was obtained by dissolving the white solid in ether, treating with decolorizing carbon, and triturating the product with ether–pentane (1:1): NMR (acetone-d_6) 2 H at δ 3.80 (s), 1 H at δ 7.08 (s), 1 H at δ 7.32 (s), and 2 H at δ 8.36 (s, broad); ir (KBr) 4.42 μ (nitrile); λ_{max} (ethanol) 290 nm (ϵ 3892). Anal. ($C_8H_6INO_2$) C, H.

3,4-Dihydroxy-6-iodophenylethylamine Hydrochloride (1·HCl). To 0.025 g (9.1×10^{-5} mol) of **8** in 0.2 ml of THF was added 0.8 ml of borane solution (Alfa, 1.1 M in THF) and the reaction mixture was allowed to stand at 25° for 10 min. The solvent was removed using a stream of N_2 and 1 ml of D_2O acidified with HCl added. This was evaporated to dryness and D_2O added. A TLC of the resulting solution on silica G using 15:3:5 BuOH–HOAc–H_2O showed one spot (uv active) with R_f 0.65 which stains prussian blue with $K_3Fe(CN)_6$-$FeCl_3$ reagent and rose gray with ninhydrin reagent. The NMR (D_2O + DSS) was identical with that of the material produced by BBr_3 cleavage of **5**.

Acetylation of 5. To 0.111 g of **5**·HCl (3.23×10^{-4} mol) in 2 ml of H_2O was added 0.5 ml of 10 M NaOH. The free base was extracted into ethyl acetate–ether (1:1). The extracts were dried (K_2CO_3) and the solvent was removed using a stream of nitrogen. To 2 ml of CH_2Cl_2 and 2 ml of BBr_3 solution (10% in CH_2Cl_2) was added, with stirring, the amine in 3 ml of CH_2Cl_2. This was stirred for 10 min and the solvent and excess BBr_3 were removed with a stream of nitrogen. An additional 2 ml of CH_2Cl_2 was added to the residue and the solvent removed again. The residue was dissolved in 3 ml of water and 1 g of $NaHCO_3$ was added followed by the dropwise addition 0.5 ml of acetic anhydride. The mixture was stirred for 15 min or until gas evolution ceased. The mixture was extracted with CH_2Cl_2, the extracts were washed with water and dried over K_2CO_3, and the solvent was removed to yield 0.098 g (75%) of **10** as a colorless oil which slowly crystallized on standing in ether: mp 76.5–78°; NMR ($CDCl_3$) 3 H at δ 1.92 (s), 6 H at δ 2.24 (s), 2 H at δ 2.8–3.0 (m), 2 H at δ 3.2–3.6 (m), 1 H at δ 5.92 (s, broad), 1 H at δ 6.96 (s), and 1 H at δ 7.54 (s); ir (KBr) 1771 cm^{-1} (C=O); MS (80 eV) m/e 405 (M^+, 8), 278 (M^+ - I, 34), 262 (100), 249 (80), 236 (40), 194 (52), 136 (85). Anal. ($C_{14}H_{16}INO_5$) C, H, N.

Animal Experiments. Two mongrel dogs (anesthetized with Surital) were injected with 100–1500 μCi of radioiodinated 6-iododopamine (1.29×10^{-6} mol) in saline. The dogs were sacrificed at 2 and 24 h. Three samples of large organs were taken and averaged and small organs (ovaries, adrenals, and thyroids) were taken intact and counted. Mice and rats were injected intravenously ($8–11 \times 10^{-8}$ mol/mouse and 3.6×10^{-8} mol/rat) and sacrificed by ether overdose. Whole organs were counted.

Acknowledgment. We thank Dr. David Christman for running the mass spectra.

References and Notes

(1) Research performed under the auspices of the U.S. Energy Research and Development Administration. By acceptance of this article, the publisher and/or recipient acknowledges the U.S. Government's right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.
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(17) Na^{123}I was obtained as reductant-free saline solution from the Brookhaven Linac Isotope Producer (BLIP) to which NaOH was added to give a 0.1 N NaOH solution.
(18) Radiochemical yield = activity in product × 2 (statistical correction)/starting activity.

Antimalarials. 8. Synthesis of Amino Ethers as Candidate Antimalarials

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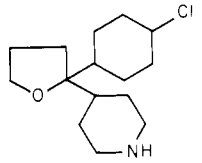
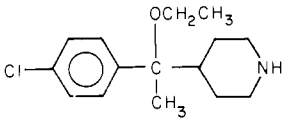
Ash Stevens Inc., Detroit, Michigan 48202. *Received May 22, 1975*

Based upon the antimalarial activities demonstrated by compounds I and II a series of amino ethers represented by structures III–VI was synthesized. These structures incorporated several modifications of compound II. The compounds prepared displayed no activity in either the Rane *P. berghei* mouse screen or the Rane *P. gallinaceum* sporozoite-induced chick test.

A series of substituted tetrahydrofuran derivatives was recently synthesized by Marxer.[1-3] One of these, 2-(4-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (I), was found to possess both prophylactic and curative antimalarial activity in animals.[3] More recently, McCaustland et al.[4] synthesized a number of compounds structurally



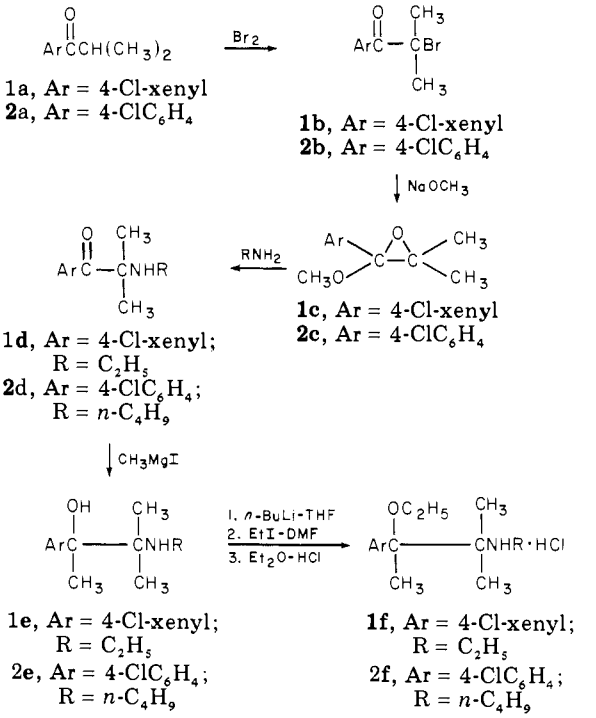
I



II

related to I in which modifications were performed on the tetrahydrofuran portion, the pyridyl ring, and the phenyl ring. One compound in particular, namely 4-[1-(4-chlorophenyl)-1-ethoxyethyl]piperidine (II), exhibited significant prophylactic and therapeutic antimalarial activity in the sporozoite-induced chick test and in the Rane mouse screen.[4] Compound II may be considered a structural analog of I in which the tetrahydrofuran ring is "opened" to give an ethoxy and a methyl group attached to the quaternary carbon atom; an alternative variation is represented by a methoxy and an ethyl group attached to the quaternary carbon atom. The objective of the work described herein was to examine structures broadly related to II in an effort to acquire compounds with superior prophylactic antimalarial activity. To this end the synthesis of a series of ethers represented by structures III–VI was undertaken. The structural modifications of compound II to be reported involved: (1) carbon atom insertion either in between the phenyl ring and the alkoxy bearing carbon or in between the piperidyl ring and the alkoxy bearing carbon (**14**, **17a**, **17b**, and **20**); (2) movement of the alkyl branch from the alkoxy-bearing carbon atom to the newly introduced α-carbon atom (**11a** and **11b**); (3) preparation of two 3-piperidyl analogs (**23** and **26**); (4) introduction of the amine function as an acyclic moiety (**1f** and **2f**); and (5) incorporation of the ether function as an epoxide (**6** and **9**).

Scheme I



1a, Ar = 4-Cl-xenyl
2a, Ar = 4-ClC$_6$H$_4$

1b, Ar = 4-Cl-xenyl
2b, Ar = 4-ClC$_6$H$_4$

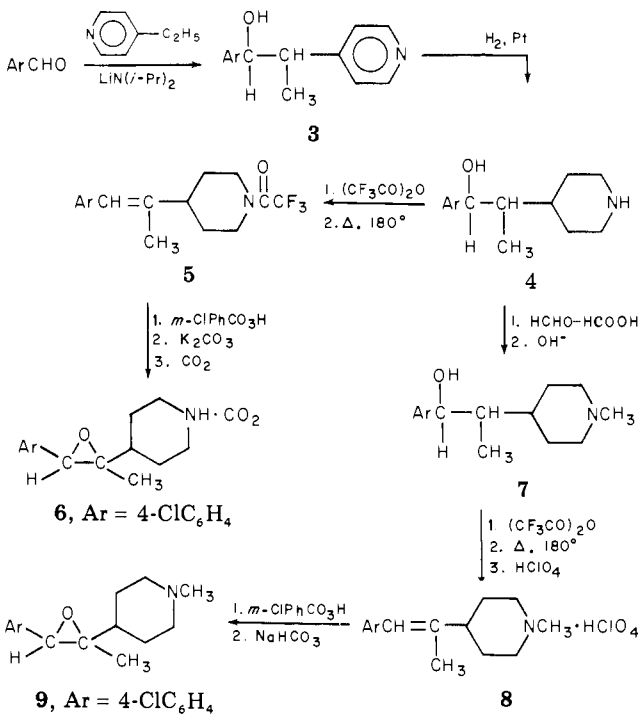
1c, Ar = 4-Cl-xenyl
2c, Ar = 4-ClC$_6$H$_4$

1d, Ar = 4-Cl-xenyl; R = C_2H_5
2d, Ar = 4-ClC$_6$H$_4$; R = n-C_4H_9

1e, Ar = 4-Cl-xenyl; R = C_2H_5
2e, Ar = 4-ClC$_6$H$_4$; R = n-C_4H_9

1f, Ar = 4-Cl-xenyl; R = C_2H_5
2f, Ar = 4-ClC$_6$H$_4$; R = n-C_4H_9

Scheme II



3

5

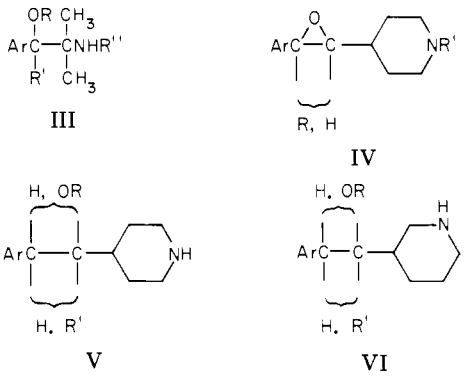
4

6, Ar = 4-ClC$_6$H$_4$

7

9, Ar = 4-ClC$_6$H$_4$

8



III

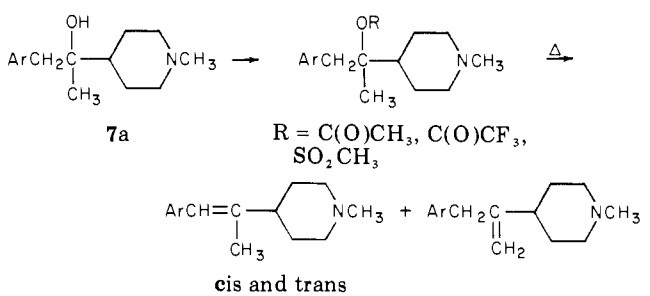
IV

V

VI

Chemistry. The acyclic amino alcohol ethers (type III) were prepared as shown in Scheme I. The amino ketone intermediates **1d** and **2d**, prepared via the epoxy ether sequence developed by Stevens and Cheng,[5] were converted to the tertiary carbinols **1e** and **2e** which were alkylated with butyllithium and ethyl iodide.

The epoxides **6** and **9** (type IV) were prepared as shown in Scheme II. Condensation of 4-ethylpyridine with 4-chlorobenzaldehyde in the presence of lithium diisopropylamide gave the carbinol **3** in good yield. Catalytic hydrogenation of **3** gave the piperidylcarbinol **4**. Attempts to convert **4** or **7** to the requisite olefins **5** and **8** via pyrolysis of the acetates gave mixtures of two olefins (by VPC), presumably the cis and trans isomers. Also, as shown below, pyrolysis of the isomeric piperidylcarbinol **7a** under a number of conditions gave mixtures of two or three olefins depending upon the derivative used. It was found, however, that carbinols **4** and **7** could be cleanly converted to the desired olefins via pyrolysis of the trifluoroacetate esters in *o*-dichlorobenzene at 180°. The

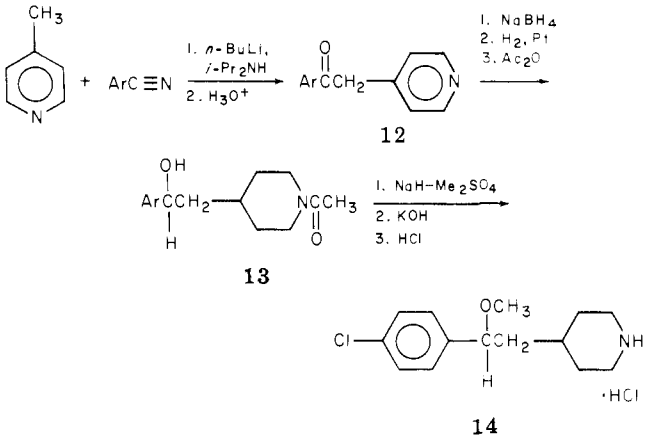


7a

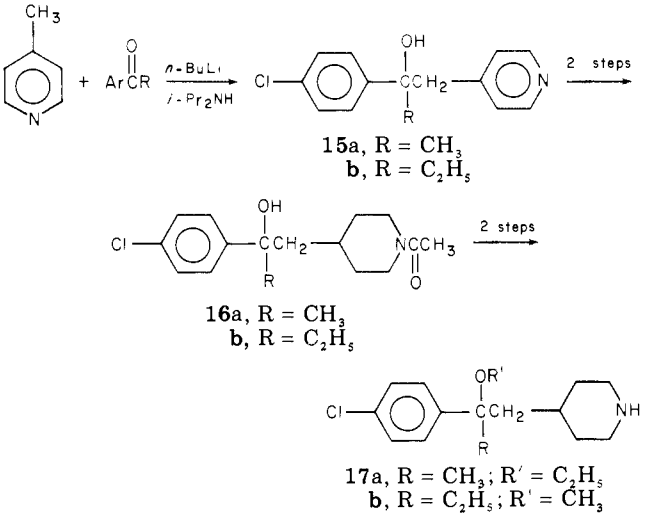
R = C(O)CH$_3$, C(O)CF$_3$, SO$_2$CH$_3$

cis and trans

Scheme III

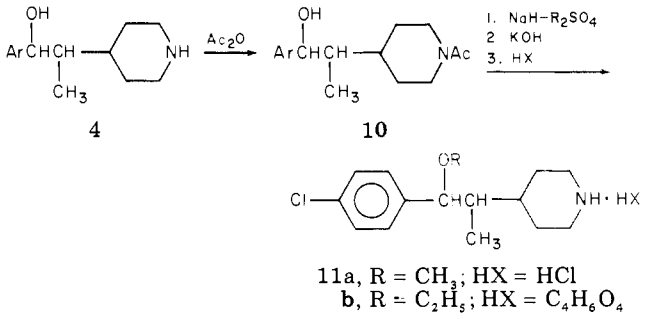


Scheme IV



olefins obtained were homogeneous by VPC analysis. Conversion of the olefins to the target compounds **6** and **9** involved standard procedures. In the conversion of **8** to **9** the piperidyl nitrogen was protected as a perchlorate salt.

Ethers **11a** and **11b** (type V) were prepared from the intermediate piperidyl alcohol **4** as shown below. Alkylation of **10** with sodium hydride and dimethyl or diethyl



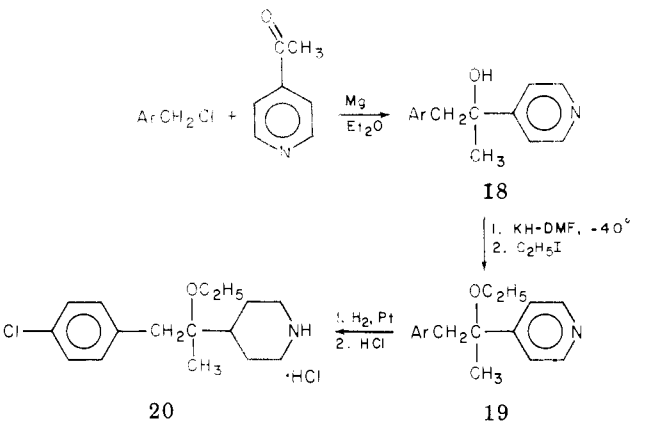
sulfate followed by base hydrolysis of the intermediate amides afforded the desired compounds.

Compound **14** (also type V) was prepared from 4-picoline and 4-chlorobenzonitrile as shown in Scheme III. The sequence was similar to that described above.

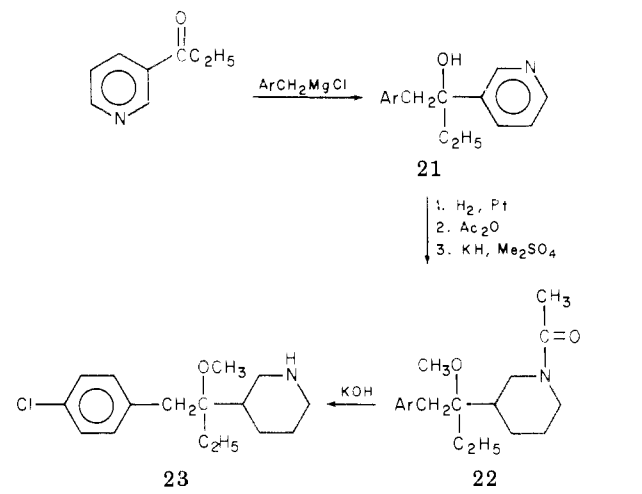
Two isomeric ethers, **17a** and **17b**, were prepared as shown in Scheme IV. The sequence is identical with that used to prepare previous examples.

An example of a benzylcarbinol ether in the 4-piperidyl series is represented by **20**, prepared as shown in Scheme V. In this case, the alkoxide was generated with potassium hydride at low temperature (−40°). Attempts to use so-

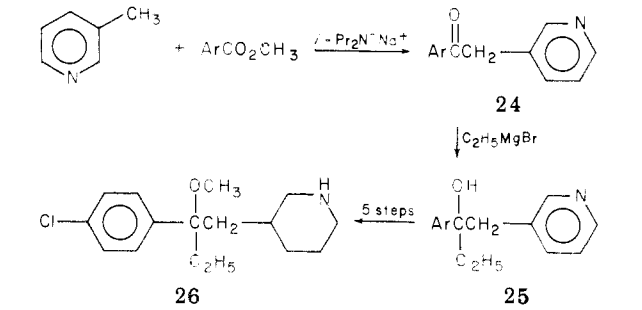
Scheme V



Scheme VI



Scheme VII



dium hydride at higher temperature (60°) resulted in considerable cleavage to 4-chlorotoluene and 4-acetylpyridine.

Two examples (**23** and **26**) in the 3-piperidyl series (type VI) were prepared as shown in Schemes VI and VII. Condensation of ethyl 3-pyridyl ketone with 4-chlorobenzylmagnesium chloride gave the carbinol **21** which was converted to the target amino ether **23** via a sequence similar to that used for the preparation of **20**. For the preparation of the amino ether **26**, 3-picoline was condensed with methyl 4-chlorobenzoate in the presence of sodium diisopropylamide to yield ketone **24**. Treatment with ethylmagnesium bromide gave the tertiary carbinol **25**. The latter was converted to **26** in the same manner as in the conversion of **21** to **23** (Scheme VI) except that the alkoxide was generated with sodium hydride at 60° rather than with potassium hydride at low temperature.

Biological Activity Data. The 12 amino ethers (**1b**,

2b, **6**, **9**, **11a**, **11b**, **14**, **17a**, **17b**, **20**, **23**, and **26**) were tested by the Rane Laboratory, University of Miami, Fla., for both blood schizontocidal antimalarial activity against *Plasmodium berghei* infected mice[7] and prophylactic antimalarial activity against *Plasmodium gallinaceum* infected chicks.[8] All 12 compounds were inactive through 640 mg/kg against *P. berghei*; some toxicity was evident at the higher dose levels. All compounds were also inactive through 480 mg/kg in the chick test against *P. gallinaceum*. None of the intermediate compounds tested displayed activity in either screen.

As set forth in the opening remarks, compound I represented the initial lead with reported prophylactic (and therapeutic) antimalarial activity.[1-3] Based on this finding, McCaustland et al. prepared compound II which demonstrated also confirmed prophylactic and therapeutic activity.[4] In view of the intense interest in improved prophylactic drugs, the lead represented by II was continued by the same group with the preparation of some 22 additional compounds, only three of which (all N-substituted) were active, albeit less so than II.[4] In an essentially parallel effort, the work reported herein was undertaken with the results reported above.

It is difficult to rationalize the disappointing negative results obtained with the compounds prepared by McCaustland and the closely related compounds prepared by us. Peters reported that compound I acts as a folic reductase inhibitor against *P. berghei* and *P. chabaudi* and "not surprisingly it has a causal prophylactic activity".[9] If this is indeed the mechanism of action, it is clear that the steric (and electronic) requirements of the enzyme active site are highly restricted. Cheng has cited compound I as an example of his triangulation theory as applied to parasite DNA intercalation,[10] but this was not applied specifically to II and analogs thereof;[4] their paper does note, however, that such compounds apparently have a rather narrow margin for structural modification. Our results confirm this observation.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR spectra were determined on a Varian Model T-60 spectrometer. Analyses indicated by elemental symbols agree with calculated values within ±0.4%.

The following procedure was used for the syntheses of ethers **1f** and **2f**.

4-*p*-Chlorophenylisobutyrophenone (1a). The title compound was prepared from 4-chlorobiphenyl (40.0 g, 0.212 mol), $AlCl_3$ (86.7 g, 0.65 mol), CS_2 (100 ml), and isobutyric anhydride (36.8 g, 0.23 mol) under standard Friedel–Crafts conditions. The yield was 35 g (64%), mp 74–75° (petroleum ether). Anal. ($C_{16}H_{15}ClO$) C, H, Cl.

4'-(4-Chlorophenyl)-2-bromo-2-methylpropiophenone (1b). The above ketone was treated with Br_2 in $CHCl_3$ under standard conditions. The yield of bromo ketone was 94%, mp 125–127°. Anal. ($C_{16}H_{14}BrClO$) C, H.

Similarly prepared was 4-chloro-2-bromoisobutyrophenone (**2b**, 97%), bp 80° (0.05 mm) [lit.[6] bp 117–119° (1 mm)].

1-(4-Chloroxenyl)-1-methoxy-2-methyl-1,2-epoxypropane (1c). The title compound was prepared from **1b** via the procedure of Stevens and Cheng.[5] The yield was 96%, mp 68–72°. This compound was used without further purification in the next step.

Similarly prepared was 1-(4-chlorophenyl)-1-methoxy-2-methyl-1,2-epoxypropane (**2c**) in 76% yield, bp 58–59° (0.25 mm).

4'-(4-Chlorophenyl)-2-ethylamino-2-methylpropiophenone Hydrochloride (1d). A solution of the above epoxy ether (8.0 g, 0.028 mol) and ethylamine (10 ml) in dry EtOH (50 ml) was heated at reflux for 4 days with periodic replenishment of ethylamine (3 × 10 ml). The mixture was concentrated and hydrolyzed with 6 N HCl to give a white solid product which was filtered and washed with Et_2O to yield 8.5 g (91%) of the title compound, mp 282° dec. A sample was recrystallized twice from EtOH–petroleum ether and gave an analytical sample, mp 291° dec. Anal. ($C_{18}H_{21}ClNO$) C, H, N.

Similarly prepared was 2-(1-butylamino)-2-methyl-4'-chloropropiophenone (**2d**) in 86% yield, bp 90° (0.1 mm). Anal. ($C_{14}H_{20}ClNO$) C, H, N.

2-(4-Chloroxenyl)-2-hydroxy-3-methyl-3-ethylaminobutane (1e). Amino ketone **1d** was converted to the title compound with methylmagnesium iodide under standard conditions. The aminocarbinol was converted to the HCl salt by treatment with ethereal HCl. The solid was triturated in hot acetonitrile and filtered to yield pure carbinol (3.8 g, 60%), mp 174–177° dec. Anal. ($C_{19}H_{25}Cl_2NO$) C, H, N.

Similarly prepared was 2-(4-chlorophenyl)-2-hydroxy-3-methyl-3-(1-butylamino)butane (**2e**, 90%), bp 120–125° (0.05 mm). This material was one peak on VPC and used without further purification.

2-(4-Chloroxenyl)-2-ethoxy-3-methyl-3-ethylaminobutane Hydrochloride (1f). To a solution of **1e** (2 g) in dry THF (30 cc) was added *n*-BuLi (6 cc, 15% in hexane, 1.5 equiv). The solution was stirred at room temperature for 30 min. The THF was evaporated under a stream of N_2 and DMF (30 ml) was added, followed by EtI (1.5 g). The solution was stirred at room temperature for 17 h. The mixture was poured into H_2O and extracted twice with Et_2O. The ether layer was washed with H_2O, dried ($MgSO_4$), and concentrated to yield the product as an oil. The oil was converted to the HCl salt and recrystallized from ethanol–ether to give the target compound (0.9 g, 45%), mp 265° dec. Anal. ($C_{21}H_{29}Cl_2NO$) C, H, N.

Compound **2f** was prepared similarly in 63% yield, mp 226–228°. Anal. ($C_{17}H_{29}Cl_2NO$) C, H, N.

The following procedure was used to prepare epoxides **6** and **9**.

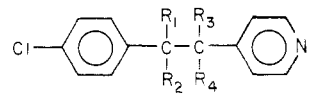
1-(4-Chlorophenyl)-1-hydroxy-2-(4-pyridyl)propane (3). To dry diisopropylamine (40.0 g, 0.4 mol) in cool (ice bath) dry THF (400 ml) was added *n*-butyllithium (15% in hexane, 244 ml, 0.4 mol). The ice bath was removed and the mixture was stirred for 15 min at room temperature. 4-Ethylpyridine (42.8 g, 0.4 mol) was added (ice bath) to the mixture which was stirred for 30 min at room temperature and cooled to ca. −78° (dry ice–acetone bath). 4-Chlorobenzaldehyde (56.0 g, 0.4 mol) in THF (100 ml) was added. After stirring at −78° for 15 min, the reaction mixture was allowed to warm to −10°. Water (100 ml) was added and the mixture was evaporated. Water (300 ml) was added to the residue. The resulting mixture was extracted exhaustively with ether–chloroform (3:2 v/v). The extracts were dried ($MgSO_4$) and concentrated to yield 104 g of a thick oil. The oil was dissolved in ethanol–water (3:1 v/v, 400 ml) with heating. The mixture was cooled (5°) and the crude racemic pyridylcarbinol (61.0 g, 61%), mp 75–80°, was collected by filtration. The racemic mixture was recrystallized from ethanol–water (4:1 v/v) to give a product with mp 85–95° (melting points vary from run to run).

Similarly prepared were compounds **15a** and **15b** (Table I).

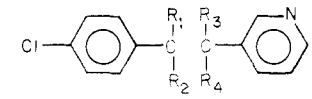
1-(4-Chlorophenyl)-1-hydroxy-2-(4-piperidyl)propane (4). The above pyridylcarbinol (6.0 g, 2.4 mmol, mp 85–95°) was dissolved in anhydrous ethanol (400 ml). Concentrated HCl (2.4 ml) and PtO_2 (0.60 g) were added and the mixture was hydrogenated at 50 psig for 4 h. The resulting mixture was filtered (Celite) and concentrated. Excess 40% NaOH was added to the residue and the mixture was extracted with $CHCl_3$ (three times). The extract was dried ($MgSO_4$) and evaporated to yield a thick oil, a racemic mixture which was used as such in the next step.

***N*-Trifluoroacetyl-1-(4-chlorophenyl)-2-(4-piperidyl)-1-propene** (5). To a solution of racemic 1-(4-chlorophenyl)-1-hydroxy-2-(4-piperidyl)propane (1.27 g, 5 mmol) in acetone (25 ml), cooled to 0°, was added trifluoroacetic anhydride (4.2 g, 0.02 mol). The ice bath was removed and the solution was stored at ambient temperature overnight. The volatiles were removed to give 1.70 g of residue which was dissolved in o-dichlorobenzene (25 ml) and the solution was heated at reflux 22 h. The solvent was distilled and the residue was triturated with petroleum ether to give 0.55 g (44%) of the title compound, mp 64–67°. An analytical sample (mp 66–67°) was obtained via chromatography over silica gel and elution with benzene. Anal. ($C_{16}H_{17}ClF_3NO$) C, H, N.

Table I. Properties of Pyridyl Alcohols



3, 15, 18

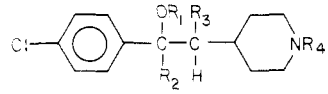


21, 25

No.	R_1	R_2	R_3	R_4	Mp, °C (solvent)	Yield, %	Formula	Analyses
3	OH	H	CH_3	H	85-95[a] ($EtOH-H_2O$)	61	$C_{14}H_{14}ClNO$	
15a	OH	CH_3	H	H	117-119.5 (CH_2Cl_2-petr ether)	78	$C_{14}H_{14}ClNO$	C, H, N
15b	OH	C_2H_5	H	H	111-113 (petr ether)	84	$C_{16}H_{18}ClNO$	C, H, N
18	H	H	OH	H	143-144 (CH_3CN)	30	$C_{14}H_{14}ClNO$	C, H, N
21	H	H	OH	C_2H_5	103-105 (Et_2O)	41	$C_{15}H_{16}ClNO$	C, H, Cl, N
25	OH	C_2H_5	H	H	89-92 (Et_2O-petr ether)	47	$C_{15}H_{16}ClNO$	C, H, Cl, N

[a] Racemic mixture, used as such in next step.

Table II. Properties of Piperidylcarbinols and Ethers



No.	R_1	R_2	R_3	R_4	Mp, °C (solvent)	Yield, %	Formula	Analyses
10	H	H	CH_3	Ac	200-202 (EtOH)	38	$C_{16}H_{22}ClNO_2$	C, H, Cl
11a	CH_3	H	CH_3	H	200-202 (CH_3CN)	42	$C_{15}H_{23}Cl_2NO$	C, H, N
11b	C_2H_5	H	CH_3	H	122-125 (CH_3CN)	89	$C_{18}H_{30}ClNO_5$	C, H, N
13	H	H	H	Ac	132-134 (CH_3CN)	37	$C_{15}H_{20}ClNO_2$	C, H, Cl, N
14	CH_3	H	H	H	184-186 (CH_3CN-Et_2O)	45	$C_{14}H_{21}Cl_2NO$	C, H, Cl, N
16a	H	CH_3	H	Ac	122-124 (CH_3CN)	76	$C_{16}H_{22}ClNO_2$	C, N; H[a]
16b	H	C_2H_5	H	Ac	111-113 (CH_3CN)	66	$C_{17}H_{24}ClNO_2$	C, H, Cl
17a	C_2H_5	CH_3	H	H	130-133 (CH_3CN)	52	$C_{20}H_{30}ClNO_5$	C, H, N
17b	CH_3	C_2H_5	H	H	141-143 (CH_3CN)	58	$C_{20}H_{30}ClNO_5$	C, H, N, Cl

[a] H: calcd, 7.05; found, 7.57.

N-**Carboxy-1-(4-chlorophenyl)-2-(4-piperidyl)-1,2-epoxypropane (6).** A solution of the above olefin (4.7 g) in dichloromethane (60 cc) was treated with *m*-chloroperbenzoic acid (3.1 g) under standard conditions. Standard work-up afforded an oil which was stirred in 7% K_2CO_3 in aqueous methanol (2:5, v/v) for 2 h. The methanol was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$ (twice). The combined chloroform layers were dried and concentrated and the residual oil was dissolved in acetonitrile. CO_2 was bubbled into the solution for 30 min. The solid was filtered and dried to yield the title compound, mp 100–105° dec. Anal. ($C_{14}H_{18}ClNO \cdot CO_2$) C, H, N.

1-(4-Chlorophenyl)-1-hydroxy-2-[4-(1-methylpiperidyl)propane (7). A racemic mixture of 4 (mp 145–155°) was converted to the title compound via standard Eschweiler–Clarke conditions. The yield was 73%, mp 212–215°. An analytical sample, mp 214–216°, was obtained by recrystallization from ethanol. Anal. ($C_{15}H_{22}ClNO$) C, H, Cl, N.

1-(4-Chlorophenyl)-2-hydroxy-2-(1-methyl-4-piperidyl)propane (7a). The title compound was prepared from 18 via the standard catalytic hydrogenation procedure followed by methylation according to the procedure described for **7**. The yield was 70%, mp 132–133° (CH_3CN). Anal. ($C_{15}H_{22}ClNO$) C, H, N.

1-(4-Chlorophenyl)-2-[4-(1-methylpiperidyl)]-1-propene Perchlorate (8). The title compound was prepared in 79% yield via the procedure used to prepare **5**. Crystallization from EtOH gave mp 146–147°. Anal. ($C_{15}H_{21}Cl_2NO_4$) C, H, N.

1-(4-Chlorophenyl)-2-[4-(1-methylpiperidyl)]-1,2-epoxypropane Tosylate (9). The title compound was prepared from **8** in 27% yield as described for the preparation of **6**, mp 174–176° (CH_3CN). Anal. ($C_{15}H_{20}ClNO \cdot C_7H_8O_3S$) C, H, N.

The following general procedure was used to prepare ethers **11a**, **11b**, **14**, **17a**, and **17b** (Table II).

1-(4-Chlorophenyl)-1-hydroxy-2-[4-(1-acetylpiperidyl)]propane (10). The racemic mixture of the piperidylcarbinol **4** was acetylated with acetic anhydride under usual conditions. The precipitated product was collected and triturated with ethanol. The title compound (6.1 g, 38%), mp 200–202°, was obtained by recrystallization from a large volume of ethanol.

Similarly prepared were amides **13**, **16a**, and **16b** (Table II).

1-(4-Chlorophenyl)-1-methoxy-2-[4-(1-acetylpiperidyl)]propane (10a). The above *N*-acetylpiperidylcarbinol (8.4 g, 0.028 mol), NaH (57% oil suspension, 2.4 g, 0.055 mol), and dry DMF (120 ml) were heated under nitrogen for 1 h in an oil bath (internal temperature 100°). Hydrogen evolution was observed at 70°. The mixture was cooled to room temperature and dimethyl sulfate (7.22 g, 0.056 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight and treated with water (300 ml). The aqueous mixture was extracted with ether (3 × 100 ml). The ether extracts were washed with water, dried ($MgSO_4$), and concentrated to give 9.4 g of oil. The NMR spectrum of the oil was consistent with the structure of the title compound.

1-(4-Chlorophenyl)-1-methoxy-2-(4-piperidyl)propane Hydrochloride (11a). The above oil (9.4 g) was converted to the title compound with 10% ethanolic KOH under usual hydrolysis conditions. The crude base was converted to the hydrochloride salt and recrystallized twice from CH_3CN to give 3.6 g (42% based on the *N*-acetylpiperidylcarbinol) of pure title compound.

4-Chlorophenyl 4-Picolyl Ketone (12). The title compound was prepared from 4-chlorobenzonitrile and 4-picoline according to the procedure described for compound **3**. Hydrolysis of the intermediate imine with hot 4 N HCl afforded the title compound in 89% yield, mp 87–90°. Anal. ($C_{13}H_{10}ClNO$) C, H.

α-Methyl-α-(4-chlorobenzyl)-4-pyridylcarbinol (18). The title compound was prepared from 4-chlorobenzylmagnesium chloride and 4-acetylpyridine under standard Grignard conditions.

1-(4-Chlorophenyl)-2-ethoxy-2-(4-pyridyl)propane (19). To a slurry of ether-washed 50% KH–oil (4.8 g) in dry DMF (100 ml) at −40°, a solution of **18** (12 g, 0.049 mol) in DMF (100 ml) was added. The mixture was allowed to slowly warm to 0° and was held at this temperature for 2 h, after which time it was slowly warmed to room temperature. The mixture was cooled to 0–5° in ice and EtI (7.2 ml) was added. The mixture was stirred at room temperature for 2 h, poured into H_2O (300 ml), and extracted with Et_2O (twice). The Et_2O was dried ($MgSO_4$) and concentrated to afford a mixture of desired product and starting material. The semisolid was slurried in petroleum ether and filtered to yield 6.3 g of starting material. The petroleum ether was concentrated to give 4.6 g (81% based on recovered starting material) of fairly

pure product which was used as such in the next step.

1-(4-Chlorophenyl)-2-ethoxy-2-(4-piperidyl)propane Hydrochloride (20). The above crude pyridyl compound (4.6 g, 0.160 mol) was reduced under the conditions described for the preparation of compound 4. The yield was 42%, mp 210–212° (CH_3CN). Anal. ($C_{10}H_{24}ClNO\cdot HCl$) C, H, N.

1-(4-Chlorophenyl)-2-hydroxy-2-(3-piperidyl)butane. The title compound was prepared from the above pyridyl alcohol via the procedure used to prepare 4, mp 148–149.5° (EtOH). Anal. ($C_{17}H_{24}ClNO_2$) C, H, Cl.

1-(4-Chlorophenyl)-2-methoxy-2-[3-(1-acetylpiperidyl)]-butane (22). The title compound was prepared from the above carbinol via the conditions described for the preparation of 19. The product was an oil which was used as such in the next step.

1-(4-Chlorophenyl)-2-methoxy-2-(3-piperidyl)butane Succinate (23). The above oil was converted to the target compound via the usual hydrolysis conditions. Crystallization from CH_3CN gave mp 137–138°. Anal. ($C_{20}H_{30}ClNO_5$) C, H, Cl, N.

α-(3-Pyridyl)-4-chloroacetophenone (24). To a suspension of phenylsodium (ca. 0.4 mol) in anhydrous benzene at 5° under nitrogen, a solution of diisopropylamine (40 g, 0.4 mol) in anhydrous benzene (40 ml) was added and the mixture was stirred at 5° for 1 h. 3-Picoline (37.2 g, 0.4 mol) diluted with anhydrous benzene (35 ml) was added to the sodium diisopropylamide suspension and the mixture was stirred at 5° for 30 min. A solution of methyl 4-chlorobenzoate (34 g, 0.2 mol) in anhydrous benzene (30 ml) was added and the mixture was stirred at 5° for 1 h. The reaction mixture was poured onto ice with stirring, made strongly acidic with concentrated HCl, and extracted with several portions of benzene to remove any unreacted ester. The aqueous phase was made basic with aqueous 20% sodium hydroxide and extracted with several portions of chloroform. The combined basic extracts were dried (Na_2SO_4) and evaporated in vacuo to give ca. 40 g of a red-brown syrup. Fractional distillation in vacuo (0.2 mm, oil bath 200°) afforded 26.5 g of crude title compound, bp 162–167° (0.2 mm), as an orange syrup that crystallized on standing at room temperature overnight. Trituration with ether gave 23 g of cream-colored solid, mp 59–64°. One additional trituration with ether–petroleum ether (1:1) yielded 21.5 g (47%) of nearly pure ketone, mp 61–64°. An analytical sample, mp 65–68°, was prepared via crystallization from ether–petroleum ether (1:1). Anal. ($C_{13}H_{10}ClNO$) C, H, Cl, N.

1-(3-Piperidyl)-2-(4-chlorophenyl)-2-butanol. The title compound was prepared from the above alcohol according to the procedure described for 4. The yield was 48%, mp 128–131° (CH_3CN). Anal. ($C_{15}H_{22}ClNO$) C, H, Cl, N.

***N*-Acetyl-1-(3-piperidyl)-2-(4-chlorophenyl)-2-butanol.** The title amide was prepared from the above piperidyl alcohol via the usual procedure. The yield was 81%, mp 127–128° ($EtOH–Et_2O$). Anal. ($C_{17}H_{24}ClNO_2$) C, H, N.

1-(3-Piperidyl)-2-(4-chlorophenyl)-2-methoxybutane Succinate (26). The title compound was prepared from the above amide (5.5 g, 0.018 mol) using the procedure described for 11a. The crude succinate (2.9 g) was recrystallized from CH_3CN to yield the title compound (2.6 g, 36%), mp 145–147°. Anal. ($C_{16}H_{24}ClNO\cdot C_4H_6O_4$) C, H, N.

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Hypoglycemic α-Cycloalkylphenylmethyl, Furanalkyl, and Thiophenealkyl Lactamimides

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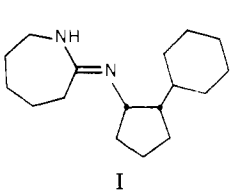
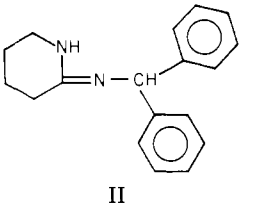
A series of α-cycloalkylphenylmethyl lactamimides and a series of furan- and thiophenealkyl lactamimides were prepared for biological evaluation as an extension of earlier finding of hypoglycemic activity in lactamimides. Compounds **7**, **20**, **23**, **25**, **29**, and **32** produced pronounced hypoglycemia after oral administration to fasted, glucose-primed rats.

We reported earlier that pronounced hypoglycemic activity is found in lactamimides, in which the α-carbon atom to which the lactamimide function is attached is highly substituted, such as I,[1,2] and in diphenylmethyl-substituted lactamimides, such as II.[3] We now wish to report an attempt to combine these features in compounds of type III, in which the α-carbon atom of phenylmethyl lactamimides is substituted by different cycloalkyl groups,



I



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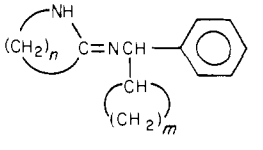
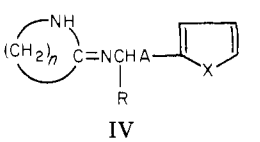


III



IV

and compounds of type IV, in which a phenyl group is replaced by a furan or thiophene ring. The new compounds are listed in Tables I and II.