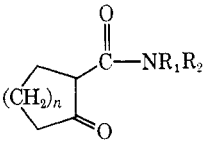
TABLE II



No.	NR_1R_2	n	Reaction time, hr	Bp (mm) and/or mp, °C	Recrystn solvent	Formula[b]
1		2	17.5	128–130 (0.05), 64.5–66.5[a]	Et_2O	$C_{12}H_9NO_2$[c]
2		2	23	145–150 (0.05), 79.5–81	Et_2O	$C_{11}H_{17}NO_3$
3		2	23	139–141 (0.05), 56–58	Hexane	$C_{13}H_{21}NO_2$
4		2	40	125–130 (0.05), 89–90.5	Et_2O	$C_{11}H_{17}NO_2$
5	Et_2	2	14 days	98–101 (0.05)		$C_{11}H_{19}NO_2$
6		1	3 days	124–126 (0.05)		$C_{11}H_{17}NO_2$

[a] H. Mohrle and H. Baumann, *Arch. Pharm. (Weinheim)*, **299**, 355 (1966), reported mp 65–67°. [b] All compounds were analyzed for C, H, N. [c] C: calcd, 68.86; found, 68.42.

cyclohexane ring with a cyclopentane ring (**17**) or benzene ring (**21**)[5b] eliminated hypoglycemic activity.

Experimental Section[6]

2-Cycloalkanonecarboxamides (1—**6**).—A mixture of the appropriate ethyl and methyl 2-cycloalkanonecarboxylates[7] (0.50 mole) and secondary amine (0.50 mole) were heated at reflux for the period of time given in Table II. After cooling, the low boiling constituents were removed on a rotary evaporator and the residue was vacuum distilled. A forerun, bp 60–70° (0.05 mm), of unreacted keto ester was collected and discarded. The higher boiling component was the desired keto amide. The physical data are listed in Table II.

2-(Substituted-amino)cycloalkanecarboxamides (**7**—**17**).—A mixture of the keto amide (I) (0.050 mole), the primary or secondary amine (0.050 mole), C_6H_6 (125 ml), and *p*-TsOH (0.5 g) was heated at reflux with an azeotropic separator until H_2O separation ceased. The solvent and excess amine were removed on a rotary evaporator and the residue was dissolved in abs EtOH (200 ml) and hydrogenated (PtO_2, 0.5 g) at an initial pressure of 3.5 kg/cm². The catalyst was filtered off and the solvent was removed on a rotary evaporator. The residue was dissolved in Et_2O (0.5 l), washed (H_2O, 2 × 75 ml), and dried ($MgSO_4$). The solvent was removed on a rotary evaporator and the residue was recrystd and/or converted into the hydrochloride. Recrystn solvents and physical data are given in Table I.

2-(Piperidino)cyclohexanecarboxamides (**18 and 19**).—A soln of the appropriate isocyanate (0.33 mole) in dry C_6H_6 (200 ml) was added dropwise to a stirred, refluxed soln of 1-(1-cyclohexen-1-yl)piperidine (0.33 mole) in C_6H_6 (200 ml). The soln was refluxed for 17 hr and then hydrogenated (PtO_2, 1.0 g) at an initial pressure of 3.5 kg/cm². The catalyst was removed by filtration and the filtrate was extracted with dil HCl (2 × 300 ml). The combined aq extracts were made basic with aq NaOH and extracted with CH_2Cl_2 (3 × 250 ml). The combined organic extracts were washed with H_2O (1 × 100 ml) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator and the residue was recrystd or converted into the hydrochloride (see Table I).

1-(2-Piperidinobenzoyl)piperidine (**21**).—A mixture of 1-anthraniloylpiperidine[8] (7.2 g, 0.035 mole,) 1,5-diiodopentane (11.5 g, 0.035 mole), K_2CO_3 (11.0 g, 0.080 mole), and PhMe (125 ml) was refluxed with stirring for 4.5 days. The ppt was removed by filtration and the filtrate was extracted with dil HCl (2 × 125 ml). The combined extracts were made basic with aq NaOH and extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts were washed with H_2O (1 × 50 ml) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to afford 6.9 g of **21** (73% yield). Repeated attempts to obtain this material in a crystalline state were unsuccessful. The ir, nmr, and mass spectra were in accord with the assigned structure. *Anal.* ($C_{17}H_{24}N_2O$) H, N.

Acknowledgment.—The authors are indebted to Dr. M. Grostic and Mr. R. J. Wnuk for mass spectra, Mr. P. A. Meulman for ir spectra, and Mr. N. H. Knight and his associates for analytical data.

(6) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds were supported by ir and nmr spectra and, in many cases, by mass spectra. Ir spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, nmr spectra on a Varian A-60A spectrometer, mass spectra on an Atlas CH_4 spectrometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(7) Aldrich Chemical Company, Inc., Milwaukee, Wis.

(8) Prepared according to the procedure of N. J. Leonard, W. V. Royle, and L. C. Bannister, *J. Org. Chem.*, **13**, 617 (1948).

Synthesis of Some 10-Cycloalkylaminodibenz[*b*,*f*]azepines[1]

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As part of our continuing study of possible novel antimalarials, we have synthesized several substituted 10-cycloalkylaminodibenz[*b*,*f*]azepines for screening.[2] Included in this report is the preparation of representative members of the 5*H*-, 5*H*-acetyl-, and 5*H*-alkyl-series of 10-cycloalkylaminodibenz[*b*,*f*]azepines.

The method of preparation of the title compounds is outlined in Scheme I. The approach we recently reported for preparation of the 10-bromo-10,11-dihydrodibenz[*b*,*f*]azepines was used to synthesize the required starting materials I.[2a] The reactions involved in the conversion of I, *via* II, into III proceeded reasonably

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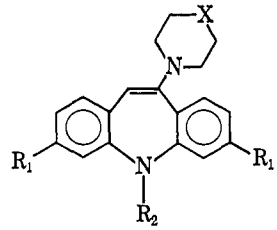
(1) We acknowledge the U. S. Army Medical Research and Development Command under Contract No. DADA17-68-C-8035 for support of this work. This is Contribution No. 846 from the Army Research Program on Malaria.

(2) (a) B. P. Das, R. W. Woodard, L. K. Whisenant, W. F. Winecoff, III, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 979 (1970). (b) N. H. Berner, R. S. Varma, and D. W. Boykin, Jr., *ibid.*, **13**, 552 (1970). (c) R. S. Varma, L. K. Whisenant, and D. W. Boykin, Jr., *ibid.*, **12**, 913 (1969).

TABLE I



No.[a]	R_1	R_2	X	Mp, °C	% yield	Recrystn solvent	Formula[a]
1	H	Ac	CH_2	148–149	70	Hexane	$C_{21}H_{22}N_2O$
2	H	Ac	$N(CH_3)$	163–164[b]	28	Hexane–Et_2O	$C_{21}H_{23}N_3O$
3	H	Ac	O	221–222	70	EtOH	$C_{20}H_{20}N_2O_2$
4	H	Ac	$N(C_6H_5)$	207–208	37	EtOH–hexane	$C_{26}H_{25}N_3O$
5	H	Ac	$N(CO_2Et)$	156–157	20	Et_2O–hexane	$C_{23}H_{25}N_3O_3$
6	H	H	CH_2	134–135	70	Hexane	$C_{19}H_{20}N_2$
7	H	H	$N(CH_3)$	170–171	85	Et_2O	$C_{19}H_{21}N_3$
8	H	CH_3	CH_2	138–139	57	Hexane	$C_{20}H_{22}N_2$
9	Cl	Ac	CH_2	203–204	20	Hexane	$C_{21}H_{20}Cl_2N_2O$
10	Cl	H	$N(CH_3)$	176–177	15	Et_2O	$C_{19}H_{19}Cl_2N_3$
11	Cl	CH_3	$N(CH_3)$	240–242	20	EtOH–Et_2O	$C_{20}H_{21}Cl_2N_3$

[a] All compounds were analyzed for C, H, N and the analytical results for these elements were within ±0.4% of the theoretical values. [b] Lit. mp 158–160°; ref 4b.

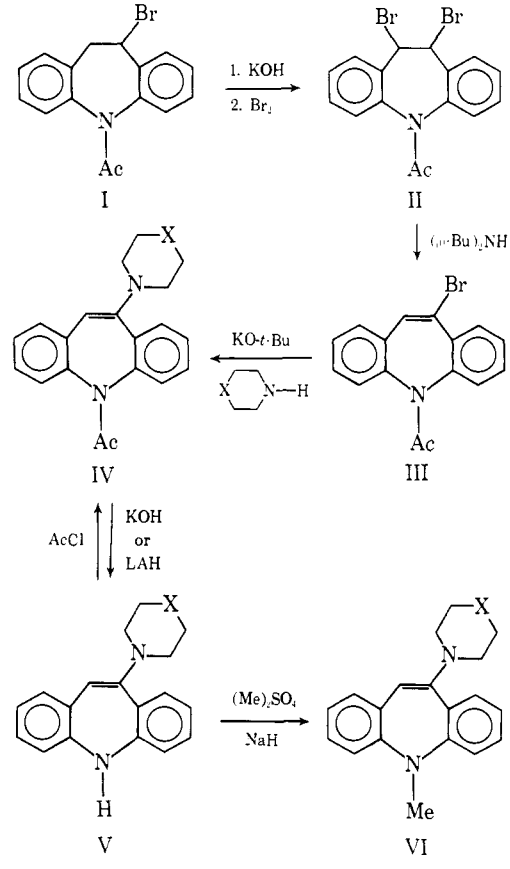
well.[3] Conversion of the 10-bromodibenz[*b*,*f*]azepines III into the cycloalkylamino derivatives could not be accomplished by heating with the appropriate amine alone. Good yields of the substituted 10-cycloalkylaminodibenz[*b*,*f*]azepines were obtained, however, when the amine and the 10-bromo compound were heated in the presence of the strong base, KO-*t*-Bu.[4]

Only cleavage of the amide bond was observed in attempts to prepare 5*H*-ethyl-10-cycloalkylaminodibenz[*b*,*f*]azepines by reduction of the 5*H*-Ac compounds with LAH. The structure of the cleavage product V was established by its identity with the product of alkaline hydrolysis of IV and by its conversion into IV by the action of AcCl.

An unexpected case of restricted rotation isomerism was detected from the nmr spectra of the 5*H*-acetyl-10-cycloaminodibenz[*b*,*f*]azepines V. For example, **1** showed, in addition to the aromatic multiplet centered at *ca.* τ 2.6 and broad 4 H and 6 H signals at τ 7.0 and 8.35, two signals at 3.75 and 3.85 which integrated for a total of 1 proton and a 3H doublet at 8.1. That the two doublets at *ca.* τ 3.8 and 8.1 arose from restricted rotation isomerism involving the amide group, rather than from the *a priori* possible restriction of rotation around N-10, enamine restricted rotation, was shown by the absence of two signals for the olefinic proton in the 5*H*- and 5*H*-Me compounds, **6** and **8**. In these compounds, the olefinic protons were sharp singlets at τ 4.05 and 3.95, respectively. All the 5*H*-Ac compounds shown in Table I exhibited two signals for the olefinic proton.

The requirement of the action of strong base to prepare the 10-cycloalkylaminodibenz[*b*,*f*]azepines suggested their formation by a dehydrohalogenation–addition mechanism (*cf.* 4a). To test this point, we treated 10-bromo-5*H*-acetyldibenz[*b*,*f*]azepine with KO-*t*-Bu in the presence of furan. The furan adduct **12** was isolated which convincingly argues for the intermediacy of a hetaryne. The structure of the adduct, whose nmr spectrum was atypical (see Experimental Section), was clearly demonstrated by its mass spectra which showed a parent ion peak at *m/e* 301.

SCHEME I

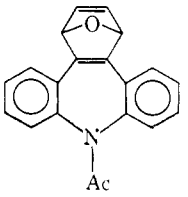


The compounds listed in Table I, except **8** and **11**, were tested for antimalarial activity against *Plasmodium berghi* in mice according to the method of Rane, *et al.*,[5] by the Walter Reed Army Institute of Research.

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

(4) *Cf.* (a) W. Tochtermann, K. Appenlander, and U. Walter, *Ber.*, **97**, 318 (1964). (b) Richardson-Merrell, S.p.A., Belgian Patent 712851. (c) Farmochimica CutoloCalosi, S.p.A., Netherlands Application 6,609,437; *Chem. Abstr.*, **67**, 90698 (1967).

The greatest increase in survival time observed was 2.5 days at a dose of 640 mg/kg when the mice were treated with **10**. Furthermore, no activity was observed when **3**, **4**, **6**, **7**, and **9** were tested against *P. gallinaceum* in chicks.



12

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 obtained using a Perkin-Elmer Model 337 spectrophotometer, nmr spectra in $CDCl_3$ solns of the compounds using a Varian Model A-60A spectrophotometer (TMS internal standard). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlab, Inc., Atlanta, Ga.

Preparation of 5*H*-Acetyl-10-bromodibenz[*b*,*f*]azepines (II).—To a soln of 5*H*-acetyl-10-bromo-10,11-dihydrodibenz[*b*,*f*]azepine[2a] (45 g) in 200 ml of EtOH was added 75 ml of a 50% aq KOH and the reaction mixture was maintained at 50–60° for 30 min. The soln was diluted with H_2O, extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$) and the Et_2O removed to yield 29 g of crude 5*H*-acetyldibenz[*b*,*f*]azepine. Recrystallization from hexane–Et_2O gave 24 g; mp 121–122°.[3]

To a cooled soln of 24 g of 5*H*-acetyldibenz[*b*,*f*]azepine in 100 ml of $CHCl_3$, cooled in an ice bath, 16 g of Br_2 in 25 ml of $CHCl_3$ was added dropwise. After addn was complete, the soln was stirred for 0.5 hr, treated with charcoal, and filtered. The filtrate was cooled at −10° and the resulting precipitate was filtered, washed with hexane (mp 136–138°, yield 35 g), and used directly as follows.

A mixture of 35 g of 5*H*-acetyl-10,11-dibromo-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine and 35 g of *n*-Bu_2NH was warmed cautiously on a steam bath until an exothermic reaction occurred after which the soln was stirred and heated on the steam bath for 20 min. The reaction mixture was extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$) and the Et_2O was removed under reduced pressure. The resulting residue crystallized on standing overnight. The crystals were filtered, washed with cold Et_2O, and recrystd from EtOH; mp 108–109°; lit. mp 109–110°;[3] yield 18 g.

5*H*-Acetyl-10-cycloalkylaminodibenz[*b*,*f*]azepines (IV).—In a typical example, to a soln of 2.05 g of 5*H*-acetyl-10-bromodibenz[*b*,*f*]azepine in 50 ml of *t*-BuOH, which had been dried over 4A molecular sieves, was added 0.8 g of KO-*t*-Bu and 8 g of *N*-methylpiperazine and the soln was refluxed for 15 hr. The reaction mixture was poured into H_2O, extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$) and the Et_2O was removed under reduced pressure to yield a gummy residue which crystd from hexane–Et_2O on standing overnight. Recrystn from hexane–Et_2O gave a solid; mp 163–164°; yield 1.4 g.

5*H*-10-Cycloalkylaminodibenz[*b*,*f*]azepines (V).—A soln of 0.9 g of *N*-(5*H*-acetyldibenz[*b*,*f*]azepine-10-yl)-*N'*-methylpiperazine in 25 ml of 50% alcoholic KOH was refluxed for 2 hr, poured into H_2O, and extracted with Et_2O. The ether layer was washed (H_2O), dried ($CaSO_4$), and evaporated under reduced pressure. The resulting yellow solid was crystd from Et_2O–hexane; mp 170–171°; yield 0.6 g.

Attempted Reduction of *N*-(5*H*-acetyldibenz[*b*,*f*]azepine-10-yl)-*N'*-methylpiperazine with LAH.—To a stirred suspension of 0.5 g of LAH in 25 ml of THF maintained at 0° was added a soln of 1 g of **2** in 25 ml of THF under N_2. The mixture was stirred for 30 min and then at room temp for 30 min, decomposed with H_2O in the usual manner, extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$), and Et_2O was removed under reduced pressure to yield 0.7 g of yellow solid which on crystn from Et_2O–hexane gave a mp of 170–171°. The compd was identified by its ir and nmr spectra and by mmp with a sample material obtained from the above experiment. It was converted back into **2** by refluxing with AcCl in C_6H_6 in a manner similar to that described previously.[2c]

5*H*-Methyl-10-cycloalkylaminodibenz[*b*,*f*]azepines (VI).—A soln of *N*-(5*H*-dibenz[*b*,*f*]azepin-10-yl)piperidine (0.5 g), 0.3 g of NaH in 50 ml of PhMe was refluxed under N_2 for 2 hr. The soln was cooled and 1.5 g of Me_2SO_4 in 10 ml of PhMe was added dropwise and refluxing was contd for an additional 20 hr. The reaction mixture was cooled, excess NaH was decompd with H_2O, extracted with C_6H_6, washed (H_2O), and dried ($CaSO_4$) and the solvent was removed under reduced pressure. The residue was dissolved in hexane; after storage at −10° 0.3 g, mp 135–136° was obtained. Recrystallization from hexane raised the melting point to 138–139°.

Trapping of the Hetaryne with Furan.—A soln of 2.1 g of 5*H*-acetyl-10-bromodibenz[*b*,*f*]azepine and 1.0 g of KO-*t*-Bu in 15 ml of *t*-BuOH, and 30 ml of furan was refluxed for 20 hr. The reaction mixture was poured into H_2O, extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$). Evapn of the Et_2O gave a residue which was triturated with hexane and crystallized from EtOH. The yield of **12** was 0.5 g which melted at 236–237°; nmr τ 8.15 (3 H singlet), 4.12 (2 H singlet), and 2.7 (10 H multiplet). *Anal.* ($C_{20}H_{15}NO_2$) C, H, N.

Acknowledgments.—We are indebted to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck for the test results. We wish to thank Dr. Steck for helpful discussions.

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

Synthesis and Chemotherapeutic Activity of Two Metabolites of Trimethoprim

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2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (trimethoprim[1]) (**1**) shows antibacterial[1] and antimalarial[2] activity and potentiates[3] sulfonamides such as 5-methyl-3-sulfanilamidoisoxazole (sulfamethazole[4]) to provide a clinically useful broad spectrum antibacterial agent.[5] Of the metabolites of **1**, isolated from the urine of man and animals and identified[6] as M_1 (**2**), M_2 (**4**), M_3 (**5**), and M_4 (**6**), the synthesis of **5** and **6** has recently been accomplished.[7] We now report a facile synthesis of the two major metabolites **2** and **4** and their chemotherapeutic activity.

Treatment of **1** with 48% HBr cleaved preferentially[8] the middle of the three MeO groups to provide the monophenol **2**, previously obtained by a multistep synthesis.[9] Oxidation of **1** with MnO_2 gave the ketone **3** which was reduced with $NaBH_4$ to afford the alcohol **4**.

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(1) B. Roth, E. A. Falco, G. H. Hitchings, and S. R. M. Bushby, *J. Med. Pharm. Chem.*, **5**, 1103 (1962).

(2) D. C. Martin and J. D. Arnold, *J. Clin. Pharmacol.*, **7**, 336 (1967).

(3) E. Grunberg and W. F. DeLorenzo, *Antimicrob. Ag. Chemother.*, **1966**, 430 (1967), and ref cited therein.

(4) GANTANOL.

(5) BACTRIM; E. Böhni, *Chemotherapy Suppl.*, **14**, 1 (1969).

(6) D. E. Schwartz, G. Englert, and W. Vetter, *Arzneim.-Forsch.*, **20**, in press (1970).

(7) G. Rey-Bellet and R. Reiner, *Helv. Chim. Acta*, **53**, 945 (1970).

(8) For related preferential O-demethylations, see S. Teitel and A. Brossi, *J. Med. Chem.* **13**, 333 (1970), and ref cited therein.

(9) B. Roth and J. Z. Strelitz, Netherland Patent 6702397 (1967).