

Potential Antimalarials. 7.
Tribromomethylquinolines and
Positive Halogen Compounds^{1,2}

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Received January 22, 1971

4-Chloro-2-tribromomethylquinoline (**1**) showed unexpected, albeit low, antimalarial activity. Structural variation (Table I) revealed that the activity was

TABLE I
 ACTIVITIES OF SOME 2-TRIBROMOMETHYLQUINOLINES AND OTHER
 ACTIVE HALOGEN COMPOUNDS^c

| No. | R ₂ | R ₄ | R ₅ | R ₃ | Dose, mg/kg | ΔMST, ^b days |
|----------------|-------------------|--|----------------|----------------|----------------|----------------------------|
| 1 ^c | CBr ₃ | Cl | H | H | 40 | 0.8 |
| | | | | | 160 | 2.3 |
| | | | | | 320 | 3.5 |
| | | | | | 640 | 7.5 |
| 2 | CHBr ₂ | Cl | H | H | 640 | 0.3 |
| 3 | CCl ₃ | Cl | H | H | 640 | 0.4 |
| 4 | H | CBr ₃ | Br | Br | 640 | 0 |
| 5 | CBr ₃ | N(CH ₃) ₂ | H | H | 640 | 1.0 |
| 6 | CBr ₃ | NHC ₄ H ₉ | H | H | 640 | 0.5 |
| 7 | CBr ₃ | NHCH ₂ (CH ₃) ₂ CH ₂ NHCO ₂ Et | H | H | 40 | 0.3 |
| | | | | | 160 | 0.5 |
| | | | | | 640 | 0.5 |
| 8 ^d | CBr ₃ | NH(CH ₃) ₂ N(CH ₃) ₂ | H | H | 640 | 1.7 |
| 9 | | N,N'-Dichlorophenobarbital | | | 640 | 1.0 |
| 10 | | Dibromobarbituric acid ^{d,e} | | | 640 | 1.6 |
| 11 | | N-Chlorobenzamide ^f | | | 640 | 1.2 |
| 12 | | 1,2-Dibromotetrachloroethane ^{d,g} | | | 640 | 0.8 |

^a Testing results supplied by the Walter Reed Army Institute of Research. ^b Increased mean survival time over that of controls in *P. berghei* test. ^c Active also in *P. gallinaceum* test at 120 mg/kg. ^d Toxic, indicating that 1 or more mice died before the controls. ^e Aldrich Chem. Co. ^f E. E. Slosson, *J. Amer. Chem. Soc.*, **29**, 305 (1903), mp 81.5–82°; our mp 71–73°. ^g Malaguti, *Justus Liebig's Ann. Chem.*, **56**, 276 (1848); F. A. Brimelow, Master's Thesis, Vanderbilt University, 1961.

dependent on the oxidizing capability of the CBr₃ group.⁴ When the CBr₃ group was altered to the CHBr₂ (in **2**) or to the CCl₃ group (in **3**), activity was lost. This response paralleled the oxidizing powers of the 3 compounds. Only **1** was capable of oxidizing *i*-PrOH under reflux to acetone (see Experimental Section). Moreover, the substituent at the 4 position of the 2-tribromomethylquinolines played a role in influencing both activity and oxidizing power. The lability of the CBr₃ group mitigated against replacement of the 4-Cl group by a wide variety of substituents, but it was found that primary or secondary amines in DMSO at 60° or less could be used to replace the 4-Cl substituent of **1** to yield **5**, **6**, **7**, and **8**. These compds showed no or

diminished activity. It appears that electron-withdrawing groups at position 4 are needed to enhance activity. Several dissimilar active halogen compds (**9**, **10**, **11**, and **12**) were tested for activity without revealing any encouraging lead.

Experimental Section⁵

4-Chloro-2-tribromomethylquinoline (1) was made from 4-chloroquinaldine by the method of Hammick,⁶ colorless plates from MeOH, 65% yield, mp 121–122°. *Anal.* (C₁₄H₈Br₃ClN) C, H, Br.

4-Chloro-2-dibromomethylquinoline (2).—Compd **1** (5 g) and 65 ml of *i*-PrOH were refluxed for 24 hr and on cooling deposited 3.1 g, 77% of **2** as needles, mp 163–164°. *Anal.* (C₁₄H₈Br₂ClN) C, H, N, Br. Other similar reductions of 2-tribromomethylquinoline have been made with 20% EtOH–80% H₂SO₄ and with tetralin, the latter suggesting a free radical mechanism.⁴ Treatment of 2-tribromomethylquinoline, or of **3**, with refluxing *i*-PrOH gave no reduction products of **2** or **3**.

4-Chloro-2-trichloromethylquinoline (3) was made from 4-chloroquinaldine by the method of Hammick⁶ except that, after the addn of 3 equivs of Cl₂ at 70°, a slow stream of Cl₂ was bubbled through the soln at reflux for 2 hr. The solid formed was filtered off, washed with aq NaHCO₃, dried, and recrystd from aq MeOH giving 50% of colorless needles, mp 63.5–65°. *Anal.* (C₁₄H₈Cl₃N) Cl. The nmr signal at 6.9 ppm for the H⁺ in the CHCl₂ group of **2** was absent in **3**.

5,8-Dibromo-4-tribromomethylquinoline (4) was made from 5,8-dibromolepidine⁸ in the same manner as **1** except for a 8 hr reflux at the end of the Br₂ addn. After recryst from aq MeOH, **4** was obt'd as colorless needles, 34%, mp 176–178°. *Anal.* (C₁₆H₄Br₅N) Br.

4-Dimethylamino-2-tribromomethylquinoline (5).—A soln of 0.012 mole of **1**, 0.026 mole of 1,3-diaminopropane, and 50 ml of DMF was heated at 60° for 18 hr and poured into cold, 10% aq NaOH. The Et₂O ext was washed, dried, and conc'd and the residue was recrystd from 85% aq MeOH yielding 1.2 g, 24%, of **5** as white crystals, mp 129–130°. *Anal.* (C₁₂H₁₁Br₃N) C, H, Br. No doubt the yield would be increased by omitting the 1,3-diaminopropane. DMF has been used previously to introduce NMe₂ groups.⁹

4-*n*-Butylamino-2-tribromomethylquinoline (6).—A soln of 0.018 mole of **1** and 0.09 mole of BuNH₂ in 60 ml of DMSO was heated at 60° for 1.5 hr, poured into H₂O, and extd with CH₂Cl₂. The residue, a heavy oil, from CH₂Cl₂ was extd with hot C₆H₁₄ which on cooling deposited white plates, 1.5 g, 18%, mp 153–154°. *Anal.* (C₁₄H₁₅Br₃N₂) Br, N.

2-(3-Ethyl carbamyl-2,2-dimethylpropylamino)-2-tribromomethylquinoline Hydrate (7).—A soln of 0.009 mole of **1** and 0.05 mole of 3-amino-2,2-dimethylpropylamine (Tennessee Eastman) in 60 ml of DMSO was heated at 60° for 6 hr and poured into H₂O. The yellow solid, 3.2 g, was filtered off, washed, dried, and dissolved in 30 ml of C₂H₅N, and the soln was treated dropwise with 4 g of ethyl chlorocarbonate. After 15 min, it was poured into H₂O and extd with CH₂Cl₂. The CH₂Cl₂ ext was washed with 10% aq HCl, dried, and conc'd. The oily residue was triturated with C₆H₁₄ to yield a solid which after recrystn from aq EtOH yielded 1.9 g, 42%, of **7** as a white solid, mp 160–161°. *Anal.* (C₁₈H₂₂Br₃N₃O₂·H₂O) Br, N, H₂O.

4-(3-Dimethylaminopropylamino)-2-tribromomethylquinoline Hydrochloride (8).—A soln of 0.012 mole of **1** and 0.07 mole of 3-dimethylaminopropylamine in 70 ml of DMSO was heated at 60° for 1.5 hr, poured into H₂O, and extd with CH₂Cl₂. The CH₂Cl₂ soln was extd with 10% aq HCl, the acid ext was carefully neutralized in the cold, and the solid quickly was filtered and redissolved in 10% aq HCl. The salt in H₂O was allowed to evaporate and recrystd from *i*-PrOH to give **8**, 1 g, 16%, mp 137–139°. *Anal.* (C₁₅H₂₀Br₃ClN₃) Br, N.

(5) Analyses are by Galbraith Laboratories, and results recorded with the Editor. Melting points are uncorrected and were taken with an A. H. Thomas Uni-Melt apparatus. Nmr spectra of new compounds were compatible with related structures and are on file with the authors.

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(2) Contribution No. 894 to the Army Research Program on Malaria.

(3) Taken in part from the Ph.D. thesis of J. C. C.

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N,N'-Dichlorophenobarbital (9).—Phenobarbital (0.03 mole) in 300 ml of MeOH was treated dropwise with 0.078 mole of Chlorox (5% NaOCl) and stirred for 4 hr. Another 0.026 mole of Chlorox was added inducing some crystn, and after refrigeration the crystals were filtered off, washed with H₂O, and recrystd from BuCl and a small amt of CH₂Cl₂ yielding colorless platelets, mp 147–152°, softening at 105°. *Anal.* (C₁₂H₁₀Cl₂N₂O₃)Cl.

Acknowledgment.—We are indebted to the U. S. Army Medical Research and Development Command for Grant D 49-193-MD-2752 in support of this program and to the National Science Foundation for aid in purchase of an nmr apparatus (grant 1683).

Synthesis of Some Adamantane Derivatives of 2-Aminobenzothiazoles

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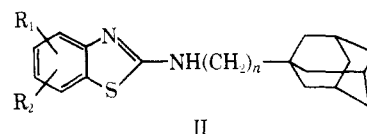
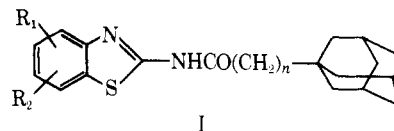
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Received April 15, 1971

We have reported² several derivatives of adamantane and their interesting pharmacological activity. Also,

logical properties to representative compounds of various classes and that in selected cases with biologically active compounds "the activity is superior in a quantitative or qualitative sense to those containing more conventional hydrocarbon groups." The purpose of this article is to describe the synthesis and pharmacological evaluation of some adamantane derivatives (amides and amines) of 2-aminobenzothiazoles.

Amides of general type I were prepared by heating under reflux of the adamantoyl or adamantylacetyl



chloride with the corresponding 2-aminobenzothiazoles in benzene. 2-(Adamantyl-1-alkyl)aminobenzothiazoles (type II) were prepared by refluxing the corresponding amides with LAH in THF–Et₂O.

TABLE I
2-(ADAMANTYL-1-CARBONYL OR -ACETYL)AMINOBENZOTHIAZOLES (I)

| No. | R ₁ R ₂ | n | Yield, % ^a | Mp, °C | Recrystn ^b solvent | Mol formula ^c |
|-----|-------------------------------------|---|--------------------------|---------|----------------------------------|---|
| 1 | H | 0 | 48 | 181–182 | B–PE | C ₁₈ H ₂₀ N ₂ OS |
| 2 | 6-C ₂ H ₅ O | 0 | 55 | 259–260 | B | C ₂₀ H ₂₄ N ₂ O ₂ S |
| 3 | 6-Cl | 0 | 70 | 199–200 | B–PE | C ₁₈ H ₁₉ ClN ₂ OS |
| 4 | 4-Cl | 0 | 76 | 258–260 | B–PE | C ₁₈ H ₁₉ ClN ₂ OS |
| 5 | 5,6-(CH ₃) ₂ | 0 | 82 | 207–208 | B–PE | C ₂₀ H ₂₄ N ₂ OS |
| 6 | H | 1 | 57 | 205–206 | B | C ₁₉ H ₂₂ N ₂ OS |
| 7 | 6-C ₂ H ₅ O | 1 | 68 | 215–217 | B–PE | C ₂₁ H ₂₆ N ₂ O ₂ S |
| 8 | 6-Cl | 1 | 60 | 250–252 | B–PE | C ₁₉ H ₂₁ ClN ₂ OS |
| 9 | 4-Cl | 1 | 88 | 216–218 | B–PE | C ₁₉ H ₂₁ ClN ₂ OS |
| 10 | 5,6-(CH ₃) ₂ | 1 | 58 | 217–218 | B–PE | C ₂₁ H ₂₆ N ₂ OS |

^a Purified comps. ^b B, PhH, PE, petr ether (35–45°), E, Et₂O, Et, abs EtOH. ^c All comps were analyzed for C, H, N.

TABLE II
2-(ADAMANTYL-1-ALKYL)AMINOBENZOTHIAZOLES (II)

| No. | R ₁ R ₂ | n | Yield, % ^a | Mp, °C | Recrystn ^b solvent | Mol formula ^c |
|-----|-------------------------------------|---|--------------------------|-------------|----------------------------------|--|
| 11 | H | 1 | 44 | 279–280 | Et–E | C ₁₈ H ₂₂ N ₂ S·HCl |
| 12 | 6-C ₂ H ₅ O | 1 | 37 | 266–268 | Et–E | C ₂₀ H ₂₆ N ₂ OS·HCl |
| 13 | 6-Cl | 1 | 48 | 241–243 | Et | C ₁₈ H ₁₉ ClN ₂ S·HCl |
| 14 | 4-Cl | 1 | 56 | 218–220 | Et–E | C ₁₈ H ₂₁ ClN ₂ S·HCl |
| 15 | 5,6-(CH ₃) ₂ | 1 | 51 | 268–270 dec | Et | C ₂₀ H ₂₆ N ₂ S·HCl |
| 16 | H | 2 | 74 | 228–230 | Et–E | C ₁₉ H ₂₄ N ₂ S·HCl |
| 17 | 6-C ₂ H ₅ O | 2 | 84 | 224–226 | Et–E | C ₂₁ H ₂₈ N ₂ OS·HCl |
| 18 | 6-Cl | 2 | 87 | 247–248 | Et | C ₁₉ H ₂₃ ClN ₂ S·HCl |
| 19 | 4-Cl | 2 | 54 | 227–229 | Et–E | C ₁₉ H ₂₃ ClN ₂ S·HCl |
| 20 | 5,6-(CH ₃) ₂ | 2 | 77 | 257–258 | Et–E | C ₂₁ H ₂₈ N ₂ S·HCl |

^{a-c} See footnote a–c, Table I.

Gerzon and his coworkers^{3–5} have shown that introduction of the adamantane group imparts interesting bio-

The structures of the resulting amides and amines (Tables I, II) have been confirmed by the elementary analysis and ir and nmr spectra. The chemical shifts and ir spectra of representative compounds are given in the Experimental Section.

The comps recorded in Tables I and II were screened on mouse behavior,^{6–8} for antiinflammatory activity

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