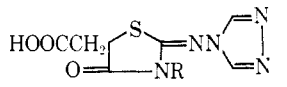
TABLE II



No.	R	Reaction time, hr	Mp, °C	Yield, %	Formula[a]
1	p-$C_2H_5OC_6H_4$	15	263–265	17	$C_{15}H_{15}N_5O_3S$
2	p-ClC_6H_4	10	260–263	20	$C_{13}H_{10}ClN_5O_3S$
3	2,4-$Me_2C_6H_3$	17	262–264	4	$C_{15}H_{15}N_5O_3S$
4	o-$CH_3OC_6H_4$	10	239–241	2	$C_{14}H_{13}N_5O_4S$

[a] See Table I, footnote *a*.

fied as degradation products. These results favor structure **3a** and such hydrolytic cleavages are known to have synthetic importance for the synthesis of thiazolidinediones.[13]

The antiviral activity was tested with Herpes simplex virus as described earlier.[14] At 3.10^{-3}–5.10^{-4} M the test compounds were found to be either toxic or inactive (**2**, R = C_6H_5; and **3**, R = p-$C_2H_5OC_6H_4$).

Experimental Section[15]

1-(1,2,4-Triazolyl-4)-3-phenylthiourea (1, **R** = C_6H_5).—A mixture of 4-amino-1,2,4(4*H*)-triazole[16] (8.4 g, 0.1 mole), phenyl isothiocyanate (13.5 g, 0.1 mole), and EtOH (30 ml) was heated on a water bath for 15 min. The product which sepd upon cooling was collected, washed with EtOH, and recrystd from the same solvent: yield 15.0 g (68%); mp 175° (lit.[17] mp 105°). *Anal.* ($C_9H_9N_5S$), C, H, N.

By the same procedure other substituted triazolylthioureas were obtained (Table I). In all cases EtOH was used as solvent for recrystn. If the product did not sep or if only a little of the product sepd, the solvent was evapd *in vacuo* to dryness and the residue was then purified by crystn.

2-[(1,2,4-Triazolyl-4)imino]-3-phenyl-5-carboxymethylthiazolidin-4-one (2, **R** = C_6H_5).—A mixture of 1 (R = C_6H_5; 4.38 g, 0.02 mole), finely powdered maleic anhydride (1.96 g, 0.02 mole), anhyd C_6H_6 (50 ml), and anhyd Me_2CO (50 ml) was heated under reflux on a water bath for 24 hr. Some Me_2CO was added and the mixture heated to boiling to give an almost clear soln. Upon filtration the filtrate was evapd to dryness *in vacuo* and the residue recrystd from Me_2CO to give 0.45 g (7%) of the pure compound, mp 251–253°. *Anal.* ($C_{13}H_{11}N_5O_3S$), C, H, N, S.

In practically the same way other 3-substituted derivatives (**2**) were prepd (Table II). All compds were purified by recrystn from EtOH.

2-Phenylimino-3-(1,2,4-triazol-4-yl)thiazolidine (3, **R** = C_6H_5).—To a soln of **1** (R = C_6H_5; 2.19 g, 0.01 mole) in DMF (10 ml) anhyd K_2CO_3 (1.39 g, 0.01 mole) and 1,2-dibromoethane (1.88 g, 0.01 mole) were added and the reaction mixture was stirred at room temp for 13 hr. The product was filtered off and recrystd from EtOH: yield 0.6 g (24%); mp 190–192°. *Anal.* ($C_{11}H_{11}N_5S$), C, H, N. The same compound could be obtained in 49% yield if instead of K_2CO_3 20 ml of DMF was used altogether.

In an analogous way the following 3-(1,2,4-triazol-4-yl)-thiazolidines were synthesized and crystd from EtOH.

2-(p-Chlorophenylimino) (**3**, R = p-ClC_6H_4) was obtained in 6% yield, mp 223–225°. *Anal.* ($C_{11}H_{10}ClN_5S$), C, H, N, S.

2-(p-Ethoxyphenylimino) (**3**, R = p-$C_2H_5OC_6H_4$) was obtained in 9% yield, mp 198–200°. *Anal.* ($C_{13}H_{15}N_5OS$), C, H, N, S.

2(p-Methoxyphenylimino) (**3**, R = p-$CH_3OC_6H_4$) was obtained in 6% yield, mp 231–233°. *Anal.* ($C_{12}H_{13}N_5OS$), C, H, N.

Hydrolysis of 2-Phenylimino-3(1,2,4-triazol-4-yl)thiazolidine.—Compd **3** (R = C_6H_5; 0.5 g) was heated with 10 ml of HCl (1:2) at 200° in a sealed tube for 1 hr. After evapn *in vacuo* to dryness the residue was sublimed *in vacuo* and afforded a colorless compd, mp 196°, which by mmp and ir spectra was identified with an authentic specimen of $PhNH_3^+Cl^-$.

Hydrolysis of 2-phenylimino-3-phenylthiazolidine[18] was done in essentially the same manner and upon evaporating the reaction mixture *in vacuo* the known 3-phenylthiazolidin-2-one[18] was isolated.

(13) H. Aspelund, *Acta Acad. Aboensis, Math. Phys.*, **24**, 1 (1964).

(14) P. Schauer and M. Likar, *Pathol. Microbiol.*, **28**, 371 (1965).

(15) Melting points were determined on a Kofler heating microscope and are corrected.

(16) C. F. H. Allen and A. Bell "Organic Syntheses," Collect. Vol. 3, Wiley, New York, N. Y., 1955, p 96.

(17) M. S. Solanki and J. P. Trivedi, *J. Indian Chem. Soc.*, **42**, 817 (1965).

(18) W. Will, *Ber.*, **15**, 344 (1882).

cis-1-[(2-Piperidinocyclohexyl)carbonyl]-piperidine and Related Compounds. Oral Hypoglycemic Agents

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Screening for antidiabetic agents revealed that *cis*-1-[(2-piperidinocyclohexyl)carbonyl]piperidine hydrochloride (**7a**, Table I), possessed good hypoglycemic activity in the glucose-primed, fasted, intact rat. This compound is a representative of a class of compounds not previously associated with hypoglycemic activity. As a result, a study aimed at obtaining insight into the various structural features necessary for hypoglycemic activity in this class of compounds was made.

Chemistry—Compounds **1**—**17** were prepared according to the synthetic sequence outlined in Scheme I. The desired synthetic intermediates (I) were obtained by refluxing a mixture of equiv amounts of the appropriate mixture of Et and Me 2-oxocycloalkanonecarboxylate and secondary amine for 17.5 hr–14 days. Treatment of these keto amides with primary or secondary amines in benzene, according to the method of Stork and coworkers,[1] afforded the enamines which were hydrogenated (PtO_2) to afford compounds II.

Compounds **18** and **19** were prepared according to the sequence outlined in Scheme II. Treatment of 1-(1-cyclohexen-1-yl)piperidine with phenyl and cyclohexyl isocyanate, according to the method of Hunig and coworkers,[2] afforded the enamine intermediates which were catalytically reduced to compounds II (NR_3R_4 = piperidino).

Biological Testing.—Glucose-primed, fasted (18–24 hr), Upjohn Sprague–Dawley, pathogen-free, male rats were the test animals. The test compound was administered orally at various dosages in 0.5 ml of sterile vehicle (6 rats/group). Immediately following admin-

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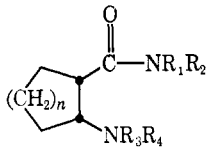
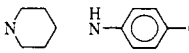
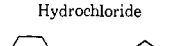
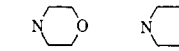
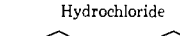
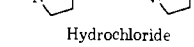
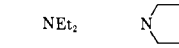
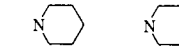
(1) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(2) S. Hunig, K. Hubner, and E. Benzing, *Chem. Rev.*, **95**, 926 (1962).

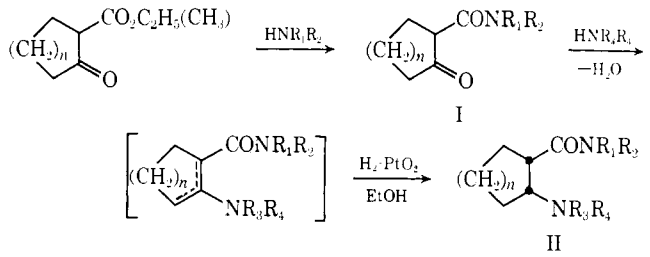
TABLE I



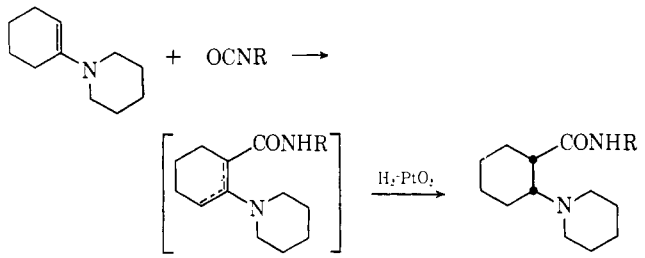
No.	n	NR_1R_2	NR_3R_4	Mp, °C	Recrystn solvent	Formula	Analysis	Relative activity[a]
7	2			84.5–86.5	Hexane	$C_{17}H_{30}N_2O$	C, H, N	0.6
7a		Hydrochloride		220–221	EtOH–Et_2O	$C_{17}H_{31}ClN_2O$	C, H, Cl, N	0.5
8	2			90–91.5	Skelly B[b]	$C_{19}H_{28}N_2O_2$	C, H, N	0.0
9	2			195–196	EtOH–Et_2O	$C_{16}H_{29}ClN_2O_2$	C, H, Cl, N	0.0
10	2			192–193.5	EtOH–Et_2O	$C_{16}H_{29}ClN_2O$	C, H, Cl, N	0.5
11	2			97.5–98.5	Et_2O	$C_{15}H_{26}N_2O_3$	C, H, N	0.0
11a		Hydrochloride		226–228	EtOH–Et_2O	$C_{15}H_{27}ClN_2O_3$	C, H, Cl, N	0.0
12	2			66.5–68	Hexane	$C_{15}H_{26}N_2O_2$	C, H, N	0.15
12a		Hydrochloride		215–216.5	EtOH–Et_2O	$C_{15}H_{27}ClN_2O_2$	C, H, Cl, N	0.0
13	2			101–102.5	Et_2O	$C_{16}H_{28}N_2O_2$	C, H, N	0.0
13a		Hydrochloride		211–213	EtOH–Et_2O	$C_{16}H_{29}ClN_2O_2$	C, H, Cl, N	0.25
14	2			191–192.5	EtOH–Et_2O	$C_{19}H_{35}ClN_2O$	C,[c] H, Cl, N	0.76
15	2			72.5–73.5	Hexane	$C_{15}H_{26}N_2O$	C, H, N	0.27
15a		Hydrochloride		223.5–225	EtOH–Et_2O	$C_{15}H_{27}ClN_2O$	C,[d] H, Cl, N	0.25
16	2			191–193	CCl_4	$C_{16}H_{31}ClN_2O$	C, H, N	0.7
17	1			86–87.5	Hexane	$C_{16}H_{28}N_2O$	C, H, N	0.0
18	2			229–230	EtOH–Et_2O	$C_{18}H_{33}ClN_2O$	C, H, Cl, N	0.0
19	2			92–94	Hexane	$C_{18}H_{26}N_2O$	C, H, N	0.0

[a] Activity in rat: tolbutamide = 1. [b] Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. [c] C: Calcd, 66.51; found, 66.05. [d] C: Calcd, 62.76; found, 63.17.

SCHEME I

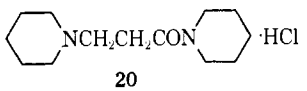


SCHEME II



istration of the test material, the animals were injected sc with 125 mg of glucose in 1 ml of 0.9% saline. Two hours later the rats were bled, *via* the vena cava, while under Cyclopal[3] anesthesia and blood glucose concentrations were determined by AutoAnalyzer, which utilizes a modification of a method described by Hoffman.[4] The relative activity of the test compound to that of tolbutamide is recorded in Table I.

Structure–Activity Relationship Considerations.—Compounds **14** and **16** possessed hypoglycemic activity comparable to that of the initial lead, **7a.** Replacement of either (**9, 13,** and **13a**) or both (**11** and **11a**) piperidino groups with morpholino groups eliminated or drastically reduced hypoglycemic activity. Replacement of either piperidino group with an aromatic amine (**8** and **19**) abolished hypoglycemic activity. Deletion of the cyclohexane ring (**20**),[5a] or replacement of the



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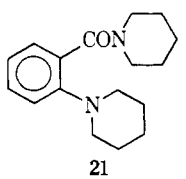


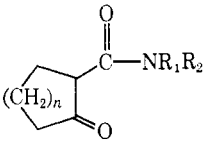
21

(3) 5-Allyl-5-(2-cyclopenten-1-yl)barbituric acid.

(4) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(5) (a) Prepd according to the procedure of E. Profft and A. Jumas, *Arch. Pharm.*, **289**, 90 (1956). (b) The prepn of this compound is described in the Experimental Section.

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).