0.02 mg/kg sc; 95% confidence limits 0.01–0.03). Also, with the exception of rather weak antihistaminic activity seen with compounds **10** ($ED_{50}$ 9.7) and **11** ($ED_{50}$ 12.5), none of the compounds retained the potent antihistaminic activity of **1** (**1**, $ED_{50}$ 0.05).

Rather weak peripheral anticholinergic activity was observed for **6**. The introduction of a methyl group on the furan ring (**7**) increased this activity to that observed for **1**, but hydrogenation of the furan ring (**13**) or N-demethylation (**8**) resulted in loss of this activity. The furanone **10** and its reduction product **11** retained the peripheral anticholinergic activity of **1**.

Table I. Anticholinergic and Antihistaminic Activities

| Compd | Anticholinergic $ED_{1.5}$ dose range,[a,b] mg/kg ip | Antihistaminic $ED_{50}$, mg/kg ip[b] (95% confidence limits) |
|---|---|---|
| 3·HCl·0.5$C_2H_5OH$ | Inactive at 324 | Inactive at 12.5 |
| 4 | Inactive at 324 | Inactive at 12.5 |
| 5 | Inactive at 324 | Inactive at 12.5 |
| 6 | 36–108 | Inactive at 12.5 |
| 7 | 4–12 | Inactive at 12.5 |
| 8 | Inactive at 324 | Inactive at 12.5 |
| 10·$C_2H_2O_4$·$CH_3OH$ | <4[c] | 9.7 (4.3–22.1) |
| 11 | 4–12 | 12.5 (4.7–33.0) |
| 12·HCl·0.5$C_2H_5OH$ | Inactive at 324 | Inactive at 12.5 |
| 13·$C_2H_2O_4$ | Inactive at 324 | Inactive at 12.5 |
| 1·HCl·$H_2O$ | 4–12 | 0.05 (0.03–0.08) |

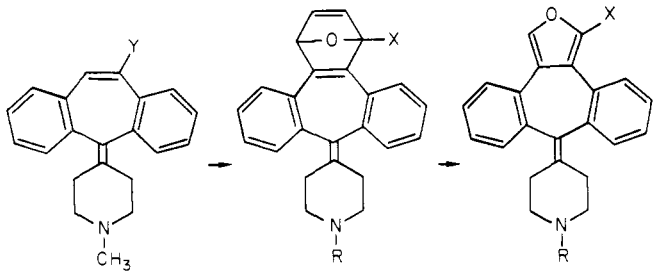
[a] The $ED_{1.5}$ dose range is defined as the dose levels producing dilation of the pupil to 1.5 μm units in less than (lower limit) and more than (upper limit) 50% of the mice. [b] See Experimental Section. [c] 100% of the mice exhibited pupillary dilation exceeding 15 μm units at the lowest dose level tested.

## Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. The IR (Perkin-Elmer Model 21 spectrophotometer) and NMR spectra [Varian T-60, $(CH_3)_4Si$] were consistent with all assigned structures.

**1-Methyl-4-(4,4a-dihydro-1,4-epoxy-1*H*-tribenzo[*a*,*c*,*e*]cyclohepten-9-ylidene)piperidine (3).** A mixture of 30.0 g (0.0816 mol) of **2**, 84 g (0.75 mol) of potassium *tert*-butoxide, 300 mL of furan, and 750 mL of $Et_2O$ was stirred and refluxed gently for 13 days. The bulk of the furan and ether was removed under reduced pressure, and the residue, after dilution with 2 L of $H_2O$, was extracted with $Et_2O$. The $Et_2O$ phase was washed with water, dried ($MgSO_4$), and filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue, dissolved in a minimum amount of EtOH, was treated with ethanolic HCl. On cooling 18.52 g (74%) of 3·HCl·0.5$C_2H_5OH$ crystallized. NMR supports the hemiethanol solvate structure. An analytical sample was prepared by recrystallization from ethanol: mp 220–222 °C. Anal. ($C_{25}H_{23}NO$·HCl·0.5$C_2H_5OH$) C, H, Cl, N.

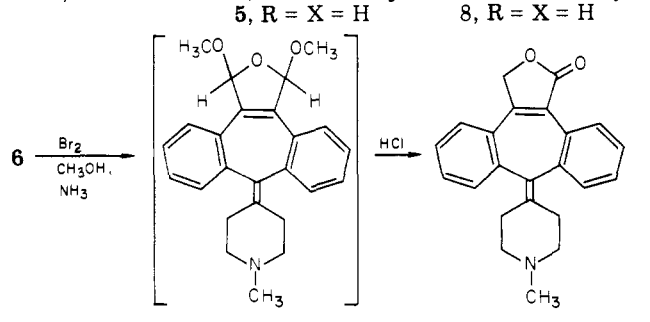
**1-Methyl-4-(1-methyl-4,4a-dihydro-1,4-epoxy-1*H*-tribenzo[*a*,*c*,*e*]cyclohepten-9-ylidene)piperidine (4).** To a solution of 10.0 g (0.0273 mol) of **2** in 50 mL of dry $Et_2O$ and 25 mL of 2-methylfuran was added 3.4 g (0.030 mol) of potassium *tert*-butoxide. The mixture was stirred and refluxed gently for 10 days after which time it was diluted with $H_2O$. The $Et_2O$ phase was separated and the aqueous phase was reextracted with $Et_2O$. The combined $Et_2O$ phases were washed with water, dried



1, Y = H
2, Y = Br

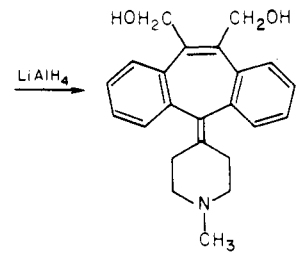
3, R = $CH_3$; X = H
4, R = X = $CH_3$
5, R = X = H

6, R = $CH_3$; X = H
7, R = X = $CH_3$
8, R = X = H

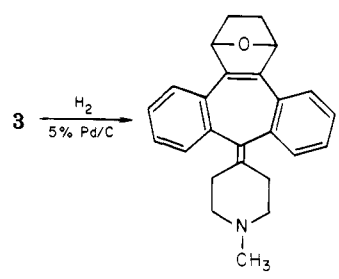


9

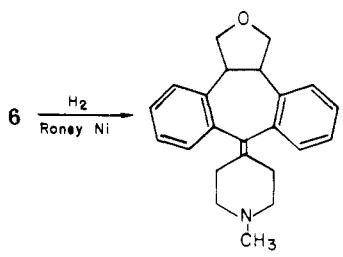
10



11



12



13

(MgSO$_4$), and filtered, and the filtrate was evaporated to dryness under reduced pressure to give 4.0 g (43%) of crystalline material that was recrystallized from MeCN to give analytically pure **4**, mp 175–177 °C. Anal. ($C_{26}H_{25}NO$) C, H, N.

**1-Methyl-4-(8*H*-dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)piperidine (6).** A solution of 12.3 g (0.035 mol) of the free base **3** and 13.7 g (0.0355 mol) of tetraphenylcyclopentadienone in 500 mL of xylene (bp 139–140 °C) was stirred and refluxed for 22 h. To the cooled solution was added slowly 200 mL of 6 N HCl. The white crystalline precipitate that formed was removed by filtration and was washed with benzene and $Et_2O$. This salt was converted to the free base form using $Na_2CO_3$ solution. The resulting solid weighed 11.09 g (97%) and was recrystallized from MeOH to give analytically pure **6**, mp 147–148 °C. Anal. ($C_{23}H_{21}NO$) C, H, N.

**1-Methyl-4-(1-methyl-8*H*-dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)piperidine (7).** A solution of 2.00 g (0.0054 mol) of **4** and 2.16 g (0.0056 mol) of tetraphenylcyclopentadienone in 60 mL of xylene was stirred and refluxed for 20 h. The reaction was worked up, as described for the preparation of **6**, to give 1.15 g (62%) of crystalline product. Recrystallization from MeOH gave 0.90 g (48%) of **7**, mp 80–86 °C (gel). Anal. ($C_{24}H_{23}NO$) C, H, N.

**1-Methyl-4-(1,3-dihydro-1-oxo-8*H*-[3,4:6,7]cyclohepta[1,2-*c*]furan-8-ylidene)piperidine (10).** A solution of 3.80 g (0.0106 mol) of **6** in a mixture of 35 mL of MeOH and 45 mL of $Et_2O$ was cooled to −40 °C using a dry ice–acetone bath. The solution was stirred and a cold (0 °C) solution of 3.80 g of $Br_2$ in 35 mL of MeOH was added dropwise over 10 min. After stirring for an additional 30 min, $NH_3$ was bubbled into the solution until it was just basic to pH paper. The solution was kept overnight in a freezer. The light yellow solution was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and was washed with $H_2O$. The $CHCl_3$ was removed under reduced pressure, and the residue was mixed with 100 mL of 1 N HCl and heated on a steam bath for 30 min. The solution was cooled and $Na_2CO_3$(s) was added until the solution was slightly basic. The precipitate that formed was extracted into $CHCl_3$. This $CHCl_3$ extract was washed with $H_2O$, dried (MgSO$_4$), and filtered, and the solvent was removed under reduced pressure to give 3.11 g (86%) of **10** as a TLC (fluorescent alumina–$CHCl_3$) homogeneous viscous oil. The hydrogen oxalate salt was prepared and recrystallized from MeOH to afford analytically pure **10**·$C_2H_2O_4$·$CH_3OH$: mp 155–158 °C; IR (KBr disk) 1750 cm$^{-1}$ (C=O); NMR ($Me_2SO$-$d_6$) δ 2.2–3.4 [m, piperidine ring H's with peaks at 2.65 ($NCH_3$) and 3.18 ($CH_3O$), 14 H], 5.49 (d of d, $J$ = 11 and 9 Hz, methylene group of lactone, 2 H), 6.58 (s, $CH_3OH$ and $CO_2H$, $D_2O$ exchangeable), 7.2–8.2 (m, aromatic, 8 H). Anal. ($C_{23}H_{21}NO_2$·$C_2H_2O_4$·$CH_3OH$) C, H, N.

**5-(1-Methyl-4-piperidylidene)-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dimethanol (11).** To a slurry of 3.61 g (0.095 mol) of $LiAlH_4$ in 25 mL of $Et_2O$ was added dropwise a solution of 2.75 g (0.008 mol) of **10** in 25 mL of THF. The mixture was stirred 3 days at room temperature and then was refluxed for 4 h. Water (4 mL) was added to the mixture, followed by the addition of 12 mL of 5 N NaOH. The supernatant liquid was decanted and the residue was extracted with hot THF and then with hot benzene. The original supernatant and the extracts were combined and the solvent was removed under reduced pressure to afford 0.80 g (29%) of crude **11**, mp 198–201 °C. Three recrystallizations of this material from benzene gave analytically pure **11**, mp 204–205 °C. Anal. ($C_{23}H_{25}NO_2$) C, H, N.

**4-(4,4a-Dihydro-1,4-epoxy-1*H*-tribenzo[*a*,*c*,*e*]cyclohepten-9-ylidene)piperidine (5).** Over a period of 45 min, 9.65 g (0.0274 mol) of **3** was added to 275 mL of ethyl chloroformate. The mixture was stirred and refluxed for 24 h. The bulk of the ethyl chloroformate was removed under reduced pressure. The solid residue was triturated with benzene and was collected by filtration to give 7.63 g (67.5%) of the intermediate urethane derivative, mp 224–226 °C. A mixture of 2.50 g (0.0061 mol) of this urethane and 10.0 g (0.018 mol) of KOH in 60 mL of *n*-BuOH was stirred and refluxed for 2 h. The *n*-BuOH was removed under reduced pressure. The resulting solid was triturated with water and collected by filtration. Two recrystallizations from benzene afforded analytically pure **5**, mp 237–241 °C. Anal. ($C_{24}H_{21}NO$) C, H, N.

**4-(8*H*-Dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)-piperidine (8).** Using the same procedure as in the preparation of **5**, 2.00 g (0.0061 mol) of **6** was N-demethylated to give 1.81 g (98%) of **8**, mp 153–157 °C. Recrystallization from ether afforded an analytical sample, mp 153–157 °C. Anal. ($C_{22}H_{19}NO$) C, H, N.

**1-Methyl-4-(2,3,4,4a-tetrahydro-1,4-epoxy-1*H*-tribenzo[*a*,*c*,*e*]cycloheptan-9-ylidene)piperidine (12).** A solution of 1.0 g (0.0028 mol) of **3** in 100 mL of EtOAc was hydrogenated over 0.1 g of 5% Pd/C for 5 min at 33 psi. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue, dissolved in a minimum amount of EtOH, was treated with ethanolic HCl. On cooling, 0.9 g (89%) of **12** hydrochloride hemiethanol solvate crystallized. NMR supports the hemiethanol solvate structure. An analytical sample, re-

crystallized from ethanol, had mp 258–259 °C. Anal. ($C_{25}H_{25}NO \cdot HCl \cdot 0.5C_2H_5OH$) C, H, N.

**1-Methyl-4-(1,3,3a,12b-tetrahydro-8*H*-dibenzo[*a*,*e*]furo[3,4-*c*]cyclohepten-8-ylidene)piperidine (13).** A solution of 4.0 g (0.012 mol) of **6** in 40 mL of EtOH was hydrogenated over 4.0 g of Raney nickel for 6 h at 150 °C and 2000 psi. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give 3.90 g of a viscous oil. This material readily formed a hydrogen oxalate salt (4.0 g) from EtOH. Two recrystallizations of this material from EtOH gave **13**·$C_2H_2O_4$, mp 197–200 °C. Anal. ($C_{23}H_{25}NO \cdot C_2H_2O_4$) C, H, N.

**Biological Test Methods.** Antiserotonin and antihistamine effects of the test compounds were determined with methods similar to those described by Engelhardt et al.[1] Antiserotonin activity was evaluated in male Sprague–Dawley rats of 160–220-g body weight. The drugs were tested for their effect on edema induced by injection of serotonin in the hind paw. The test drugs, suspended in 1% methylcellulose, were administered subcutaneously (sc) 30 min prior to the injection of serotonin (base), also sc, into the hind paw. Saline, 0.05 mL, was injected sc into the other hind paw which served as the basis for comparison. Thirty minutes after serotonin, the animals were sacrificed and both feet removed and weighed. The results were expressed as the dose necessary to produce 50% inhibition of the weight gain due to serotonin. Each compound was used at three doses with four rats per dose level. Anihistamine activity was evaluated in guinea pigs of the Duncan–Hartley strain of either sex and 200–300-g body weight. The test compounds, suspended in 1% methylcellulose, were administered intraperitoneally (ip). Thirty minutes later the animals were placed in individual chambers and exposed to histamine aerosol spray (0.5% base) for 3 min. The effectiveness of the test compounds was determined as the dose necessary to protect 50% of the animals from death caused by histamine aerosol-induced bronchoconstriction. The test compounds were used at four dose levels with five animals per dose.

Anticholinergic activity was evaluated by the ability of the compound to dilate the pupil of the mouse. Compounds were administered to female Carworth Farms (CF-1) mice at doses of 4, 12, 36, 108, and 324 mg/kg ip, at five mice per dose level. The diameter of the pupil was measured with the aid of an ocular micrometer 55 min after treatment with the test compound using a method previously described.[7] The $ED_{1.5}$ dose range is defined as the dose levels producing dilation of the pupil to 15 μm units in less than (lower limit) and more than (upper limit) 50% of the mice.

**Acknowledgment.** The authors are indebted to Mr. Lars Flataker and Mr. Carl Ludden for their technical assistance in the biological evaluation of the test compounds. Analytical data were provided by Mr. Y. Lee and his associates.

## References and Notes

(1) E. L. Engelhardt, H. C. Zell, W. S. Saari, M. E. Christy, C. D. Colton, C. A. Stone, J. M. Stavorski, H. C. Wenger, and C. T. Ludden, *J. Med. Chem.*, **8**, 829 (1965).
(2) (a) W. Tochtermann, K. Oppenländer, and U. Walter, *Chem. Ber.*, **97**, 1318 (1964); (b) R. W. Hoffman in "Dehydrobenzene and Cycloalkanes, Organic Chemistry—A Series of Monographs", Vol. 11, A. T. Blomquist, Ed., Academic Press, New York, N.Y., 1967, pp 304, 347.
(3) W. Tochtermann, C. Franke, and D. Schafer, *Chem. Ber.*, **101**, 3122 (1968).
(4) J. D. Prugh, U.S. Patent 3968115 (1976).
(5) (a) J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950); (b) N. Elming in "Advances in Organic Chemistry", Vol. 2, Interscience, New York, N.Y., 1960, p 67.
(6) P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.*, **7**, 460 (1966).
(7) C. A. Stone, K. L. Meckelnburn, and M. L. Torchiana, *Arch. Int. Pharmacodyn. Ther.*, **117**, 419 (1958).

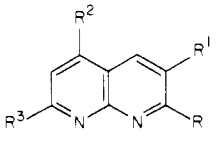
# 2,3-Disubstituted 1,8-Naphthyridines as Potential Diuretic Agents. 2.[1] 5,7-Dimethyl Derivatives

Edward M. Hawes,* Dennis K. J. Gorecki, and Ronald G. Gedir

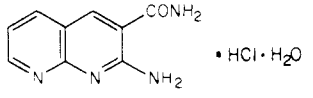
*College of Pharmacy, University of Saskatchewan, Saskatoon, S7N OWO, Canada.* *Received November 12, 1976*

A variety of 2,3-disubstituted 5,7-dimethyl-1,8-naphthyridines was synthesized and tested in saline-loaded rats for their diuretic properties. The 2-amino-3-carbomethoxy and four 2-amino-3-*N*-alkylcarbamoyl compounds exhibited significant activity as measured by volume output; however, they were generally less potent than the corresponding 5,7-unsubstituted naphthyridines previously reported. Further screening without saline-loading indicated that the amides lacked kaliuretic properties; while, interestingly, the ester lacked an effect on either urine volume or sodium excretion.

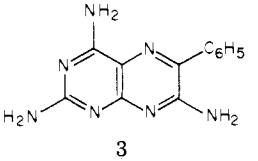
An earlier paper disclosed that a series of 2,3-disubstituted 1,8-naphthyridines (**1a**) possessed in many cases potent diuretic activity with lack of a kaliuretic effect.[1] This study prompted the investigation of the corresponding 5,7-dimethylnaphthyridines (**1b**). Dimethyl substitution was chosen in view of the enhanced lipophilicity, minimal change in electronic and steric effects, and easier synthetic accessibility in comparison to **1a**. Screening comparison was made to 2-amino-1,8-naphthyridine-3-carboxamide hydrochloride monohydrate (**2**), the most potent member of **1a**, and triamterene (**3**).



1a, $R^2 = R^3 = H$
b, $R^2 = R^3 = CH_3$



2



3

**Chemistry.** The general synthetic schemes developed for 2,3-disubstituted 1,8-naphthyridines were suitable for their 5,7-dimethyl analogues reported in Table I.[1] The Friedländer condensation of 2-amino-4,6-dimethylnicotinaldehyde (**4**) with various methylene compounds afforded compounds **5–22** as outlined in Scheme I. The condensation was accomplished with piperidine or, in the case of less activated methylene, with sodium hydroxide as catalyst. Experimental variation in the previously described[2] preparation of the starting material (**4**) from *N*-(2-amino-4,6-dimethylnicotinoyl)-*N'*-*p*-tolylsulfonyl-