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.

Acknowledgment.—The authors are thankful to Professor Wahid U. Malik for providing necessary laboratory facilities and Dr. Nityanand, Assistant Director, C.D.R.I. Lucknow, for local anesthetic testing of the compounds. The authors are also thankful to the University Grant Commission for providing a Junior Research Fellowship (P. N. S.).

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

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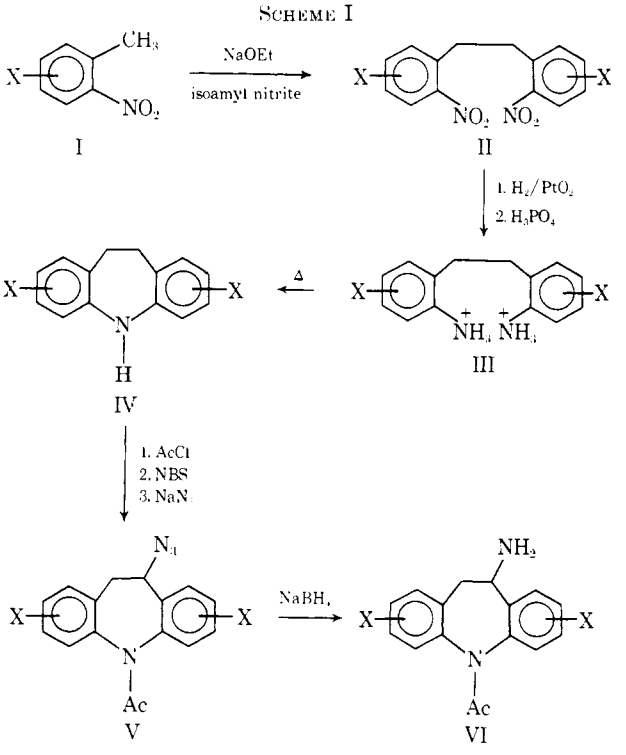
As part of a continuing[2] investigation of potential novel antimalarials, we have prepared some representative 10-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines for evaluation. For comparative purposes, we have also prepared some 10-hydroxy-10,11-dihydrodibenz[*b*,*f*]azepines. The synthetic approach 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

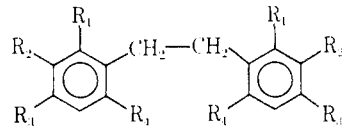


(1) We acknowledge the U.S. Army Medical Research and Development Command under Contract DADA17-68-C-8035 for support of this work. This is Contribution No. 797 from the Army Research Program on Malaria.

(2) (a) N. H. Berner, R. S. Varma, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 552 (1970); (b) R. S. Varma, L. K. Whisenant, and D. W. Boykin, Jr., *ibid.*, **12**, 913 (1969).

(3) (a) A. Lapworth, *J. Chem. Soc.*, **79**, 1265 (1901); (b) J. R. Geigy A.-G., British Patent, 777,546; *Chem. Abstr.*, **52**, 1255 (1958).

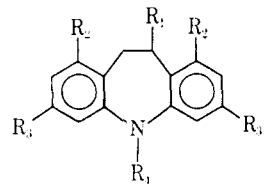
TABLE I



No.[a]	R_1	R_2	R_3	R_4	% yield	Mp, °C	Formula	Analyses
1	Cl	H	H	NO_2	65	142–143[b]	$C_{14}H_{10}Cl_2N_2O_4$	
2	Cl	H	H	NH_2	85	160–161	$C_{14}H_{14}Cl_2N_2$	C, H, N
3	H	Cl	H	NO_2	60	151–152	$C_{14}H_{10}Cl_2N_2O_4$	C, H, N
4	H	Cl	H	NH_2	78	161–163	$C_{14}H_{14}Cl_2N_2$	C, H, N
5	H	H	Cl	NO_2	50	194–195[c]	$C_{14}H_{10}Cl_2N_2O_4$	
6	H	H	Cl	NH_2	90	137–138	$C_{14}H_{14}Cl_2N_2$	C, H, N

[a] Recrysd from EtOH. [b] Lit. mp 143–144°. W. Schindler and F. Hafliger, U. S. Patent 2,800,470; *Chem. Abstr.*, **52**, 4691 (1958). [c] Lit. mp 192–194°. Reference 3b.

TABLE II



No.	R_1	R_2	R_3	R_4	% yield	Mp, °C	Formula	Analyses	Recrystn solvent
7	H	Cl	H	H	50	108–111[a]	$C_{14}H_{11}Cl_2N$		Hexane
8	NH_2	Cl	H	Ac	48	216–217	$C_{16}H_{14}Cl_2N_2O$	C, H, N	EtOH
9	N_3	H	H	Ac	78	131–132 dec	$C_{16}H_{14}N_4O$	C, H, N	Et_2O
10	NH_2	H	H	Ac	73	94–98	$C_{16}H_{16}N_2O$	C, H, N	Et_2O
11	H	H	Cl	H	62	113–114[b]	$C_{14}H_{11}Cl_2N$		Hexane
12	N_3	H	Cl	Ac	76	99–100 dec	$C_{16}H_{12}Cl_2N_4O$	C, H, N	Et_2O
13	NH_2	H	Cl	Ac	60	108–112	$C_{16}H_{14}Cl_2N_2O$	C, H, N	Et_2O
14	OH	H	H	Ac	70	139–140	$C_{16}H_{15}NO_2$	C, H, N	Hexane–EtOH
15	OH	H	H	H	67	106–107	$C_{14}H_{13}NO$	C, H, N	EtOH
16	OH	H	H	CH_3	78	78–79	$C_{15}H_{15}NO$	C, H, N	Hexane

[a] Lit. mp 114–115°. Reference 3b. [b] Lit. mp 114–115°. Reference 3b.

2,2′-diamino-5,5′-dichlorodibenzyl. The latter compound did not give a detectable quantity of the corresponding 2,8-dichloro-10,11-dihydrodibenz[*b,f*]azepine. Conversion of IV into the 10-azido compound V was accomplished by standard procedures;[4] although different conditions were required for the reaction of the dichloro substituted compounds. Attempts to reduce V with H_2–Pd–C failed[4] to yield a compound identifiable as an amine by its ir spectra, however, reduction with $NaBH_4$ gave good yields of the 10-amino compounds VI.[5]

The 10-hydroxy compounds were obtained by $NaBH_4$ reduction of the corresponding 10-keto derivatives. The latter were prepared essentially according to published procedures;[6] deviations are noted in the Experimental Section along with the synthetic details for all the procedures employed.

No significant antimalarial activity was found for the 10-amino or 10-hydroxy compounds shown in Table II when tested against *Plasmodium berghei* in mice by the method of Rane, *et al.*,[7] by the Walter Reed Army Institute of Research.[8]

Experimental Section

All melting points were obtained on a Thomas-Hoover Uni-Melt and are uncorrected. Satisfactory ir and nmr spectra were recorded for all new compounds. The ir spectra were observed using a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60A spectrophotometer (TMS internal standard). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlab, Inc., Atlanta, Ga. Where analyses are indicated only by symbols of the elements, analytical results for these elements were within ±0.4% of the theoretical values.

o,o′-Dinitrodibenzyls.—In a typical preparation, (*cf.* ref 3) 1 mole of NaOEt was prepared by allowing 23 g of Na to react with 500 ml of EtOH. After the reaction was complete, the excess EtOH was removed *in vacuo* and the resulting NaOEt dried at 50 ± 5° *in vacuo*. The NaOEt was suspended in Et_2O (300 ml) and the resulting slurry was stirred at −5°. A solution of 172 g of 6-chloro-2-nitrotoluene, 117 g of isoamyl nitrite, and 700 ml of cyclohexane was added dropwise to the stirred slurry. The temperature was maintained between −10 and 5° during addition (*ca.* 2 hr) and for an additional 6 hr, after which the mixture was

(4) E. E. van Tamelen, T. A. Spencer, D. S. Allen, and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961).

(5) P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Amer. Chem. Soc.*, **84**, 485 (1962).

(6) W. Schindler and H. Blattner, Swiss Patent 405,319; *Chem. Abstr.*, **65**, 16952 (1966).

(7) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(8) All the intermediates shown in Tables I and II except **4**, **6**, **7**, **11**, and **12** were also tested in the mouse screen and exhibited no activity.

stirred for 12 hr at room temperature. During the reaction period, if the temperature is allowed to exceed *ca.* 8°, the reaction goes exothermically out of control and the yields are drastically reduced. The reaction mixture was worked up by pouring into 1 l. of H_2O, filtered, washed with Et_2O, and dried. This material was sufficiently pure to proceed with the next step. Isoamyl formate can be used without a significant difference in yield, however, the product was consistently cleaner when isoamyl nitrite was used and, therefore, it is the reagent of choice. The yield was 112 g, mp 137–139°. Recrystallization from EtOH gave mp 142–143°.

o,o′-Diaminodibenzyls.—In a typical reaction, 9 g of 2,2′-dinitro-4,4′-dichlorodibenzyl was suspended in 200 ml of EtOH and reduced with H_2 over PtO_2 (0.5 g) at *ca.* 3.15 kg/cm². When the theoretical amount of H_2 was absorbed, the reaction mixture was filtered. In order to isolate the diamine, the EtOH was evaporated under reduced pressure and the residue (6.6 g) was recrystallized from EtOH–hexane, mp 137–138°.

In normal synthetic sequence the filtered EtOH solution of diamine was treated with 15 ml of concd H_3PO_4 and the resulting diphosphate salt was filtered, washed with Et_2O, and dried *in vacuo* at 100°.

10,11-Dihydro-5*H*-dibenz[*b,f*]azepines.—In a typical example, 15 g of the dried diphosphate salt of 2,2′-diamino-4,4′-dichlorodibenzyl was heated at 280–300° in an open flask for 30 min, cooled, and extracted by refluxing with two 200-ml portions of C_6H_6. The C_6H_6 solution was washed with dilute HCl, H_2O and dried; the solvent was removed under vacuum. The yield of 3,7-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine was 5 g; mp 110–112°, recrystallization from hexane raised the mp to 113–114°.

5-Acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—A suspension of 2.1 g of 5-acetyl-3,7-dichloro-10,11-dihydro-5*H*-dibenz-*b,f*]azepine (prepared by the reaction of AcCl with 3,7-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine[9]) in 80 ml of CCl_4 and 1.2 g of NBS was stirred and irradiated with a 200-W sunlamp for 2 hr, the temperature being maintained at 60–65° (*cf.* ref 9). The reaction mixture was cooled and the precipitated succinimide was filtered. The filtrate was evaporated under reduced pressure and the resulting residue was triturated with hexane. The resulting solid was filtered and used in the next step without further purification.

5-Acetyl-10-azido-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—To a stirred solution of 7 g of 5-acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepine and 600 ml of Et_2O a solution of 5.5 g of NaN_3 in 25 ml of H_2O was added. The mixture was stirred for 16 hr at room temperature and the Et_2O layer was separated, washed, dried ($CaSO_4$), and Et_2O removed to yield 5.4 g of solid mp 128–131° dec; recrystallization from MeOH raised the mp to 132–133° dec. The 10-bromodichlorodihydrodibenz[*b,f*]azepines failed to react under the above conditions. The following was used to prepare the 10-azido derivatives for the dichloro series.

A solution of 2 g of 3,7-dichloro-5-acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepine, 1.5 g of NaN_3, and 35 ml of MeOH was refluxed for 8 hr, cooled, poured into H_2O, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and evaporated under reduced pressure. The resulting gummy residue was dissolved in hexane–EtOH and after *ca.* 2 days at −10° crystals were obtained. Recrystallization from hexane gave a mp of 99–100° dec. The 10-azido compounds are *severe skin irritants* and should be handled accordingly. 5-Acetyl-10-azido-1,9-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine was used directly in the next step without purification.

10-Amino-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—A solution of 9 g of 5-acetyl-10-azido-10,11-dihydro-5*H*-dibenz[*b,f*]azepine, 4.5 g of $NaBH_4$, and 150 ml of *i*-PrOH was refluxed for 14 hr, cooled, poured into H_2O, and extracted with Et_2O. The Et_2O layer was washed (H_2O), dried ($CaSO_4$), and evaporated under reduced pressure. The residual material was purified by chromatography over Al_2O_3, the eluent C_6H_6–EtOH (99:1) gave the expected amine, yield 6 g, mp 95–98°. The amines apparently form stable solvates and must be fused *in vacuo* prior to combustion analyses.

5*H*-10,11-Dihydro-10-dibenz[*b,f*]azepinones (*cf.* Ref 10). A.—To a slurry of 19.5 g of NaOMe in 100 ml of DMSO at 140° was added a suspension of 12 g of 5-acetyl-10,11-dibromo-10,11-5*H*-dihydrodibenz[*b,f*]azepine in 20 ml of DMSO. The temperature was maintained for 1.5 hr at 130–140° and the mixture was cooled, poured into H_2O, and extracted with Et_2O. The Et_2O was washed (H_2O), dried ($CaSO_4$), and evaporated under reduced pressure to yield a solid. The crude residue was not characterized; it is presumably 10-methoxy-5*H*-dibenz[*b,f*]-azepine (*cf.* ref 11), however, it was used directly to prepare the 10-keto derivative and is referred to below as crude methoxy compound.

B.—The crude methoxy compound obtained from above was dissolved in 50 ml of dry xylene and 10 g of NaH (56% mineral oil dispersion) was added and the mixture was refluxed for 2 hr. To this solution 5 g of $(Me)_2SO_4$ in 20 ml of xylene was added dropwise, refluxing was continued for 14 hr. The solution was cooled, the excess NaH was decomposed with H_2O and it was extracted with Et_2O. The Et_2O layer was washed (H_2O), dried ($CaSO_4$), and evaporated *in vacuo*. The crude product was passed through an Al_2O_3 column and 3.5 g [mp 145–146° (lit.[10] mp 145–146°)] of 5-methyl-10-methoxy-5*H*-dibenz[*b,f*]azepine was obtained.

C.—In a separate experiment, 2.4 g of crude methoxy compound from part A was refluxed with 75 ml of 2 *N* HCl for 1 hr; the mixture was cooled, extracted with C_6H_6, washed (H_2O), dried ($CaSO_4$) and the C_6H_6 removed under reduced pressure to yield 2 g of solid which on recrystallization from EtOH–Et_2O gave 5*H*-10,11-dihydro-10-dibenz[*b,f*]azepinone, mp 142–144°, lit.[12] mp 145–146°. 5-Methyl-10,11-dihydro-10-dibenz[*b,f*]azepinone (mp 103–104°, lit.[10] mp 104°) was prepared from the corresponding 5*H*-methyl-10-methoxy compound by similar HCl hydrolysis.

D.—A solution of 2 g of crude 5*H*-keto compound (part C), 2 g of AcCl, and 25 ml of C_6H_6 was refluxed for 2.5 hr, cooled, and poured into H_2O. The C_6H_6 layer was washed ($NaHCO_3$), separated, and dried ($CaSO_4$). Evaporation of the C_6H_6 gave 1.3 g, mp 137–138°, of 5-acetyl-10,11-dihydro-5*H*-10-dibenz[*b,f*]-azepinone (**17**). *Anal.* ($C_{16}H_{13}NO_2$) C, H.

10-Hydroxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—The procedure outlined is typical for the preparation of the three 10-hydroxy compounds shown in Table II. A solution of 8 g of 5*H*-10,11-dihydro-10-dibenz[*b,f*]azepinone and 5 g of $NaBH_4$ in 40 ml of EtOH was stirred for 15 hr at room temperature. The EtOH was removed *in vacuo* and the solid was treated with H_2O and extracted with Et_2O. The Et_2O solution was washed (H_2O), dried ($CaSO_4$), and evaporated under reduced pressure. The residual oily mass was triturated with hexane and the resulting solid was crystallized from EtOH–hexane; yield 6 g; mp 106–107°.

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(9) W. Schindler and H. Blattner, *Helv. Chim. Acta*, **44**, 753 (1961).

(10) W. Schindler and H. Blattner, Swiss Patent 389,619; *Chem. Abstr.*, **64**, 8159 (1966).

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(12) J. R. Geigy A.-G., British Patent, 943,277; *Chem. Abstr.*, **61**, 1815 (1964).

A New Class of 1,3-Benzoxazinones as Potential Central Nervous System Agents

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Salicylic acid, salicylamide, and their derivatives constitute a widely used family of analgetics, antipyretics, and antirheumatic agents[2] Numerous ana-

(1) (a) Taken in part from the M.S. Thesis of L. A. S., Lehigh University, 1969. (b) Supported by a grant (1 RO1MH-13562) from the National Institute of Mental Health.

(2) A. Burger in "Medicinal Chemistry," A. Burger, Ed., Interscience, New York, N. Y., 1960, pp 345–349.