Journal of Medicinal Chemistry, 1971, Vol. 14, No. 12 1221

Potential Antimalarials. 7. Tribromomethylquinolines and Positive Halogen Compounds[1,2]

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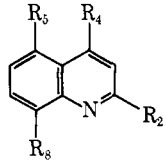
Received January 22, 1971

4-Chloro-2-tribromomethylquinoline (**1**) showed unexpected, albeit low, antimalarial activity. Structural variation (Table I) revealed that the activity was dependent on the oxidizing capability of the CBr_3 group.[4] When the CBr_3 group was altered to the $CHBr_2$ (in **2**) or to the CCl_3 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 CBr_3 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.

TABLE I

ACTIVITIES OF SOME 2-TRIBROMOMETHYLQUINOLINES AND OTHER ACTIVE HALOGEN COMPOUNDS[a]



No.	R_2	R_4	R_5	R_8	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_4H_9	H	H	640	0.5
7	CBr_3	$NHCH_2(CH_3)_2CH_2NHCO_2Et$	H	H	40	0.3
					160	0.5
					640	0.5
8[d]	CBr_3	$NH(CH_2)_3N(CH_3)_2$	H	H	640	1.7
9		*N,N'*-Dichlorophenobarbital			640	1.0
10		Dibromobarbituric acid[d,e]			640	1.6
11		*N*-Chlorobenzanilide[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 Liebigs Ann. Chem.*, **56**, 276 (1848); F. A. Brimelow, Master's Thesis, Vanderbilt University, 1961.

Experimental Section[5]

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.* ($C_{16}H_5Br_3ClN$) 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.* ($C_{10}H_6Br_2ClN$) C, H, N, Br. Other similar reductions of 2-tribromomethylquinoline have been made with 20% EtOH–80% H_2SO_4[7] 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 Hammick[6] except that, after the addn of 3 equivs of Cl_2 at 70°, a slow stream of Cl_2 was bubbled through the soln at reflux for 2 hr. The solid formed was filtered off, washed with aq $NaHCO_3$, dried, and recrystd from aq MeOH giving 50% of colorless needles, mp 63.5–65°. *Anal.* ($C_{10}H_5Cl_4N$) Cl. The nmr signal at 6.9 ppm for the H^+ in the $CHCl_2$ group of **2** was absent in **3**.

5,8-Dibromo-4-tribromomethylquinoline (**4**) was made from 5,8-dibromolepidine[8] in the same manner as **1** except for a 8 hr reflux at the end of the Br_2 addn. After recryst from aq MeOH, **4** was obtd as colorless needles, 34%, mp 176–178°. *Anal.* ($C_{10}H_4Br_5N$)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 Et_2O ext was washed, dried, and concd and the residue was recrystd from 85% aq MeOH yielding 1.2 g, 24%, of **5** as white crystals, mp 129–130°. *Anal.* ($C_{12}H_{11}Br_3N$) C, H, Br. No doubt the yield would be increased by omitting the 1,3-diaminopropane. DMF has been used previously to introduce NMe_2 groups.[9]

4-*n*-Butylamino-2-tribromomethylquinoline (**6**).—A soln of 0.018 mole of **1** and 0.09 mole of $BuNH_2$ in 60 ml of DMSO was heated at 60° for 1.5 hr, poured into H_2O, and extd with CH_2Cl_2. The residue, a heavy oil, from CH_2Cl_2 was extd with hot C_6H_{14} which on cooling deposited white plates, 1.5 g, 18%, mp 153–154°. *Anal.* ($C_{14}H_{15}Br_3N_2$) 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 H_2O. The yellow solid, 3.2 g, was filtered off, washed, dried, and dissolved in 30 ml of C_5H_5N, and the soln was treated dropwise;with 4 g of ethyl chlorocarbonate. After 15 min, it was poured into H_2O and extd with CH_2Cl_2. The CH_2Cl_2 ext was washed with 10% aq HCl, dried, and concd. The oily residue was triturated with C_6H_{14} 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.* ($C_{18}H_{22}Br_3N_3O_2 \cdot H_2O$) Br, N, H_2O.

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 H_2O, and extd with CH_2Cl_2. The CH_2Cl_2 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 H_2O was allowed to evap and recrystd from *i*-PrOH to give **8**, 1 g, 16%, mp 137–139°. *Anal.* ($C_{15}H_{20}Br_3ClN_3$) Br, N.

(1) Paper 6: J. B. Wommack, Jr., K. N. Subbaswami, T. G. Barbee, Jr., and D. E. Pearson, *J. Med. Chem.*, **14**, 1218 (1971).

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

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

(4) B. R. Brown, J. O. Grice, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1149 (1951).

(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.

(6) D. L. Hammick, *J. Chem. Soc.*, **123**, 2882 (1923).

(7) A. Astell-Burt and D. L. Hammick, *ibid.*, 1186 (1952).

(8) We are indebted to Dr. Marshall Gordon, Murray State University, Murray, Ky., for a supply of this compound.

(9) J. J. D'Amico, S. T. Webster, R. H. Campbell, and C. E. Twine, *J. Org. Chem.*, **30**, 3618 (1965).

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 H_2O, and recrystd from BuCl and a small amt of CH_2Cl_2 yielding colorless platelets, mp 147–152°, softening at 105°. *Anal.* ($C_{12}H_{10}Cl_2N_2O_3$)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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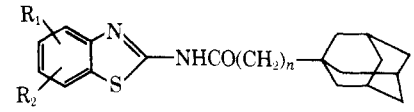
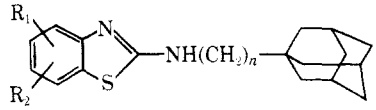
Received April 15, 1971

We have reported[2] several derivatives of adamantane and their interesting pharmacological activity. Also, Gerzon and his coworkers[3–5] have shown that introduction of the adamantane group imparts interesting biological 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



I



II

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–Et_2O.

TABLE I

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

No.	R_1R_2	n	Yield, %[a]	Mp, °C	Recrystn[b] solvent	Mol formula[c]
1	H	0	48	181–182	B–PE	$C_{18}H_{20}N_2OS$
2	6-C_2H_5O	0	55	259–260	B	$C_{20}H_{24}N_2O_2S$
3	6-Cl	0	70	199–200	B–PE	$C_{18}H_{19}ClN_2OS$
4	4-Cl	0	76	258–260	B–PE	$C_{18}H_{19}ClN_2OS$
5	5,6-(CH_3)	0	82	207–208	B–PE	$C_{20}H_{24}N_2OS$
6	H	1	57	205–206	B	$C_{19}H_{22}N_2OS$
7	6-C_2H_5O	1	68	215–217	B–PE	$C_{21}H_{26}N_2O_2S$
8	6-Cl	1	60	250–252	B–PE	$C_{19}H_{21}ClN_2OS$
9	4-Cl	1	88	216–218	B–PE	$C_{19}H_{21}ClN_2OS$
10	5,6-(CH_3)$_2$	1	58	217–218	B–PE	$C_{21}H_{26}N_2OS$

[a] Purified compds. [b] B, PhH, PE, petr ether (35–45°), E, Et_2O, Et, abs EtOH. [c] All compds were analyzed for C, H, N.

TABLE II

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

No.	R_1R_2	n	Yield, %[a]	Mp, °C	Recrystn[b] solvent	Mol formula[c]
11	H	1	44	279–280	Et–E	$C_{18}H_{22}N_2S\cdot HCl$
12	6-C_2H_5O	1	37	266–268	Et–E	$C_{20}H_{26}N_2OS\cdot HCl$
13	6-Cl	1	48	241–243	Et	$C_{18}H_{21}ClN_2S\cdot HCl$
14	4-Cl	1	56	218–220	Et–E	$C_{18}H_{21}ClN_2S\cdot HCl$
15	5,6-(CH_3)$_2$	1	51	268–270 dec	Et	$C_{20}H_{26}N_2S\cdot HCl$
16	H	2	74	228–230	Et–E	$C_{19}H_{24}N_2S\cdot HCl$
17	6-C_2H_5O	2	84	224–226	Et–E	$C_{21}H_{28}N_2OS\cdot HCl$
18	6-Cl	2	87	247–248	Et	$C_{19}H_{23}ClN_2S\cdot HCl$
19	4-Cl	2	54	227–229	Et–E	$C_{19}H_{23}ClN_2S\cdot HCl$
20	5,6-(CH_3)$_2$	2	77	257–258	Et–E	$C_{21}H_{28}N_2S\cdot HCl$

[a–c] See footnote *a–c*, Table I.

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 compds recorded in Tables I and II were screened on mouse behavior,[6–8] for antiinflammatory activity

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(2) G. Tsatsas, E. Costakis, S. Casadio, B. Lumachi, and E. Marazzi-Uberti, *Ann. Pharm. Fr.*, **27**, 363 (1969).

(3) K. Gerzon and D. Kau, *J. Med. Chem.*, **10**, 189 (1967).

(4) K. Gerzon, E. F. Krumkains, R. L. Brindle, F. J. Marshall, and M. Root, *ibid.*, **6**, 760 (1963).

(5) R. T. Rapala, R. J. Kraay, and K. Gerzon, *ibid.*, **8**, 580 (1965).

(6) J. R. Boissier, *Actual. Pharmacol.*, **12**, 7 (1959).

(7) C. Bianchi, *Arch. Int. Pharmacodyn. Ther.*, **111**, 227 (1957).

(8) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **98**, 470 (1948).