14	CH_3CO		13.1	EtOH	250.5–252.5	$C_{16}H_{20}N_2O \cdot HCl$	C, H, Cl, N	A	>20
15	NO_2	$-CH{=}NCH_3$	30.7	EtOH	244–246.5	$C_{10}H_{11}N_3O_2 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
16	NO_2		42.5	EtOH	281–282	$C_{12}H_{13}N_3O_2 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
17	NO_2		22.2	EtOH	268.5–270.5	$C_{14}H_{17}N_3O_2 \cdot HCl$	C, H, Cl, N	W	20
dl-Amphetamine sulfate								A	1.3
Bemegride								A	14.4

[a] Based on analytically pure sample. Many of these experiments were conducted only once and the optimal conditions were not established. [b] A = active. [c] W = weakly active. [d] C: calcd, 61.66; found, 62.21.

15, and bemegride had ED_{50}'s of 10 mg/kg sc or less, **1, 3, 7, 10, 11, 12, 14,** and **16** had ED_{50}'s of 11 to 35 mg/kg sc, and **4** was inactive. Further testing in the rat of the 4 most active compounds by the tail flick method[6] and the $AgNO_3$ inflamed joint test[7] indicated that none of these compounds possessed significant analgetic properties.

The results of analeptic screening show that **8** and **13** compare favorably with bemegride as analeptics, and warrant further evaluation in the CNS area.

Experimental Section

1-Formimidoylindolines.—A solution of equimolar amounts of indoline and appropriate amide in 1,2-dichloroethane [250 ml (0.1 m)] was treated dropwise with an equimolar solution of $POCl_3$ in 1,2-dichloroethane [50 ml (0.1 m)] over a period of 0.5–1 hr. The mixture, after being stirred for 15 hr, was poured onto crushed ice, and made strongly basic with 20% NaOH with stirring. The organic layer was separated and extracted with dilute HCl. The acid solution was made basic with 20% NaOH and extracted again (Et_2O). The extract was concentrated to obtain the crude product. The HCl salt was prepared in the usual manner and recrystallized from appropriate solvent as shown in Table I.

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Synthesis of Some Local Anesthetics

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It has been found by many workers[1,2] that the essential structure requirements for a local anesthetic are a lipolytic end containing an aromatic nucleus, a hydropilic end consisting of a tertiary amino group, and an intermediate alkyl or substituted alkyl chain. Compounds having a dialkylamino alkylamino group connected to an aromatic or heterocyclic nucleus as a lipolytic moiety confer greater activity and less toxicity. Therefore, it was thought worthwhile to synthesize some pyridine-2-aminoacetyl-2-aminobenzothiazole and *N*,*N*-diethylanilino-*p*-aminoacetyl-2-aminobenzothiazole derivatives, by condensation of chloroacetyl chloride with different 2-aminobenzothiazoles followed by treatment with 2-aminopyridine and *p*-amino-*N*,*N*-diethylaniline, respectively.

Experimental Section

Different 2-aminobenzothiazoles were prepared according to Hugershoff.[3] Chloroacetyl-2-aminobenzothiazoles were prepared by known methods.[4]

Pyridine-2-aminoacetyl-2-aminobenzothiazole.—2-Chloroacetylaminobenzothiazole (5 g) dissolved in EtOH (30 ml) was added to 2-aminopyridine (3 g) dissolved in EtOH (20 ml) and the reac-

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(3) A. Hugershoff, *Chem. Ber.*, **34**, 3130 (1901); **36**, 3121 (1903).
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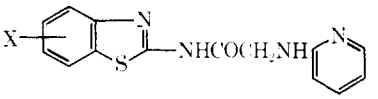
Table I

2-Pyridylaminoacetyl-2-aminobenzothiazoles

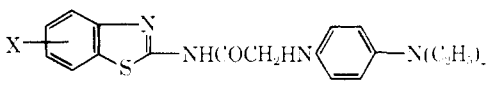


No.	X	% yield[a]	Mp, °C	Formula[b]	Mp, °C, hydrochloride	Mp, °C, picrate
1	H	65	90	$C_{14}H_{12}N_4OS$	175–177	247
2	4-CH_3	68	114	$C_{15}H_{14}N_4OS$	193–194	148
3	6-CH_3	60	100	$C_{15}H_{14}N_4OS$	235–237	228
4	4,7-Me_2	72	141	$C_{16}H_{16}N_4OS$	185–186	226
5	5-OCH_3	64	121	$C_{15}H_{14}N_4O_2S$	156–157	243
6	6-OCH_3	70	127	$C_{15}H_{14}N_4O_2S$	218–220	237
7	5-Cl	75	148	$C_{14}H_{11}ClN_4OS$	226–227	206
8	6-Cl	55	41	$C_{14}H_{11}ClN_4OS$	185–186	220
9	6-Br	70	129	$C_{14}H_{11}BrN_4OS$	199–200	212

[a] All compounds were crystallized from EtOH. [b] All compounds were analyzed for N and S and found to be within ±0.6%.

Table II

N,N-Diethylanilino-*p*-aminoacetyl-2-aminobenzothiazoles



No.	X	% yield[a]	Mp, °C, base	Formula[b]	Mp, °C, hydrochloride	Mp, °C, picrate
1	H	70	86	$C_{18}H_{22}N_4OS$	229–230	186
2	4-CH_3	72	39	$C_{20}H_{24}N_4OS$	218–220	227
3	6-CH_3	60	109	$C_{20}H_{24}N_4OS$	207–209	195
4	4,7-Me_2	75	104	$C_{21}H_{26}N_4OS$	213–214	222
5	5-OCH_3	64	35	$C_{20}H_{24}N_4O_2S$	150–152	182
6	6-OCH_3	55	46	$C_{20}H_{24}N_4O_2S$	224–226	151
7	5-Cl	70	132	$C_{19}H_{21}ClN_4OS$	235–236	227
8	6-Cl	62	32	$C_{19}H_{21}ClN_4OS$	242–244	144
9	6-Br	68	67	$C_{19}H_{21}BrN_4OS$	230–231	204

[a] All compounds were crystallized from EtOH. [b] All compounds were analyzed for N and S and found to be within ±0.6%.

Table III

2-Pyridylaminoacetyl-2-aminobenzothiazole

	Surface anesthesia				Infiltration anesthesia			
No.	Drug concn (%)	Intensity	Duration (min)	Remarks	Drug concn (%)	Intensity	Duration (min)	Remarks
1	1	Nil						
	2	Complete	2		0.2	Nil		
2	1	Nil						
		Complete	4		0.2	Nil		
3	1	Nil						
	2	Complete	3		0.2	Nil		
4	1	Nil						
	2	Nil			0.2	Nil		
5	1	Partial	4					
	2	Complete	5		0.2	Nil		
6	1	Partial	3		0.1	Nil		
	2	Complete	30		0.2	Partial	8	
					0.25	Complete	15	
7	0.025	Nil						
	0.05	Complete	8		0.05	Nil		
	0.1	Complete	7		0.1	Nil		
	0.2	Complete	20		0.2	Partial	10	
	0.25	Complete	25		0.25	Partial	15	
	0.5	Complete	60		0.4	Partial	15	
					0.5	Complete	15	
8	1	Nil						
	2	Complete	8		0.2	Nil		
9	1	Nil						
		Complete	6		0.2	Nil		

tion mixture was refluxed for 6 hr. Excess EtOH was distilled off and the residue was washed ($NaHCO_3$, H_2O). The product was crystallized from EtOH, mp 90°, yield 4.9 g. 2-Aminoacetyl pyridine derivatives of other 2-aminobenzothiazoles were prepared similarly. Their hydrochlorides were prepared as usual (see Table I).

***N,N*-Diethylanilino-*p*-aminoacetyl-2-aminobenzothiazoles.**—To 2-chloroacetylaminobenzothiazole (5 g) dissolved in EtOH (50 ml), *p*-amino-*N,N*-diethylaniline (3 ml) was added. The reaction mixture was refluxed for 6 hr. Excess EtOH was distilled off and the residue was washed ($NaHCO_3$, H_2O). The product was crystallized from EtOH, mp 86°, yield 5.39. *N,N*-

TABLE IV
N,N-DIETHYL-p-AMINOACETYL-2-AMINOBENZOTHIAZOLE

	Surface anesthesia				Infiltration anesthesia			
No.	Drug concn (%)	Intensity	Duration (min)	Remark	Drug concn (%)	Intensity	Duration (min)	Remarks
1	1	Nil						
	2	Nil			0.2	Nil		
2	1	Nil						
	2	Complete	30		0.2	Nil		
3	1	Nil						
	2	Partial	4		0.2	Nil		
4	0.5	Complete	10		0.2	Partial	10	
	1.0	Complete	16		0.25	Complete	8	
	2.0	Complete	60	Haziness on the cornea	0.5	Complete	60	
5	1	Nil			0.2	Nil		
	2	Complete	25		0.1	Nil		
					0.2	Nil		
6	1	Nil			0.25	Complete	10	
	2	Complete	10		0.5	Complete	60	
7	1	Nil						
	2	Complete	10		0.2	Nil		
8	1	Nil						
	2	Nil			0.2	Nil		
					0.05	Nil		
9	0.5	Complete	10		0.1	Nil		
	1.0	Complete	16		0.2	Partial	8	
	2.0	Complete	60	Haziness on the cornea	0.25	Complete	15	
					0.5	Complete	60	

Diethylanilino-*p*-aminoacetyl derivatives of other 2-aminobenzothiazoles were prepared similarly. For their hydrochlorides see Table II.

Pharmacologic Testing.—The compounds were investigated for their local anesthetic activity, which was evaluated by employing (1) surface anesthesia in the rabbit cornea and (2) infiltration anesthesia in the guinea-pig cornea. The results of the preliminary study are reported in Tables III and IV.

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Synthesis of Some Substituted 10-Amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines[1]

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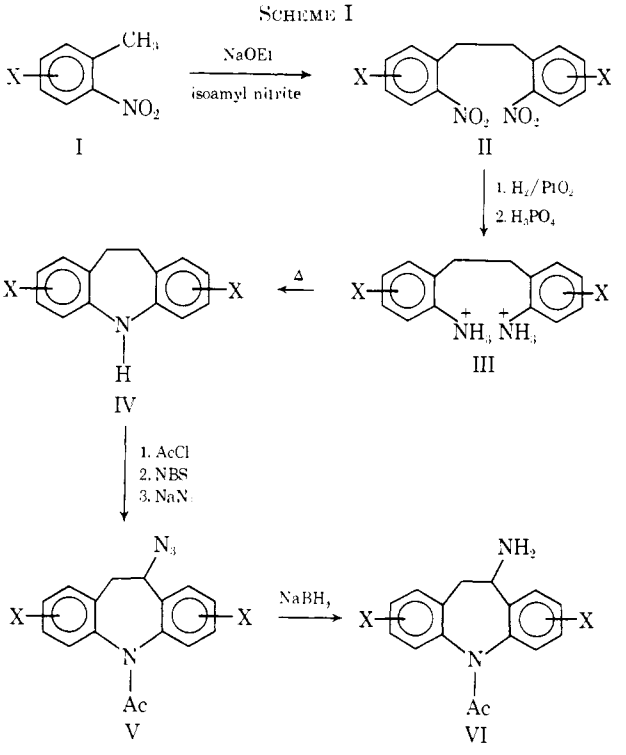
As part of a continuing[2] investigation of potential novel antimalarials, we have prepared some representative 10-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines for evaluation. For comparative purposes, we have also prepared some 10-hydroxy-10,11-dihydrodibenz[*b*,*f*]azepines. The synthetic approach employed for the 10-amino compounds is outlined in Scheme I. The key intermediates, *o*,*o*′-dinitrodibenzyls (II), in the synthesis of the dihydrodibenz[*b*,*f*]azepine ring system are prepared by the oxidative coupling of *o*-nitrotoluenes using isoamyl formate or nitrite in the presence of NaOEt.[3] The *o*,*o*′-dinitrodibenzyls are smoothly converted into the corresponding diamines by catalytic hydrogenation. Pyrolysis of the diphosphate salts of the diamines III gives reasonable yields of the dihydrodibenz[*b*,*f*]azepines IV with the exception of the salt of

SCHEME I



(1) We acknowledge the U.S. Army Medical Research and Development Command under Contract DADA17-68-C-8035 for support of this work. This is Contribution No. 797 from the Army Research Program on Malaria.

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