2,10-dodecadienoic acid as a pale yellow oil. The acid was placed in 300 ml of BuOH and heated to 100°, and Na (10 g) was added in lumps during 30 min with stirring. The mixture was cooled, and about 200 ml of BuOH was removed under reduced pressure; then 150 ml of 1:1 MeOH–H_2O was added, and the mixture was refluxed 1 hr and reduced to a volume of about 100 ml at a pressure of 20 mm. The remainder was acidified with aqueous HCl and extracted with Et_2O. The Et_2O phase was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was treated with ethereal CH_2N_2 to give methyl 3,7,11-trimethyl-10-dodecenoate (3.0 g, 52%) which had bp 80–88° (0.5 mm). *Anal.* ($C_{16}H_{30}O_2$) C, H.

Methyl 10,11-Epoxy-3,7,11-trimethyldodecanoate.—Methyl 3,7,11-trimethyl-10-dodecenoate was epoxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 in the usual way. An analytical sample was collected on preparative glpc. *Anal.* ($C_{16}H_{30}O_3$) C, H.

Methyl 10,11-Epoxy-3,7,11-trimethyl-6-dodecenoate.—Methyl *trans*-6-farnesate was hydrolyzed, reduced, and esterified as for the preparation of methyl 3,7,11-trimethyl-10-dodecenoate. The product had bp 97–103° (0.1 mm) and was obtained in 47% yield. *Anal.* ($C_{16}H_{28}O_2$) C, H.

Epoxidation with *m*-chloroperbenzoic acid in CH_2Cl_2 in the usual way followed by purification by preparative glpc gave analytical samples for bioassay. *Anal.* ($C_{15}H_{28}O_3$) C, H.

Synthesis of Some Substituted 5H-Dibenz[*b*,*f*]azepines as Potential Antimalarials[1]

R. S. VARMA, L. K. WHISENANT, AND D. W. BOYKIN

Department of Chemistry, Georgia State College, Atlanta, Georgia 30303

Received May 21, 1969

As part of an investigation of potential novel antimalarials, we have prepared several of the 5-substituted 5H-dibenz[*b*,*f*]azepines for evaluation. The synthetic scheme employed begins with 9-chloroacridines and is essentially as reported by Bergmann, *et al.*[2] The details of the procedures are included in the Experimental Section.

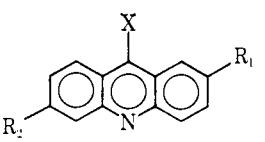
All of the compounds listed in Tables I–III were screened for antimalarial activity against *Plasmodium berghei* in mice by the method of Rane, *et al.*,[3] by the Walter Reed Army Institute of Research. All compounds except **12** and **13** were tested against *Plasmodium gallinaceum* in mosquitos.[4] Production of abnormal oocysts by **15** in the mosquito screen was observed, but no significant activity was noted for it in the mouse screen. None of the other compounds showed any significant activity in either of these tests. We are indebted to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck for these results.

Experimental Section

All melting points were obtained on a Thomas–Hoover Unimelt and are uncorrected. Satisfactory uv, ir, and nmr spectra were recorded for all new compounds. The uv and ir spectra were recorded using a Perkin-Elmer 202 spectrophotometer and a Perkin-Elmer Model 337 spectrophotometer, respectively. Nmr spectra were recorded on a Varian Model A-60A spectrophotometer (TMS internal standard). Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for these elements were within ±0.4% of the theoretical values.

9-Methylacridines.—The 9-chloroacridines used were prepared from the corresponding diphenylaminecarboxylic acids by the published methods.[5] In a typical preparation, to a solution of 35.4 g (0.52 mole) of NaOEt and 88 g (0.55 mole) of diethyl malonate in 350 ml of EtOH, was added 81.2 g (0.35 mole) of 2-fluoro-9-chloroacridine in 350 ml of PhMe, and the mixture was refluxed with stirring for 16 hr. To this mixture was added 800 ml of 18% HCl, the EtOH–PhMe was removed by distillation, and the resultant mixture was refluxed for 4 hr. To this mixture was added 800 ml of H_2O and the solution was filtered hot. The filtrate was cooled, the crystals were collected, and the crystalline material was suspended in 1 l. of H_2O and made alkaline with 10% NaOH solution. Filtration gave the crude 2-fluoro-9-methylacridine which was washed with cold H_2O, dried (30 g crude), and recrystallized from MeCN: yield 22 g (30%).

TABLE I



No.	X	R_1	R_2	Yield, %	Mp, °C[a]	Formula	Analyses	Recrystn solvent
1	CH_3	F	H	30	121–123	$C_{14}H_{10}FN$	C, H, N	MeCN
2	CHO	F	H	65	167–168	$C_{14}H_8FNO$	C, H, N	MeCN
3	CH_3	Cl	H	50	123–124 (124–125)[b]	$C_{14}H_{10}ClN$		EtOH
4	CHO	Cl	H	60	170–171 (169)[c]	$C_{14}H_8ClNO$		PhH
5	CH_3	OCH_3	Cl	65	167–169 (169–170)[d]	$C_{15}H_{12}ClNO$		EtOH
6	CHO	OCH_3	Cl	40	183–185 (185–186)[d]	$C_{15}H_{10}ClNO_2$		PhH

[a] Numbers in parentheses are literature melting points. [b] A. Champbell, C. S. Franklin, E. N. Morgan, and D. J. Tivey, *J. Chem. Soc.*, 1145 (1958). [c] O. Tsuge, M. Nishinohara, and M. Tashiro, *Bull. Chem. Soc. Japan*, **36**, 1477 (1963); *Chem. Abstr.*, **60**, 5455 (1964). [d] T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 583 (1949).

(1) We gratefully acknowledge the support of this investigation by the U. S. Army Medical Research and Development Command under Contract No. DADA17-68-C-8035. This is Contribution No. 592 from the Army Research Program on Malaria.

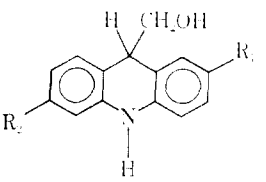
(2) E. D. Bergmann, M. Rabinovitz, and A. Bromberg, *Tetrahedron*, **24**, 1281 (1968).

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

(4) E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(5) A. Albert, "The Acridines," 2nd ed, St. Martin's Press, New York, N. Y., 1966, p 50.

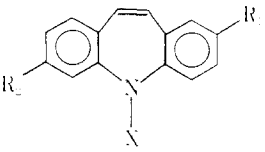
TABLE II



No.	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses	Recrystn solvent
7	F	H	85	148–149	$C_{14}H_{12}FNO$	C, H, N	PhH
8	Cl	H	90	119–120	$C_{14}H_{12}ClNO$	C, H, N	PhH–hexane
9	OCH_3	Cl	75	151–153 (153–154)[a]	$C_{15}H_{14}ClNO_2$		PhH–hexane

[a] Reference 2.

TABLE III



No.	X	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses	Recrystn solvent
10	H	F	H	30	175–177	$C_{14}H_{10}FN$	C, H, N	Cyclohexane
11	$(CH_2)_4N(CH_3)_2 \cdot C_4H_4O_4$[a]	F	H	15	133–134	$C_{23}H_{25}FN_2O_4$	C, H, N	EtOH–Et_2O
12	H	Cl	H	30	168–170	$C_{13}H_{10}ClN$	C, H, N	Cyclohexane
13	$(CH_2)_4N(CH_3)_2 \cdot C_4H_4O_4$[a]	Cl	H	50	125–128	$C_{23}H_{25}ClN_2O_4$	C, H, N	PhH–Et_2O
14	H	OCH_3	Cl	30	173–175 (176)[b]	$C_{15}H_{12}ClNO$		Cyclohexane
15	$(CH_2)_4N(CH_3)_2$	OCH_3	Cl	65	82–85 (88)[b]	$C_{20}H_{23}ClN_2O$	C, H, N	PhH–hexane
16	$(CH_2)_4N(CH_3)_2 \cdot C_4H_4O_4$[a]	H	H	50	146–148 (148–149)[c]	$C_{23}H_{26}N_2O_4$		PhH

[a] Maleate salt. [b] Reference 2. [c] P. N. Craig, B. M. Lester, A. J. Saggiomo, C. Kaiser, and C. R. Zirkle, *J. Org. Chem.*, **31**, 135 (1961).

9-Acridinecarboxaldehydes.- In a typical reaction, a mixture of 23.4 g (0.11 mole) of 2-fluoro-9-methylacridine, 35.3 g (0.24 mole) of N,N-dimethyl-4-nitrosoaniline, 20 drops of piperidine, and 150 ml of 2-pentanol was refluxed for 5 hr. The mixture was cooled, and the residue was filtered and washed with 95% EtOH. The nitrone was not purified but was used directly. A stirred slurry of crude nitrone in 300 ml of 12% HCl was heated on a steam bath for 5 min. Filtration gave the hydrochloride which was treated with excess 20% NaOAc solution to liberate the base, (21 g crude). Recrystallization from MeCN gave 16 g (65%).

9-Hydroxymethyl-9,10-dihydroacridines.- In a typical example, to a stirred suspension of 9.0 g of LAH in 200 ml of Et_2O under N_2, 18.9 g (0.084 mole) of 2-fluoro-9-acridinecarboxaldehyde was added in portions. After completion of addition, the mixture was stirred and refluxed for 3 hr. The mixture was cooled and worked up in the usual manner. The yield was 16.1 g (85%).

5H-Dibenz[*b*,*f*]azepines.- A mixture of 15 g of sea sand, 15 g of P_2O_5, and 50 ml of xylene under N_2 was heated to reflux and 2 g (0.009 mole) of 2-fluoro-9-hydroxymethyl-9,10-dihydroacridine was added quickly; the mixture was refluxed for 2 hr. Longer reflux time, in our hands, resulted in isolation of only 9-methylacridines (*cf.* ref 2). The mixture was cooled and extracted (PhH), the organic layer was dried ($CaSO_4$), and the solvent was removed under reduced pressure. The residue was taken up in PhH and chromatographed on an alumina column packed in hexane; PhH was used as the eluent. The yield after one recrystallization from cyclohexane was 0.6 g (30%).

5-(3-Dimethylaminopropyl)-5H-dibenz[*b*,*f*]azepines.- A mixture of 1.0 g (0.0047 mole) of 2-fluoro-5H-dibenz[*b*,*f*]azepine, 0.78 g of NaH (58% in an oil dispersion) and 70 ml of xylene were refluxed 2 hr under N_2. To this mixture was added dropwise a solution of 4.7 g (0.04 mole) of 3-N,N-dimethylaminopropyl chloride in 50 ml of xylene and the mixture was refluxed for 20 hr. The reaction mixture was treated with H_2O and extracted with Et_2O, the organic layer was dried ($CaSO_4$) and evaporated under reduced pressure, and the residue was chromatographed over alumina as described above. The oil obtained from the PhH eluent was treated with 0.27 g (0.023 mole) of maleic acid dissolved in 60 ml of EtOAc. Cooling overnight at −5° produced 0.25 g (15%) which was recrystallized from EtOH–Et_2O.

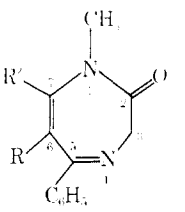
1,3-Dihydro-1-methyl-5,6- (and 5,7-) diaryl-2H-1,4-diazepin-2-ones

CORBIS M. HOFMANN and S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received April 11, 1969

Although a number of 2H-1,4-benzodiazepin-2-ones closely related to diazepam have been reported to show CNS depressant properties,[1] the monocyclic 1,3-



I

dihydro-2H-1,4-diazepin-2-one ring system I has not been described. This paper describes the preparation

(1) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Leir in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, p 237.