theoretical values. Ir spectra were determined on a Perkin-Elmer 237B grating spectrophotometer; $^1$H NMR spectra were determined on JEOL MH-100 or C-60 NMR spectrometers; uv spectra were determined using a Perkin-Elmer 402 ultraviolet–visible spectrophotometer.

**Materials.** 2- and 4-chloro-3,5-dinitrobenzoic acid were obtained from Aldrich Chemical Co., Inc. 6-MP was obtained as the monohydrate from Aldrich Chemical Co., Inc., and from the National Cancer Institute.

**Esters.** All esters used were prepared from the chlorodinitrobenzoic acid chlorides. The acid chlorides were prepared from the acid by treatment under reflux with thionyl chloride. The appropriate acid chloride was then treated with a slight excess of the alcohol and warmed for several hours. Cooling the reaction mixture afforded solid ester which was recrystallized from methanol to yield crystalline products having sharp melting points and appropriate $^1$H NMR spectra.

**Purine Derivatives.** All of the purine adducts were prepared by the following procedure with the exception of the high molecular weight hexadecyl compounds. A sample of the sodium salt of 6-MP was dissolved in a small portion of dry, freshly distilled dimethylformamide. To the resulting solution was added a slight molar excess (10–20%) of the appropriate chloro ester. The reaction mixture immediately turned light orange and proceeded to lighten in color to a bright yellow solution upon stirring at room temperature for approximately 18 h. The cloudy mixture was cooled for several minutes and filtered through a fine-fritted filter to remove most of the NaCl. The filtrate was then evaporated under partial vacuum at 50° to yield a thick dark-orange oil. The oil was treated with a few milliliters of methanol and a large portion of $Et_2O$. The resulting yellow powder was filtered and washed with several portions of water, followed by several portion of $Et_2O$. The product was dried under vacuum at 62°. All compounds were characterized by melting point, ir, $^1$H NMR, uv, and analysis.

For the hexadecyl compounds, after evaporation yielded the oil, it was treated with a few milliliters of methanol and a large portion of water. After stirring, the resulting mixture was filtered and the powder washed with a few small portions of ether and larger portions of water. These compounds were dried and characterized in the same manner as the others.

**Partition Coefficients.** Partition coefficients for the compounds **4a–e** and **5a–e** were determined in an octanol–water system, each phase being saturated with the other solvent. Solutions of the compounds to be partitioned were prepared from freshly distilled octanol. In partitioning these samples gentle inversion was carried out at room temperature (25 ± 5°) for 15 min. Longer mixing times generally gave no significantly different results. The volume ratio of the two solvents and the concentration of the sample were chosen such that the uv absorption of the partitioned sample fell in the range of 0.2–1.0 absorbance units using a 1-cm cell. The samples were taken from the octanol layer of the system after adequate separation had been accomplished and were centrifuged for 15–30 min. These were then used to record the uv spectrum from which the partitioned concentrations could be determined. The partition coefficients were calculated as $P = C_{octanol}/C_{water}$. $P$ values were determined for each compound in duplicate using various concentrations of sample and at least two different solvent volume ratios.

Log $P$ values for the methyl, ethyl, propyl, isopropyl, and butyl ester fell in the range from 1.2 to 1.6. The value of 1.9 for the cetyl derivative was significantly greater as expected. All of the esters were found to be considerably more lipophilic than 6-MP. The determined log $P$ for the parent drug was 0.8 (lit.[8] 1.0).

**Biological Testing.** The curve for each of the compounds **4** and **5** (Figure 1) represents the results from two tests. The treatment schedule involved one ip dose per day for 5 days beginning with the first day of infection. The compounds were administered as suspensions in water–Tween mixtures.

**Acknowledgment.** The authors wish to thank the Drug Development Branch, Division of Cancer Treatment (National Cancer Institute), the American Cancer Society (Grant No. C1-118), the Vermont Regional Cancer Center, and Professor James Holland, Mount Sinai School of Medicine, for their interest and/or support of this research. Biological screening was done by A. D. Little (Boston, Mass.) under contract with the Drug Evaluation Branch, Drug Research and Development, National Cancer Institute.

## References and Notes

(1) W. H. Oldendorf, *Proc. Soc. Exp. Biol. Med.*, **147**, 813 (1974).
(2) D. G. Johns, D. Farquhar, B. A. Chabner, M. K. Wolpert, and R. H. Adamson, *Experientia*, **29**, 1104 (1973).
(3) G. B. Elion, S. Bieber, and G. H. Hitchings, *Cancer Chemother. Rep.*, **14**, 93 (1961).
(4) G. B. Elion, S. Callahan, R. W. Rundles, and G. H. Hitchings, *Cancer Res.*, **23**, 1207 (1963).
(5) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(6) J. Miller, "Reaction Mechanisms in Organic Chemistry", Monograph 8, Elsevier, Amsterdam, 1968.
(7) G. B. Elion, S. Bieber, and G. H. Hitchings, *Cancer Chemother. Rep.*, 8, 36 (1960).
(8) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).

# Some 10-Substituted 5-Ethyl-10-dialkylaminoalkyl-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines as Potential Antiarrhythmic Agents

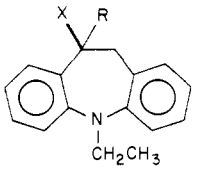
Charles R. Ellefson* and John W. Cusic

*Department of Chemical Research, Searle Laboratories, Division of G. D. Searle & Company, Chicago, Illinois 60680.*
*Received March 15, 1976*

A series of 10-dialkylaminoalkyl-10-(cyano-, carboxamido-, aminomethyl-, and acyl-)-5-ethyl-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines was prepared by alkylation and further reaction of 10-cyano-10,11-dihydro-5-ethyl-5*H*-dibenz[*b*,*f*]azepine (**5**). Several of these compounds showed good activity in three assays for antiarrhythmic potential.

In the course of some alterations of the 5*H*-dibenz[*b*,*f*]azepine ring system, we prepared 10-cyano-10,11-dihydro-5-ethyl-5*H*-dibenz[*b*,*f*]azepine (**5**). The activated proton at the 10 position thus made 10-alkylated products readily accessible. This report describes the preparation and the antiarrhythmic activity of some 10-dialkylaminoalkyl-10-(cyano-, carboxamido-, aminomethyl-, and acyl-)-10,11-dihydro-5-ethyl-5*H*-dibenz[*b*,*f*]azepines. The 10-carboxamido compounds may be seen as analogues of the potent antiarrhythmic agent disopyramide[1] (Norpace),

Table I




| Compd | X | R | Mp, °C | Crystn solvent | Yield, % | Formula | Analyses |
|---|---|---|---|---|---|---|---|
| 5 | CN | H | 127-129 | Abs EtOH | 77 | $C_{17}H_{16}N_2$ | C, H, N |
| 7a | CN | $(CH_2)_2N(Me)_2 \cdot HCl$ | 243-246 | Abs EtOH | 75 | $C_{21}H_{26}ClN_3$ | C, H, N |
| 7b | CN | $(CH_2)_2N(Et)_2 \cdot HCl$ | 211.5-213.5 | Abs EtOH | 51 | $C_{23}H_{30}ClN_3$ | C, H, N |
| 7c | CN | $(CH_2)_2N(i\text{-}Pr)_2 \cdot HCl$ | 230-233 | Abs EtOH-$Et_2O$ | 91 | $C_{25}H_{34}ClN_3$ | C, H, N |
| 7d | CN | $(CH_2)_3N(Me)_2 \cdot HCl$ | 217-218.5 | Abs EtOH-$Et_2O$ | 90 | $C_{22}H_{28}ClN_3$ | C, H, N |
| 6 | $CONH_2$[a] | $H \cdot CH_3OH$ | 70-95[b] | MeOH | 81 | $C_{18}H_{22}N_2O_2$[c] | C, H, N |
| 8a | $CONH_2$[a] | $(CH_2)_2N(Me)_2$ | 148.5-151 | EtOAc-hexane | 63 | $C_{21}H_{27}N_3O$ | C, H, N |
| 8b | $CONH_2$[a] | $(CH_2)_2N(Et)_2$ | 95-97 | Hexane | 58 | $C_{23}H_{31}N_3O$ | C, H, N |
| 8c | $CONH_2$[a] | $(CH_2)_2N(i\text{-}Pr)_2$ | 103.5-105.5 | Hexane | 62 | $C_{25}H_{35}N_3O$ | C, H, N |
| 8d | $CONH_2$[d] | $(CH_2)_3N(Me)_2 \cdot 0.5(CO_2H)_2$ | 118-120 | MeOH-EtOAc | 51 | $C_{23}H_{30}N_3O_3$ | C, H, N |
| 8e | $CONH_2$[d] | $(CH_2)_2N(Me)CH_2Ph \cdot (CO_2H)_2$ | 153-156 | MeOH-EtOAc | 41 | $C_{29}H_{33}N_3O_5$ | C, H, N |
| 9a | $CH_2NH_2$ | $(CH_2)_2N(Et)_2 \cdot 2HBr$ | 234-236.5 | Abs EtOH-$Et_2O$ | 56 | $C_{23}H_{35}Br_2N_3$ | C, H, N |
| 9b | $CH_2NH_2$ | $(CH_2)_2N(i\text{-}Pr)_2 \cdot 2HBr$ | 239-240 | Abs EtOH | 51 | $C_{25}H_{39}Br_2N_3$ | C, H, N |
| 10a | $COCH_2CH_3$ | $(CH_2)_2N(Me)_2 \cdot HCl \cdot H_2O$ | 182-183 | Abs EtOH-$Et_2O$ | 83 | $C_{23}H_{33}ClN_2O_2$ | C, H, N |
| 10b | COPh | $(CH_2)_2N(Me)_2 \cdot HCl \cdot H_2O$ | 213-216 | Abs EtOH-$Et_2O$ | 76 | $C_{27}H_{33}ClN_2O_2$ | C, H, N |

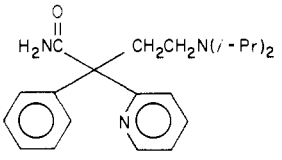
[a] Prepared by method A. [b] Melts over broad range with loss of MeOH. [c] Contains mole of MeOH of solvation. [d] Prepared by method B.

Table II. Activity against Induced Ventricular Arrhythmias[a]

| Compd | Aconitine ($n$)[b] | Ouabain MED[c] | Ouabain $n$[b] | Ouabain Duration[d] | Coronary ligation MED[c] | Coronary ligation $n$[b] | Coronary ligation Duration[d] |
|---|---|---|---|---|---|---|---|
| Quinidine[e] | A (2/2) | 7.5 | 4/5 | >30 | 12.8 | 9/11 | 23 |
| $1 \cdot H_3PO_4$[e] | A (2/3) | 6.6 | 5/6 | >30 | 6.9 | 13/14 | 29 |
| 5 | I (0/2) | | | | | | |
| 7a | A (2/2) | I | 0/2 | | | | |
| 7b | I (0/2) | 20 | 2/3 | 22 | 7.5 | 2/2 | 16 |
| 7c | A (2/2) | I | 0/2 | | | | |
| 7d | A (2/2) | 15 | 2/2 | 15 | I | 0/2 | |
| 6 | A (2/2) | I | 0/2 | | | | |
| 8a | I (0/2) | 10 | 2/3 | 31 | I | 0/2 | |
| 8b | A (2/2) | 5 | 1/1 | 40 | L | | |
| 8c | A (2/2) | 12.5[f] | 2/2 | 30 | L | | |
| 8d | I (1/3) | 15 | 2/2 | 35 | 7.5 | 2/2 | 25 |
| 8e | A (2/2) | 15 | 2/2 | 15 | 12.5 | 2/2 | 20 |
| 9a | I (0/2) | I | 1/3 | | | | |
| 9b | A (2/3) | 15 | 2/2 | 20 | L | | |
| 10a | A (2/2) | I | 0/2 | | | | |
| 10b | A (2/2) | 10 | 2/2 | 30 | I | 0/2 | |

[a] Ratings: active (A), inactive (I), or lethal (L) under the test conditions described in the Experimental Section. [b] $n$ = no. of tests active/no. of tests. [c] Activity expressed as average minimum effective dose (mg/kg) in the intact dog. [d] Minutes. [e] See also ref 7. [f] Lethal 1/3.

$1 \cdot H_3PO_4$, in which an extra carbon atom has been inserted between the two aryl groups and the two aryl groups have been connected via an amino bridge.




1

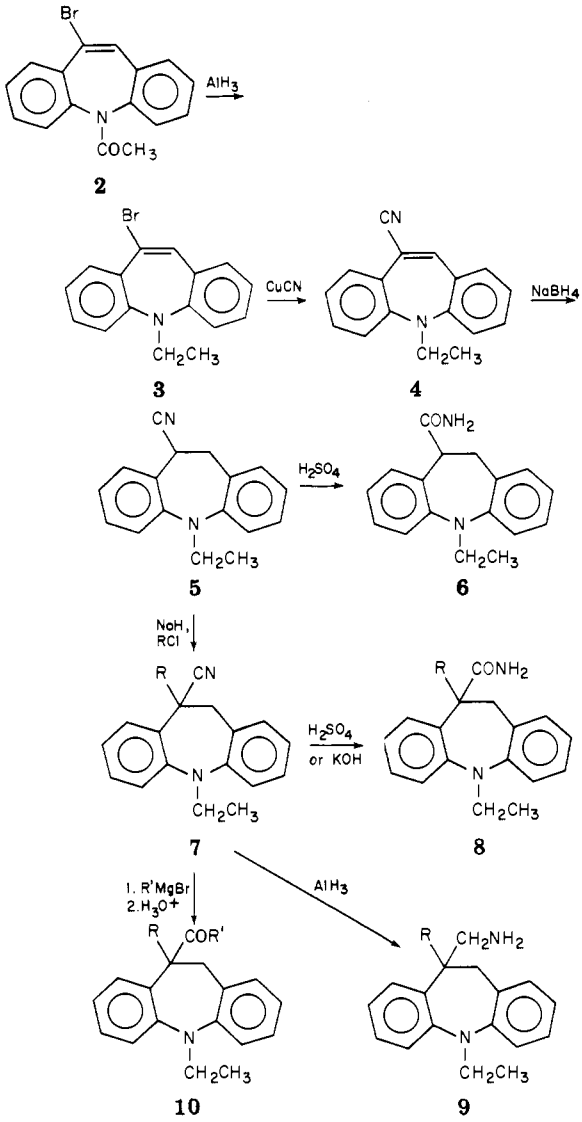
**Chemistry.** The title compounds were prepared from **5** as outlined in Scheme I. Intermediate **5** was prepared from 5-acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine[2] (**2**) as shown. For the alkylation procedure (**5** → **7**) a mixture of the alkylating agent, sodium hydride, and **5** in anhydrous THF containing approximately 15% dry DMF was stirred at reflux until TLC (10% v/v EtOAc–$C_6H_6$ on neutral alumina) indicated absence of **5**. Generally a green-yellow color indicated formation of the carbanion and reaction was complete when the color disappeared. Often additional NaH was necessary to effect initiation of the reaction.

Hydrolysis to the carboxamide (**8**) was accomplished by two procedures. Heating the nitrile **7** in concentrated $H_2SO_4$ was a facile procedure for this conversion. However, lower than anticipated yields were probably due to some sulfonation of the aromatic rings producing by-products that were washed away in the work-up. An alternative method was the use of KOH in refluxing EtOH containing a small amount (3–4%) of $H_2O$.

Aluminum hydride[3] was an efficient reagent for both the reduction of the 5-acetyl substituent of **2** and the reduction of the cyano group of **7** to the primary amine **9**. Details of the physical properties of the compounds **6–10** are given in Table I. Details of experimental procedures for representatives of each class of compounds (**7–10**) are given in the Experimental Section.

**Biological Results.** Test results for these compounds and two standards, $1 \cdot H_3PO_4$ and quinidine, in three assays

Scheme I




for antiarrhythmic activity are given in Table II. In the assay against aconitine induced ventricular arrhythmia in the isolated rabbit heart,[4] a compound was rated active if it caused a 50% or greater reduction in the ventricular rate for drug concentrations up to 40 mg/l. Active compounds were then assayed against ouabain-induced ventricular arrhythmia in the intact anesthetized dog.[5] A compound was rated active if there was a return to normal sinus rhythm for a period of 15 min or more in half or more of the dogs tested at a dose of 20 mg/kg or less. Finally, compounds found active in the second assay were tested against ventricular arrhythmia induced by Harris two-stage coronary ligation.[6] They were rated active if there was observed a 25% or greater reduction in ectopic beats for at least 10 min in half or more of the dogs tested.

Compounds of all four classes (**7–10**) possessed some antiarrhythmic activity. The compounds whose structures had an X group (Table I) closely resembling **1** (e.g., the carboxamides **8b–e** and the nitriles **7b,d**) exhibited the most consistent and most potent activity. The effect of placing an extra carbon atom between the two aryl groups of **1** and connecting the two aryl groups via an amino bridge has been that antiarrhythmic activity has been retained. However, even though some of these compounds had antiarrhythmic activity similar[7] to **1** in the coronary ligation assay, there seemed to be a considerable degree of toxicity associated with them in this model.

## Experimental Section

NMR (Varian A-60d), ir (Beckman IR-12), and uv (Beckman DK2) spectra where applicable were consistent with all structures. Analytical results as indicated by symbols for the elements were within 0.4% of the theoretical values. Melting points were determined in open capillary tubes in a Mel-Temp apparatus or on a Fisher-Johns hot stage and are uncorrected.

**10-Bromo-5-ethyl-5*H*-dibenz[*b,f*]azepine (3).** Concentrated $H_2SO_4$ (0.80 ml, 15 mmol) was added slowly to 30 ml of 1.0 M lithium aluminum hydride in THF at 0 °C. After stirring the mixture for 1 h a solution of 6.3 g (20 mmol) of **2**[2] in 20 ml of dry THF was added slowly. Stirring at 0 °C was continued for 1 h, and then the following solutions were added successively: 6 ml of 33% $H_2O$ in THF, 3 ml of 25% NaOH, and 3 ml of $H_2O$. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure leaving 5.8 g of crude yellow solid that was recrystallized from *i*-PrOH yielding 5.0 g (83%) of yellow crystals: mp 147.5–148.5 °C; uv $\lambda_{max}^{MeOH}$ 257.5 nm ($\epsilon$ 27300) and 282.5 (6400). Anal. ($C_{16}H_{14}BrN$) C, H, N.

**10-Cyano-5-ethyl-5*H*-dibenz[*b,f*]azepine (4).** A mixture of 2.4 g (8 mmol) of **3** and 1.5 g (17 mmol) of cuprous cyanide in 20 ml of DMF was stirred at reflux for 1.5 h. After cooling to ambient temperature the solution was poured into 100 ml of concentrated $NH_3$ and this mixture was extracted with $CH_2Cl_2$. The extracts were washed with 1 N HCl and $H_2O$ and were dried over anhydrous $MgSO_4$. Concentration of the $CH_2Cl_2$ solution to dryness under reduced pressure produced a solid that was recrystallized from 95% EtOH, yielding 1.8 g (91%) of yellow-gold crystals: mp 144–146.5 °C; ir $\nu$ ($CHCl_3$) 2222 and 2228 $cm^{-1}$; uv $\lambda_{max}^{MeOH}$ 220 nm ($\epsilon$ 19700), 258 (27800), and 296 (7900). Anal. ($C_{17}H_{14}N_2$) C, H, N.

**10-Cyano-10,11-dihydro-5-ethyl-5*H*-dibenz[*b,f*]azepine (5).** A mixture of 2.5 g (10 mmol) of **4** in 100 ml of absolute EtOH was warmed to 70 °C and 3.8 g (100 mmol) of $NaBH_4$ was added in portions. Heating was continued for 1 h and then the solvent was distilled off under reduced pressure. The solid residue was washed with water and recrystallized from absolute EtOH yielding 1.9 g (77%) of pale yellow crystals: mp 127–129 °C; ir $\nu$ ($CHCl_3$) 2241 $cm^{-1}$; uv $\lambda_{max}^{MeOH}$ 253.5 nm ($\epsilon$ 9900). Anal. ($C_{17}H_{16}N_2$) C, H, N.

**10-Carboxamido-10,11-dihydro-5-ethyl-5*H*-dibenz[*b,f*]azepine (6).** A mixture of 3.0 g (12 mmol) of **5** and 30 ml of concentrated $H_2SO_4$ was warmed on a steam bath for 15 min and then was poured into 100 ml of ice–$H_2O$. The mixture was extracted with $CHCl_3$ and dried over anhydrous $K_2CO_3$. Concentration of the $CHCl_3$ solution to dryness under reduced pressure left an oil that solidified on trituration with MeOH. Recrystallization from MeOH yielded 2.9 g (81%) of pale yellow crystals as a MeOH solvate: mp 70–95 °C (with loss of MeOH); ir $\nu$ ($CHCl_3$) 1685 $cm^{-1}$. Anal. ($C_{18}H_{22}N_2O$) C, H, N.

**General Procedure for Alkylation of 5.** Sodium hydride dispersion in oil (50 mmol) was added to a solution of 10 mmol of **5** in 30 ml of anhydrous THF containing 5 ml of dry DMF. The mixture was stirred under reflux for 1 h and then 15 mmol of the dialkylaminoalkyl halide (as the free amine or as the hydrochloride) was added. Reflux was continued and additional NaH was added as needed until TLC (10% v/v EtOAc–$C_6H_6$ on neutral alumina) indicated that no more **5** remained. The reaction mixture was cooled to ambient temperature and $H_2O$ was added until gas evolution ceased. Solvent was removed under reduced pressure and the residue was partitioned between $Et_2O$ and $H_2O$. The $Et_2O$ solution was washed with $H_2O$ and dried over anhydrous $MgSO_4$. Removal of the solvent gave a residual oil that was purified as the hydrochloride (see Table I). One specific example follows.

**10-Cyano-10-diethylaminoethyl-10,11-dihydro-5-ethyl-5*H*-dibenz[*b,f*]azepine Hydrochloride (7b).** NaH (3 g of 57% NaH dispersion in mineral oil) was added to a solution of 3.0 g (12 mmol) of **5** in 30 ml of anhydrous THF containing 5 ml of dry DMF and the mixture was stirred under reflux for 1 h. Diethylaminoethyl chloride hydrochloride (3.0 g, 17 mmol) was added and on continuing reflux and the addition of 1 g more of NaH suspension a greenish color appeared, and when the color was gone a TLC (10% v/v EtOAc–$C_6H_6$ on neutral alumina) indicated that reaction was complete. After cooling the reaction

mixture, water was added to destroy the excess NaH; then the solvent was removed under reduced pressure. The residual oil was dissolved in ether and dried over anhydrous $MgSO_4$. The ethereal solution was treated with 20% hydrogen chloride in *i*-PrOH and the paste that separated was extracted into $H_2O$ and washed with ether. The aqueous solution was made alkaline by the addition of 50% NaOH; the oil was isolated by extraction into ether and dried over anhydrous $MgSO_4$ and the ether removed by distillation under reduced pressure, yielding 4.2 g of clear yellow oil. This was converted to the hydrochloride in *i*-PrOH yielding 3.6 g of white crystals that were recrystallized from absolute EtOH yielding 3.3 g (51%) of white crystals: mp 211–214 °C; ir $\nu$ ($CHCl_3$) 2180 $cm^{-1}$. Anal. ($C_{23}H_{30}ClN_3$) C, H, N.

**Procedures for the Hydrolysis of the Nitriles to the Carboxamides.** Two methods were used for the preparation of carboxamides. An example of each method is given below.

**Method A. Hydrolysis with Concentrated $H_2SO_4$. 10-Carboxamido-10,11-dihydro-10-dimethylaminoethyl-5-ethyl-5*H*-dibenz[*b,f*]azepine (8a).** A solution of 2.4 g (6.6 mmol) of 10-cyano-10,11-dihydro-10-dimethylaminoethyl-5-ethyl-5*H*-dibenz[*b,f*]azepine (free base of **7a**) in 24 ml of concentrated $H_2SO_4$ was warmed on a steam bath for 1.5 h. The reaction mixture was poured onto ice and the resultant solution was made alkaline with 50% NaOH. The solid was extracted into ether and dried over anhydrous $MgSO_4$. The solid residue remaining on removal of the ether under reduced pressure was recrystallized from EtOAc–hexane yielding 1.4 g (63%) of white crystals: mp 148.5–151 °C; ir $\nu$ ($CHCl_3$) 3520, 3410, and 1680 $cm^{-1}$. Anal. ($C_{21}H_{27}N_3O$) C, H, N.

**Method B. Hydrolysis with KOH. 10-Carboxamido-10,11-dihydro-10-dimethylaminopropyl-5-ethyl-5*H*-dibenz[*b,f*]azepine Hemioxalate (8d).** A solution of 13 g (39 mmol) of 10-cyano-10,11-dihydro-10-dimethylaminopropyl-5-ethyl-5*H*-dibenz[*b,f*]azepine (free base of **7d**) and 25 g (450 mmol) of KOH in 65 ml of EtOH containing 2.5 ml of $H_2O$ was stirred at reflux for 22 h, cooled, and poured into ice–$H_2O$. The oil that separated was extracted into ether, washed with $H_2O$, and dried over anhydrous $MgSO_4$. Removal of the solvent gave 12.0 g of a clear amber oil: ir $\nu$ ($CHCl_3$) 3535, 3419, and 1676 $cm^{-1}$.

To a solution of 5.5 g of the oil in *i*-PrOH was added 1.5 g of oxalic acid in a minimal amount of *i*-PrOH. On addition of ether a paste separated that solidified on scratching, yielding 5.5 g of white powder. Recrystallization from MeOH–EtOAc yielded 3.6 g (51%) of the hemioxalate: mp 118–120 °C. Anal. ($C_{23}H_{30}N_3O_3$) C, H, N.

**10-Aminomethyl-10,11-dihydro-10-diisopropylaminoethyl-5-ethyl-5*H*-dibenz[*b,f*]azepine Dihydrobromide (9b).** A solution of 4.0 g (105 mmol) of 10-cyano-10,11-dihydro-10-diisopropylaminoethyl-5-ethyl-5*H*-dibenz[*b,f*]azepine (free base of **7c**) in 40 ml of dry THF was added dropwise with stirring at 0 °C to a freshly prepared solution of $AlH_3$ (from 30 ml of 1.0 M $LiAlH_4$ in THF and 0.8 $cm^3$ of concentrated $H_2SO_4$).[3] After the addition the cooling bath was removed and stirring was continued at ambient temperature for 1.5 h. The mixture was decomposed successively with 6 ml of 33% v/v $H_2O$–THF, 3 ml of 25% NaOH, and 3 ml of $H_2O$. The mixture was filtered and the filtrate was dried over anhydrous $MgSO_4$. Removal of the solvent left 4.1 g of yellow oil that was dissolved in EtOH and treated with excess 15% HBr in EtOH. The oil that formed initially solidified on trituration with ether, yielding 5.4 g of off-white powder. Two recrystallizations from absolute EtOH produced 2.9 g (51%) of white crystals: mp 239–240 °C. Anal. ($C_{25}H_{37}Br_2N_3$) C, H, N.

**10,11-Dihydro-10-dimethylaminoethyl-5-ethyl-10-propionyl-5*H*-dibenz[*b,f*]azepine Hydrochloride (10a).** A solution of 5.0 g (16 mmol) of the free base of **7a** in 10 ml of toluene was added dropwise to 20 ml of 3.1 M ethylmagnesium bromide in ether and the reaction mixture was stirred at reflux for 3.5 h. After brief cooling the reaction mixture was poured into a solution of 20 ml of concentrated HCl in 50 ml of $H_2O$, allowing the toluene to boil off of the vigorous reaction. The aqueous solution was stirred under nearly reflux for 1 h; on standing at ambient temperature overnight and then cooling in an ice bath, 6.7 g of crystals was collected. Recrystallization from 95% EtOH yielded 5.4 g (83%) of white crystals. Analytical material was obtained by conversion of these crystals to the free amine and reforming the salt in absolute EtOH with 2-propanolic HCl which produced white crystals as the monohydrate: mp 182–183 °C; ir $\nu$ ($CHCl_3$) 1712 $cm^{-1}$. Anal. ($C_{23}H_{33}ClN_2O_2$) C, H, N.

**Assay against Aconitine-Induced Ventricular Arrhythmia.** The procedure is essentially that described by Lucchesi,[4] modified in certain particulars as follows. Hearts are obtained from adult albino rabbits of either sex and perfused in apparatus modeled after that devised by Anderson and Craver.[8] The composition of the perfusion solution is the same as Lucchesi's, but the volume is increased to 200 ml and the temperature lowered to 28 °C. Aconitine (ordinarily as the nitrate) is administered as soon as the heart beat is regular and the EKG pattern normal, the dose being so selected as to at least double the rate. Typically, 0.05 ml of 0.1% aconitine nitrate in physiological saline is injected. EKG's are recorded at 5-min intervals after onset of ventricular tachycardia until two successive readings show stabilization of the rate. Perfusate collected during this time is discarded and replaced with fresh solution, q.s., 200 ml. Promptly following stabilization, 2 mg of compound dissolved or suspended in 1 ml of physiological saline is mixed with the perfusion solution. Ten minutes later a like amount is introduced, followed after a further 10 min by double the first amount. Final concentration of compound in the perfusion solution is thus 40 mg/l. Recording of EKG's is continued at 5-min intervals throughout this time and for 10 min thereafter. A compound is considered antiarrhythmic if, at any time during the 30 min immediately following initial administration in at least half of a minimum of two tests, it reduces by 50% or more the rate recorded 10 min after onset of tachycardia.

**Assay against Ouabain-Induced Ventricular Arrhythmia.**[5] Male mongrel dogs are connected to a physiograph to follow heart and blood action. At the onset of the testing, an initial dose of 40 $\mu$g/kg of ouabain is administered intravenously in a saline solution. This is followed 30 min later by a dose of 20 $\mu$g/kg of ouabain and, at 15-min intervals, by a dose of 10 $\mu$g/kg of ouabain until ventricular arrhythmia occurs and persists for 20 min. Then, a saline solution of test compound is administered intravenously at a dose of 5 mg/kg. If the heart action does not become normal, additional test compound is administered at a dose of 5 mg/kg at 15-min intervals until heart action becomes normal or until the total dose of test compound administered is 20 mg/kg. A compound is considered antiarrhythmic if it causes a return to normal heart action for a period of 15 min or more in half or more of the dogs tested at a dose of 20 mg/kg or less.

**Assay against Ventricular Arrhythmia Induced by Harris Two-Stage Coronary Ligation.**[6] The ligation technique involves anesthetizing the animal with 32.5 mg/kg of sodium pentobarbital, administered intravenously, and maintaining respiration mechanically via tracheal intubation while the chest cavity is opened on the left side at the fourth interspace and (1) the artery is tied against a 20-gauge hypodermic needle at a point approximately 1 cm from the atrial tip, (2) the needle is removed, (3) 30 min later the artery is completely occluded by ligation, and (4) the opening is closed. On the first postoperative day, if an EKG reveals at least 75% ectopic beats, 5 mg/kg of compound dissolved or suspended at a concentration of 1% in aqueous 0.9% sodium chloride or other physiologically inert vehicle is administered during 5 min via a scalp-vein needle placed in the cephalic vein. EKG's are recorded at 2.5-min intervals, and the drug dose is repeated at 15-min intervals until there is either a reduction in ectopic beats amounting to at least 25% and lasting for a minimum of 10 min or a total drug dose of 20 mg/kg has been administered. A compound is considered antiarrhythmic in this test if the aforesaid reduction is induced in more than half of at least two dogs.

**Acknowledgments.** The authors express their appreciation to Dr. R. R. Dean, Dr. R. L. Novotney, and Mrs. E. Muir for the biological data, to Mr. Aristides Damascus for spectral data, to Mr. Emanuel Zielinski for microanalytical data, to Mr. C. M. Woo for his assistance, and to Mrs. Lorraine Eng for her help in preparation of the manuscript.

## References and Notes

(1) (a) C. M. Mokler and C. G. Van Arman, *J. Pharmacol. Exp.*

Ther., 136, 114 (1962); (b) M. J. Katz, C. E. Meyer, A. El-Etr, and S. Slodki, Curr. Ther. Res., Clin. Exp., 5, 343 (1963).
(2) B. P. Das and D. W. Boykin, Jr., J. Med. Chem., 14, 56 (1971).
(3) H. C. Brown and N. M. Yoon, J. Am. Chem. Soc., 88, 1464 (1966).
(4) B. R. Lucchesi, J. Pharmacol. Exp. Ther., 137, 291 (1962).
(5) B. R. Lucchesi and H. F. Hardman, J. Pharmacol. Exp. Ther., 132, 372 (1961).
(6) A. S. Harris, Circulation, 1, 1318 (1950).
(7) R. R. Dean, Angiology, 26, 67 (1975).
(8) F. F. Anderson and B. N. Craver, J. Pharmacol. Exp. Ther., 93, 135 (1948).

# Iodo-Bis(quaternary ammonium) Salts. Potential Cartilage-Selective X-Ray Contrast Agents

Steven P. Van Ootegham, Ronald G. Smith, G. Doyle Daves, Jr.,*

*Department of Chemistry, Oregon Graduate Center, Beaverton, Oregon 97005*

Aziza El-Mazati, Edwin M. Chan, George D. Olsen, and William K. Riker

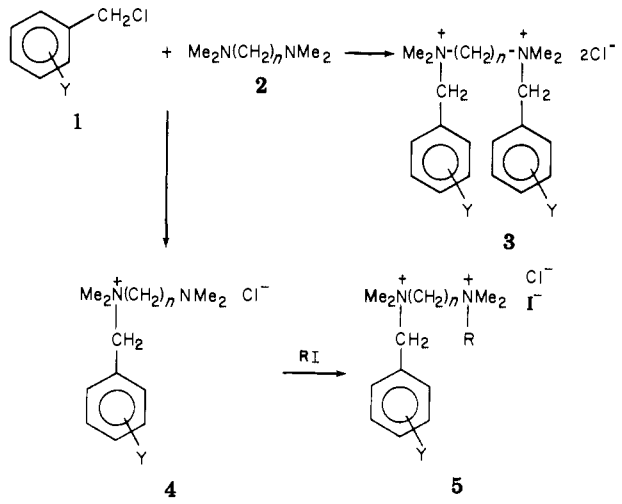
*Department of Pharmacology, University of Oregon Health Sciences Center, Portland, Oregon 97201.*
*Received February 9, 1976*

Bis(quaternary ammonium) compounds in which one or both quaternary nitrogens bear iodinated benzyl moieties and the charged centers are separated by 2, 4, 6, or 10 methylene units have been synthesized and evaluated for (a) binding to cartilaginous material, (b) radiocontrast characteristics, and (c) in vitro pharmacological effects. Also prepared was 1,5-diiodo-2,4-bis(β-trimethylammonioethyl)benzene diiodide, an analogue in which the iodinated aryl group lies between the charged nitrogen centers. Biological studies show that these compounds bind to cartilage but at relatively slow rates and with low persistence, resulting in low and transient levels of radiopacity. In common with simpler bisquaternary compounds, these compounds block synaptic transmission.

The density and anatomical location of cartilage is such that, under ordinary conditions of clinical radiography, it is indistinguishable from adjacent soft tissues and body fluids. Thus, to date, the visualization of cartilage-lined joint spaces has required the intraarticular injection of artificial contrast agents (radiolucent gases or radioopaque fluids). It has recently been demonstrated by Asghar and Roth,[1] by Wassermann,[2] and by Shindo et al.[3] that radioactive ($^{14}C$, $^{3}H$) bis(quaternary ammonium) salts [e.g., hexamethonium, $Me_3N^+(CH_2)_6N^+Me_3$] administered intravenously or intraperitoneally to rats or mice are bound selectively to cartilaginous structures.[4] These reports suggested to us that iodinated bis(quaternary ammonium) compounds might be useful for the selective radiographic visualization of cartilage. To test this hypothesis a number of bis(quaternary ammonium) compounds bearing one or two iodinated aryl moieties have been synthesized and evaluated for (a) binding to cartilaginous material, (b) radiocontrast characteristics, and (c) in vitro pharmacological effects.

**Synthesis.** A series of bis(quaternary ammonium) compounds bearing iodinated benzyl groups was prepared as shown in Scheme I. Quaternization of an α,Ω-bis(dimethylamino)alkane (**2**) with 2 equiv of 3-iodobenzyl chloride[5] (**1**, Y = 3-I) in acetone or dimethylformamide occurred readily to yield the corresponding bis(quaternary ammonium) compounds **3a–c** (see Table I). However, when more highly substituted benzyl chlorides [e.g., 2,4,5-triiodobenzyl chloride[6] (**1**), Y = 2,4,5-I] were used, these reaction conditions produced, in low yield, a mixture of mono- and bis(benzyl quaternary ammonium) salts (**4** and **3**, respectively). Use of 4 equiv (i.e., 100% excess) of the substituted benzyl chloride **1** and prolonged reaction time (~60 h) allowed preparation of bis(iodobenzyl) quaternary compounds **3e–j** although, in most instances, it was necessary to separate some monoquaternary compound **4** which was also present in the crude reaction product. This separation of **3** from **4** was accomplished readily since the monoquaternary salts **4** are soluble in

Scheme I




ethanol at room temperature whereas the poly(iodobenzyl)-bisquaternary compounds **3** are not. Changing the stoichiometry of the reactions such that the bis(tertiary amine) **2** was present in excess allowed the monoquaternary compounds **4** to be prepared as intermediates for synthesis of the unsymmetrical bis(quaternary ammonium) compounds **5**. It was necessary to exercise care in the purification of compounds in the mono series (**4**) since heating solutions of **4** sometimes led to disproportionation, producing mixtures of **2** and **3**.

We have also prepared a bis(quaternary ammonium) compound, 1,5-diiodo-2,4-bis(β-trimethylammonioethyl)benzene diiodide (**13**), in which the iodine-bearing aryl group is inserted in the carbon chain separating the charged nitrogens (Scheme II). 1,4-Bis(β-acetamidoethyl)benzene (**9**), prepared in four steps from 1,4-benzenedimethanol (**6**) as described previously,[7] was iodinated using iodine and periodic acid[8] to yield the 1,5-bisiodo derivative **10**. Hydrolysis of the amide groups