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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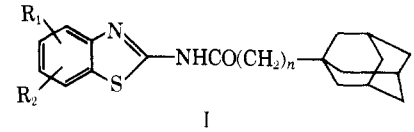
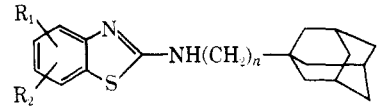
We have reported[2] several derivatives of adamantane and their interesting pharmacological activity. Also, Gerzon and his coworkers[3–5] have shown that introduction of the adamantane group imparts interesting biological properties to representative compounds of various classes and that in selected 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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in rats,[9] analgetic activity in mice and rats,[10-12] antipyretic activity in mice,[13] action on rabbits' cardivascular system, action on this isolated rabbit heart,[14] local anesthetic activity,[15] antibacterial and antifungal actions,[16] and other activities. None of them showed anything worthy of note, with the exception of 4 compounds (**2**, **7**, **12**, **17**) which demonstrated inhibition of gastric secretion in the rat at doses of 50 mg/kg (MED_{50}), administered ip. Compd **7** was found to be more potent than **2**, **12**, and **17**.

Experimental Section[17]

2-(Adamantyl-1-carbonyl or -acetyl)aminobenzothiazoles.—To a soln (or suspension) of 2-aminobenzothiazole (or its derivative) (0.05 mole) in 200 ml of dry C_6H_6 was added dropwise with stirring, a soln of adamantyl-1-carbonyl (or -acetyl) chloride (0.055 mole) in 30 ml of dry C_6H_6. The mixt, after completion of the addn (15 min), was refluxed for 2 hr. The solvent was then evapd, the residue was treated with 100 ml of a satd $NaHCO_3$ soln, and the amide was extd with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), and distd. See Table I.

2-(Adamantyl-1-alkyl)aminobenzothiazoles.—A soln of the amide I (0.01 mole) in 120 ml of anhyd THF was added dropwise to a stirred suspension of LAH (0.02 mole) in Et_2O (50 ml) and the mixt was refluxed with vigorous stirring for 5–6 hr. After cooling, hydrolysis was accomplished with H_2O and 15% sol of NaOH. The white ppt formed was filtered and thoroughly washed (Et_2O). The org phase was dried (Na_2SO_4) and distd. All the amines thus obtd were solid and were characterized as their hydrochlorides (see Table II).

Nmr and Ir Spectra.[18-20]—(a) 2-(Adamantyl-1-carbonyl)-aminobenzothiazole (1) showed nmr ($CDCl_3$) δ 2.01 (β- and γ-H), 1.71 (δ-H) of 1-substituted adamantane.[21] Other peaks are found at δ 7.46–8.14 (m, arom protons), 9.67 (broad, NH); ir (KBr) cm^{-1} 3225 (NH), 1680 (C=O), 1590 (C=C), 1530 (C=N).

(b) 2-(Adamantyl-1-acetyl)aminobenzothiazole (6) showed nmr ($CDCl_3$) δ 1.32 (β-H), 1.78 (γ-H), 1.53 (δ-H).[21] Other peaks at δ 2.17 (s, $COCH_2$), 7.36–8.25 (m, arom protons), 11.90 (broad, NH); ir (KBr) cm^{-1} 3195 (NH), 1690 (C=O), 1595 (C=C), 1540 (C=N).

(c) 2-(Adamantyl-1-methyl)aminobenzothiazole (base)[22] showed nmr ($CDCl_3$) δ 1.59 (β-H), 1.95 (γ-H), 1.67 (δ-H).[21] Other peaks at δ 3.13 (s, NCH_2), 6.42 (broad, NH), 7.05–7.83 (m, arom protons); ir (KBr) cm^{-1} 3224 (NH), 1614 (broad, C=C, C=N).

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(22) The free amine was liberated from its HCl salt.

Antimicrobials. 1. Benzothiazolylbenzylamines

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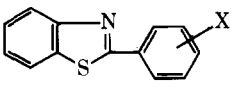
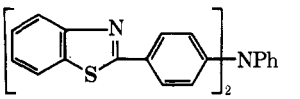
In previous publications from this laboratory, the antimicrobial properties of 2-arylbenzothiazole basic ethers[1] and of 2-arylbenzothiazolines[2] have been described. As an extension to this work, we have investigated the preparation and biological activity of a series of benzothiazolylbenzylamines. Some of the amines were also converted into dichloroacetyl amides to obtain compounds resembling the amebicide chlorbetamide.

Chemistry.—Bromination of 2-*p*-tolylbenzothiazole with NBS gave the bromomethyl compd Ia which was treated with a series of primary and secondary aliphatic amines to afford the benzylamines Ib. The primary amine (Ib, $R_1 = R_2 = H$) was obtained from Ia by Gabriel synthesis, and the meta analog Ie was prepared similarly from Id. The ortho analog If was available in moderate yield by hydrogenation of 2-*o*-cyanophenylbenzothiazole over Raney Ni. Reaction of Ia with aniline gave the bis-substituted compd II, and with substituted anilines complex reaction mixtures were obtained. Compds Ic were therefore synthesized by



I

a, X = *p*-CH_2Br e, X = *m*-CH_2NH_2
b, X = *p*-$CH_2NR_1R_2$ f, X = *o*-CH_2NH_2
c, X = *p*-CH_2NHAr g, X = *p*-$CH_2NHCH_2CH_2NEt_2$
d, X = *m*-CH_2Br h, X = *p*-CHO



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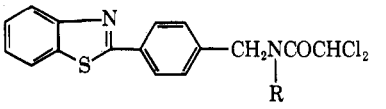

III

reaction of Ia with the tosyl derivative of the appropriate aniline followed by acid hydrolysis. Sommelet reaction of Ia afforded in high yield the aldehyde Ih, and this, by condensation with $Et_2N(CH_2)_2NH_2$ and subsequent LAH reduction gave the amine Ig. The dichloroacetamides III were obtained from the appropriate amine by dichloroacetylation using standard procedures.

Biological Activity.—The compounds described were all screened *in vitro* against a range of Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, *Entamoeba histolytica*, and a few representative dermatophytes. The highest antituberculous activity

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