

TABLE IV
N,N-DIETHYL-*p*-AMINOACETYL-2-AMINOBENZOTHAZOLE

No.	Surface anesthesia				Infiltration anesthesia			
	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			0.2	Nil		
	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*]azepines¹

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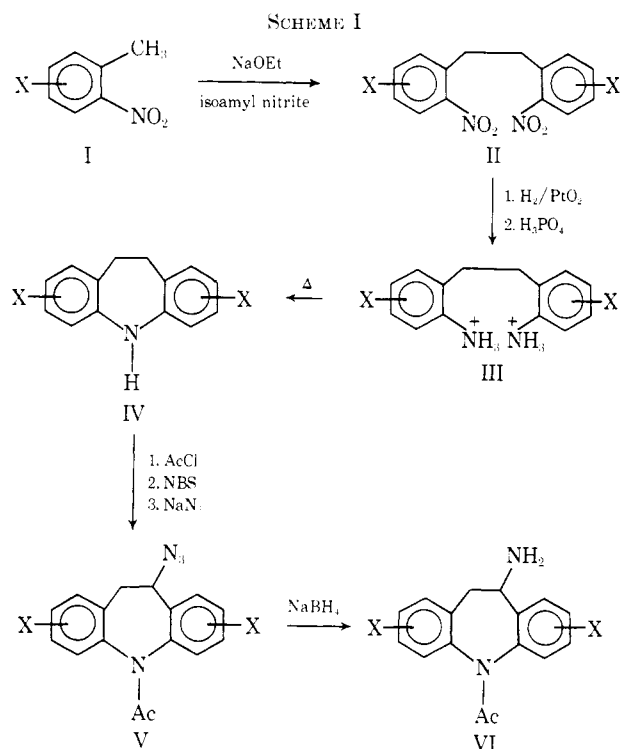
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As part of a continuing² investigation of potential novel antimalarials, we have prepared some representative 10-amino-10,11-dihydro-5*H*-dibenz[*b,f*]azepines for evaluation. For comparative purposes, we have also prepared some 10-hydroxy-10,11-dihydrodibenz[*b,f*]azepines. The synthetic approach employed for the 10-amino compounds is outlined in Scheme I. The

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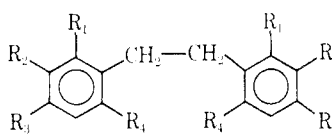
(2) (a) N. H. Berner, R. S. Varma, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 552 (1970); (b) R. S. Varma, L. K. Whisenant, and D. W. Boykin, Jr., *ibid.*, **12**, 913 (1969).



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

(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).

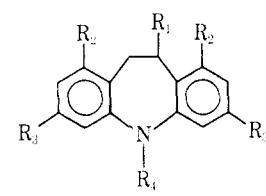
TABLE I



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 ₂ N ₂ O ₄	
2	Cl	H	H	NH ₂	85	160-161	C ₁₄ H ₁₄ Cl ₂ N ₂	C, H, N
3	H	Cl	H	NO ₂	60	151-152	C ₁₄ H ₁₀ Cl ₂ N ₂ O ₄	C, H, N
4	H	Cl	H	NH ₂	78	161-163	C ₁₄ H ₁₄ Cl ₂ N ₂	C, H, N
5	H	H	Cl	NO ₂	50	194-195 ^c	C ₁₄ H ₁₀ Cl ₂ N ₂ O ₄	
6	H	H	Cl	NH ₂	90	137-138	C ₁₄ H ₁₄ Cl ₂ N ₂	C, H, N

^a Recrystd 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 ₂ N		Hexane
8	NH ₂	Cl	H	Ac	48	216-217	C ₁₆ H ₁₄ Cl ₂ N ₂ O	C, H, N	EtOH
9	N ₃	H	H	Ac	78	131-132 dec	C ₁₆ H ₁₄ N ₄ O	C, H, N	Et ₂ O
10	NH ₂	H	H	Ac	73	94-98	C ₁₆ H ₁₆ N ₂ O	C, H, N	Et ₂ O
11	H	H	Cl	H	62	113-114 ^b	C ₁₄ H ₁₁ Cl ₂ N		Hexane
12	N ₃	H	Cl	Ac	76	99-100 dec	C ₁₆ H ₁₂ Cl ₂ N ₄ O	C, H, N	Et ₂ O
13	NH ₂	H	Cl	Ac	60	108-112	C ₁₆ H ₁₄ Cl ₂ N ₂ O	C, H, N	Et ₂ O
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 H₂-Pd-C failed⁴ to yield a compound identifiable as an amine by its ir spectra, however, reduction with NaBH₄ gave good yields of the 10-amino compounds VI.⁵

The 10-hydroxy compounds were obtained by NaBH₄ 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 $\pm 0.4\%$ of the theoretical values.

***o,o'*-Dinitrobenzyls.**—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 $50 \pm 5^\circ$ *in vacuo*. The NaOEt was suspended in Et₂O (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. Oslen, 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 H₂O, filtered, washed with Et₂O, 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 H₂ over PtO₂ (0.5 g) at ca. 3.15 kg/cm². When the theoretical amount of H₂ 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 H₃PO₄ and the resulting diphosphate salt was filtered, washed with Et₂O, and dried *in vacuo* at 100°.

10,11-Dihydro-5H-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 C₆H₆. The C₆H₆ solution was washed with dilute HCl, H₂O and dried; the solvent was removed under vacuum. The yield of 3,7-dichloro-10,11-dihydro-5H-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-5H-dibenz[b,f]azepines.—A suspension of 2.1 g of 5-acetyl-3,7-dichloro-10,11-dihydro-5H-dibenz[b,f]azepine (prepared by the reaction of AcCl with 3,7-dichloro-10,11-dihydro-5H-dibenz[b,f]azepine⁹) in 80 ml of CCl₄ 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-5H-dibenz[b,f]azepines.—To a stirred solution of 7 g of 5-acetyl-10-bromo-10,11-dihydro-5H-dibenz[b,f]azepine and 600 ml of Et₂O a solution of 5.5 g of NaN₃ in 25 ml of H₂O was added. The mixture was stirred for 16 hr at room temperature and the Et₂O layer was separated, washed, dried (CaSO₄), and Et₂O 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-5H-dibenz[b,f]azepine, 1.5 g of NaN₃, and 35 ml of MeOH was refluxed for 8 hr, cooled, poured into H₂O, and extracted with Et₂O. The Et₂O layer was washed with H₂O, 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-5H-dibenz[b,f]azepine was used directly in the next step without purification.

10-Amino-10,11-dihydro-5H-dibenz[b,f]azepines.—A solution of 9 g of 5-acetyl-10-azido-10,11-dihydro-5H-dibenz[b,f]azepine, 4.5 g of NaBH₄, and 150 ml of *i*-PrOH was refluxed for 14 hr, cooled, poured into H₂O, and extracted with Et₂O. The Et₂O layer was washed (H₂O), dried (CaSO₄), and evaporated under reduced pressure. The residual material was purified by chromatography over Al₂O₃, the eluent C₆H₆-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.

5H-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-

10,11-5H-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 H₂O, and extracted with Et₂O. The Et₂O was washed (H₂O), dried (CaSO₄), and evaporated under reduced pressure to yield a solid. The crude residue was not characterized; it is presumably 10-methoxy-5H-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)₂SO₄ in 20 ml of xylene was added dropwise, refluxing was continued for 14 hr. The solution was cooled, the excess NaH was decomposed with H₂O and it was extracted with Et₂O. The Et₂O layer was washed (H₂O), dried (CaSO₄), and evaporated *in vacuo*. The crude product was passed through an Al₂O₃ column and 3.5 g [mp 145–146° (lit.¹⁰ mp 145–146°)] of 5-methyl-10-methoxy-5H-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 C₆H₆, washed (H₂O), dried (CaSO₄) and the C₆H₆ removed under reduced pressure to yield 2 g of solid which on recrystallization from EtOH-Et₂O gave 5H-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 5H-methyl-10-methoxy compound by similar HCl hydrolysis.

D.—A solution of 2 g of crude 5H-keto compound (part C), 2 g of AcCl, and 25 ml of C₆H₆ was refluxed for 2.5 hr, cooled, and poured into H₂O. The C₆H₆ layer was washed (NaHCO₃), separated, and dried (CaSO₄). Evaporation of the C₆H₆ gave 1.3 g, mp 137–138°, of 5-acetyl-10,11-dihydro-5H-10-dibenz[b,f]azepinone (17). *Anal.* (C₁₆H₁₃NO₂) C, H.

10-Hydroxy-10,11-dihydro-5H-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 5H-10,11-dihydro-10-dibenz[b,f]azepinone and 5 g of NaBH₄ 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 H₂O and extracted with Et₂O. The Et₂O solution was washed (H₂O), dried (CaSO₄), 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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(1) W. Schindler and H. Blattner, Swiss Patent 392,515; *Chem. Abstr.*, **64**, 3506 (1966).

(2) 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 agents². Numerous ana-

(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).

(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.