gave the *l* isomer **3a**: mp 138–142°; $[\alpha]^{25}_{578}$ −10.6° (MeOH).

Equal portions of **3a** and **3b** were ground together to obtain a mixture melting point of 156–159°, coincident with that of racemic **3** (157–159°).

Pharmacology. Cardiac depressant activity was estimated using electrically stimulated (frequency 1 Hz, voltage 10–15% above threshold, pulse width 1 msec) cat right ventricular papillary muscle, under 1 g of tension, suspended in oxygenated Krebs solution at 37°. After equilibration, contraction amplitude was measured and cumulative doses (0.25–256 μg/ml) of drug were added every 10 min, doubling the concentration each time. Results were calculated on the concentration of drug causing 50% depression of contraction amplitude.

Acknowledgments. We thank Messrs. P. Adam, N. Panes, T. Miller, D. C. Mills, and Mesdames B. Broughton, C. Bubb, and S. Amos for their able technical assistance. We are grateful to Dr. M. J. Sewell and his staff for analytical and spectral data and to our colleagues of the Medicinal Biology Department for the biological results.

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Partly Reduced Biphenyls as Central Nervous System Agents. 3. *cis*- and *trans*-4-Aryl-4-methoxycyclohexylamines

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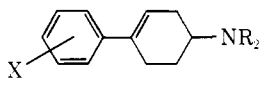
The two isomeric 4-tolyl-4-methoxycyclohexylamines were prepared and their configurations determined. A series of analogs bearing differing substitution in the aromatic ring was then synthesized by stereoselective routes, starting from the corresponding substituted cyclohexanones. The thus produced amines were converted to the 4′-fluoro-4-butyrophenones and selected compounds to the piperidines. The products were tested in a series of assays for CNS activity; the former were particularly active on both overt behavior and biochemical parameters.

We have recently reported on the preparation and intriguing CNS activity of the substituted arylcyclohexylamines **1** and **2**.[1,2] The effects of substitution at the ring carbon bearing the aromatic ring in the phenylpiperidines on biological activity have been amply documented.[3,4] It was thus of some interest to determine the effect on activity of the corresponding modification in our previously reported series.



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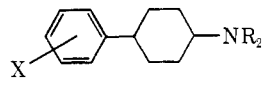


2

Synthesis. The key intermediate for the present work was the hydroxycyclohexanones **3**, obtained as described earlier,[1] from the reaction of hydroxycyclohexanone with appropriate arylmagnesium bromides. Treatment with MeOH in the presence of a catalytic amount of CF_3CO_2H led cleanly to the ketal. This was then alkylated by means of NaH and CH_3I (Scheme I). The crude alkylation product was then deketalized with aqueous Me_2CO; since the alkylations seldom went to completion, chromatography was employed to separate the product.

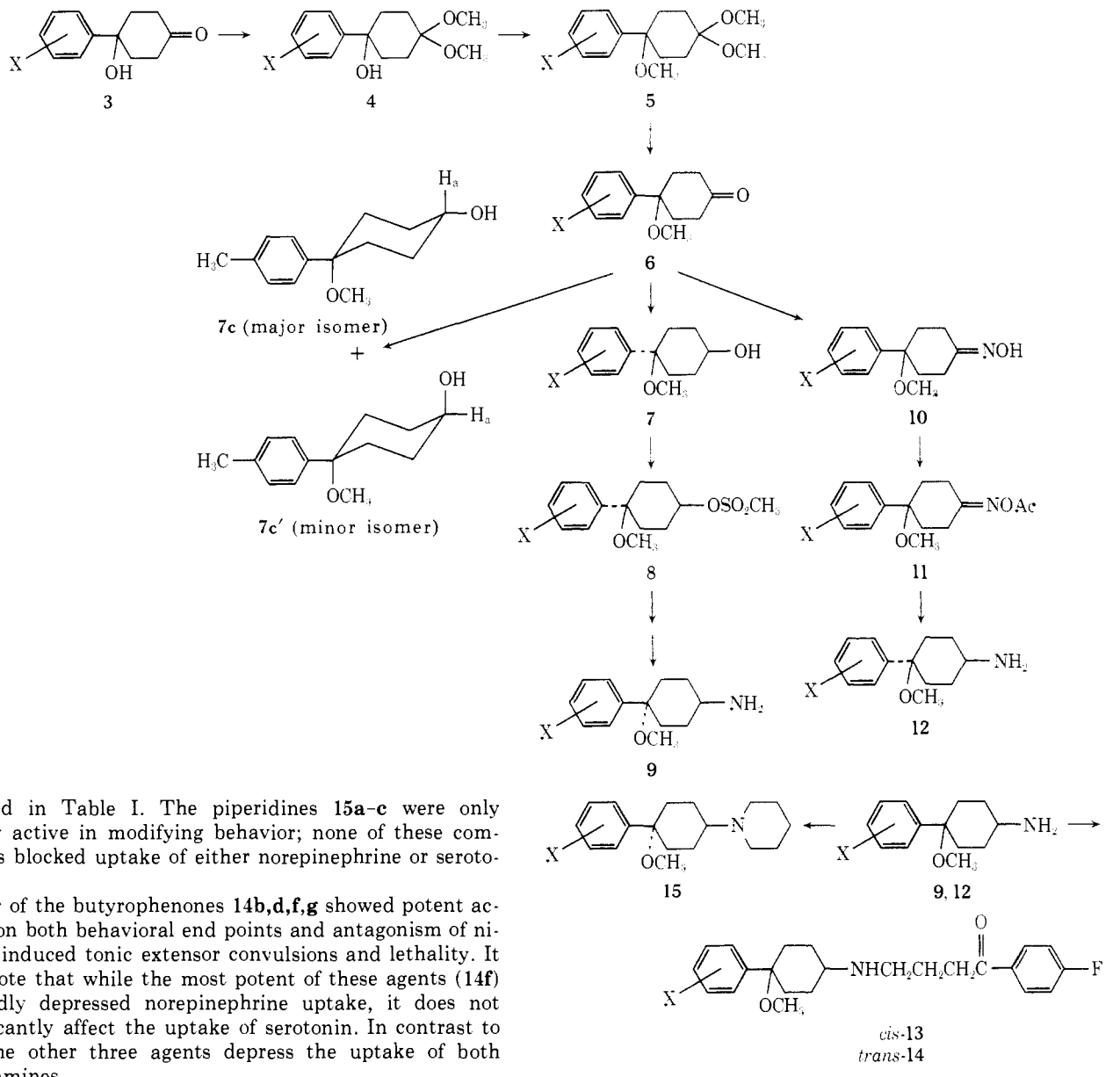
Reduction of the ketone **6c** by means of $NaBH_4$ gave a mixture of diols in the ratio of 17:3. Careful chromatography afforded the less polar minor isomer as a gum and the major isomer as a crystalline solid. The nmr spectrum of the latter showed H_a as a peak at δ 3.65 ($W_{1/2}$ = 20 Hz); the corresponding proton in the minor isomer appears at δ 4.0 ($W_{1/2}$ = 10 Hz). This then leads us to assign the major isomer to the equatorial series and the minor product to the axial series. If the tolyl group is in the expected equatorial orientation, the major alcohol is thus the trans compound. In practice, the crude reduction mixtures were purified so as to isolate only the major isomer. These alcohols were then taken on to the corresponding mesylates **8**. Displacement with NaN_3 in DMF led by SN2 reaction to the azides of the opposite configuration to that of starting mesylate. Reduction by means of $LiAlH_4$ completed the preparation of the primary cis amines. (Cis and trans in this context refer to the relationship of the aromatic ring and the amine.)

Preparation of the trans amines started by formation of the oximes **10**. Treatment with Ac_2O in pyridine gave the corresponding acetate. Reduction to the amines **12** was achieved by treatment with B_2H_6 in THF. Since the steric requirements of this reaction are quite similar to the $NaBH_4$ reduction of the ketones, the product should be the equatorial (trans) amine. The fact that the products are clearly isomeric with the corresponding compounds obtained by the inversion route bears out the assignment.

Treatment of the amines with the neopentyl glycol ketal of *p*-fluoro-4-chlorobutyrophenone in DMF followed by deketalization in aqueous methanol gave the corresponding alkylation products. Three of the primary amines in the cis series were taken on to the piperidines by means of 1,5-diiodopentane. It should be noted that in all cases where salts of the amines were prepared care was taken to avoid working with an excess of acid to preclude elimination of the benzylic methoxyl group.

Pharmacology. The effects of the substituted amines on both behavioral and biochemical end points are sum-

Scheme I



marized in Table I. The piperidines **15a-c** were only weakly active in modifying behavior; none of these compounds blocked uptake of either norepinephrine or serotonin.

Four of the butyrophenones **14b,d,f,g** showed potent activity on both behavioral end points and antagonism of nicotine-induced tonic extensor convulsions and lethality. It is of note that while the most potent of these agents (**14f**) markedly depressed norepinephrine uptake, it does not significantly affect the uptake of serotonin. In contrast to this the other three agents depress the uptake of both brain amines.

In a given pair of isomers (*e.g.*, **13b** and **14b**) the trans was more potent than the cis by a factor of 2-20. This is in agreement with our earlier findings in the 4-phenylcyclohexylamine series[2] where the more potent agent of an isomeric pair was again that in which the aromatic ring and the nitrogen were disposed trans to one another. This, taken together with the observed good activity of the Δ^4 compounds,[1] leads to the suspicion that some nearly planar arrangement of these two moieties is necessary for optimum activity.

Experimental Section†

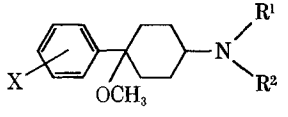
4-Hydroxy-4-arylcyclohexanone Dimethyl Ketals (Table II). A solution of 0.048 mol of the cyclohexanone and 2 ml of TFA in 200 ml of MeOH was allowed to stand at room temperature for 5 hr. $NaHCO_3$ (10 g) was then added and the solid collected on a filter; the filtrate was taken to dryness. The residue was then thoroughly extracted with C_6H_6 and this last solution taken to dryness. The residual solid was then recrystallized.

4-Methoxy-4-arylcyclohexanones (Table III). Sodium hydride (2.18 g of 57%) was added to a solution of 0.052 mol of the ketal in 60 ml of DMF and 180 ml of C_6H_6. Following 1 hr of stirring at room temperature and 1 hr at reflux there was added 20 ml of CH_3I. Heating was continued for 8 hr; the mixture was allowed to cool and then washed well with H_2O and brine. The organic layer was taken to dryness. To a solution of the residue in 250 ml of MeOH there was added 25 ml of 2.5 *N* HCl. At the end of 2 hr the bulk of the solvent was removed *in vacuo* and the residue dissolved in Et_2O. The organic layer was washed in turn with H_2O, $NaHCO_3$ and brine and taken to dryness. The residual gum was chromatographed on Florisil (elution with SSB followed by 5% Me_2CO-SSB and then 20% Me_2CO-SSB). There was obtained first the product and then recovered hydroxy ketone. The former was recrystallized from petroleum ether.

4-Methoxy-4-(*p*-tolyl)cyclohexanols. To a solution of 2.0 g (9.2 mmol) of the ketone in 40 ml of EtOH there was added 1.0 g of $NaBH_4$. At the end of 4 hr the solvent was removed *in vacuo*. The residue was dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The oil which remained was chromatographed on 200 ml of silica gel (elution with 20% Me_2CO-SSB). There was obtained first 0.22 g of the less polar alcohol as a gum. This was followed by a crystalline material. Recrystallization from petroleum ether gave 1.40 g of solid, mp 60-62°.

†All melting points are uncorrected and recorded as obtained on a Thomas-Hoover capillary melting point apparatus. The authors are indebted to the Department of Physical and Analytical Chemistry Research of The Upjohn Company for C, H, and N determinations. All compounds in the tables were analyzed for C and H; they were analyzed for N as well when this element was present. Analytical results for compounds indicated by empirical formulas were within ±0.4% of the theoretical values. Nmr spectra were determined in $CDCl_3$ on a Varian A-60A spectrometer. Skellysolve B is a petroleum fraction, bp 60-70°, sold by the Skelly Oil Co.

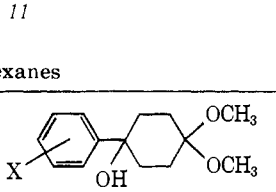
Table I. Pharmacological Testing Results of 4-Methoxy-4-arylcyclohexylamines[a]



	X	R^1	R^2	Series	LD_{50}	LRR_{50}	Tr_{50}	Ch_{50}	D_{50}	P_{50}	Nicotine[b] TE	Nicotine[b] L	Effect on amine uptake, % of control[c] ^3H NE heart	Effect on amine uptake, % of control[c] ^{14}C 5HT spleen
Chlorpromazine					>100	32	6.3	4	1.3	2.3	1.3	2	32	94
Haloperidol					>100	>100	2.0	4	1.4	2.3	9	10	66	92
13a	*o*-CH_3	H	BuF[d]	c[e]	>200	>200	178	1.6	0.8	5	8	13	73	82
14a	*o*-CH_3	H	BuF	t[f]	100	>50	36	13	1.0	5.6	3.6	5	43	68
13b	*m*-CH_3	H	BuF	c	89	>50	>50	40	1.8	11	20	23	73	78
14b	*m*-CH_3	H	BuF	t	89	>50	32	2.8	0.4	0.9	1.1	1.2	23	59
13c	*p*-CH_3	H	BuF	c	159	>100	40	13	16	16	9	10	107	101
14c	*p*-CH_3	H	BuF	t	142	>100	20	2.5	1.1	2	4.0	4.5	33	102
14d	*o*-OCH_3	H	BuF	t	>100	>50	>50	5.6	0.8	3.6	1.0	2.5	40	48
14e	*p*-Cl	H	BuF	t	>100	>100	63	11	2.5	13	13	11	39	83
13d	*p*-F	H	BuF	c	100	>50	28	9	2.8	6	7	8	86	101
14f	*p*-F	H	BuF	t	112	71	23	2.5	0.09	1.3	0.4	0.4	14	86
13e	*m*-CF_3	H	BuF	c	178	>100	32	1	0.4	1.8	5.6	7.0	90	89
14g	*m*-CF_3	H	BuF	t	225	>100	56	2.3	0.8	10	3.6	4.5	53	73
15a	*o*-CH_3	$-(CH_2)_5-$		c	>200	142	100	32	40	>100	40	45	95	95
15b	*m*-CH_3	$-(CH_2)_5-$		c	126	>50	>50	>50	28	>50	23	28	96	89
15c	*p*-CH_3	$-(CH_2)_5-$		c	>200	>200	>200	142	56	142	11	11	106	99

[a] Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all the studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered ip. [b] Procedures for measuring acute toxicity (LD_{50}) and the effect of the compound on overt behavior, loss of righting reflex (LRR_{50}), traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), pedestal (P_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) and death (L) have been described previously [G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DeVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964)]. [c] The procedure for measuring the effect on uptake of [^{14}C]serotonin [R. A. Lahti, P. A. Platz, and B. J. McAllistar, *ibid.*, **13**, 681 (1970)] and [^3H]norepinephrine [J. W. Daly, C. R. Creveling, and B. Witkop, *ibid.*, **9**, 273 (1966)] was carried out using previously described procedures. Test compounds were dissolved or suspended in saline and administered by ip route at 10 mg/kg 1 hr before the intravenous administration of the radioactive materials. All animals were sacrificed 3 hr after the administration of the radioactive compounds. Values are expressed as per cent of control. A change of 17% from control is significant at the $p = 0.05$ level. [d] BuF denotes $-CH_2CH_2CH_2CO(p\text{-}FC_6H_4)$. [e] Cis (amine and aromatic ring). [f] Trans (amine and aromatic ring).

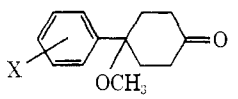
Table II. 1,1-Dimethoxy-4-hydroxy-4-arylcyclohexanes



Compd no.	X	Yield, %	Mp, °C	Recrystn solvent	Formula
4a	*o*-CH_3	85	86–89	Et_2O–PE[a]	$C_{15}H_{22}O_3$
4b	*m*-CH_3	68	71–74	PE	$C_{15}H_{22}O_3$
4c	*p*-CH_3	75	93–97	SSB[b]	$C_{15}H_{22}O_3$
4d	*o*-OCH_3	86	68–71	SSB	$C_{15}H_{22}O_4$
4e	*p*-Cl	60	91.5–97	PE	$C_{14}H_{19}ClO_3$
4f	*p*-F	90	97–100	SSB	$C_{14}H_{19}FO_3$
4g	*m*-CF_3	99	*c*		$C_{15}H_{19}F_3O_3$

[a] Petroleum ether. [b] Skellysolve B. [c] Noncrystalline oil; not analyzed.

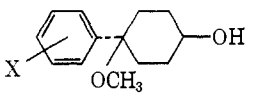
Table III. 4-Aryl-4-methoxycyclohexanones



Compd no.	X	Yield,[a] %	Mp, °C	Formula
6a	*o*-CH_3	73	73–75.5	$C_{14}H_{18}O_2$
6b	*m*-CH_3	85	42–45	$C_{14}H_{18}O_2$
6c	*p*-CH_3	76	75–76.5	$C_{14}H_{18}O_2$
6d	*o*-OCH_3	62	68–70	$C_{14}H_{18}O_3$
6e	*p*-Cl	81	55.5–59	$C_{13}H_{15}ClO_2$
6f	*p*-F	60	68–70	$C_{13}H_{15}FO_2$
6g	*m*-CF_3	94	*b*	$C_{14}H_{15}F_3O_2$

[a] Based on SM consumed. [b] Oil, not analyzed.

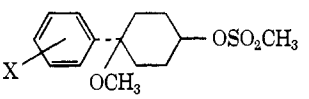
Table IV. *trans*-4-Aryl-4-methoxycyclohexanols



Compd no.	X	Yield, %	Mp, °C	Recrystn solvent	Formula
7a	*o*-CH_3	90	62–66	PE	$C_{14}H_{20}O_2$
7b	*m*-CH_3	95	*a*		$C_{14}H_{20}O_2$
7c	*p*-CH_3	81	60–62	PE	$C_{14}H_{20}O_2$
7d	*p*-F	79	82–85	SSB	$C_{13}H_{17}FO_2$
7e	*m*-CF_3	78	*a*		$C_{14}H_{17}F_3O_2$

[a] Noncrystalline; purified by chromatography on silica gel; not analyzed.

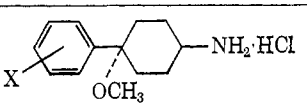
Table V. 4-Aryl-4-methoxycyclohexanol Methanesulfonates



Compd no.	X	Yield, %	Mp, °C	Recrystn solvent	Formula
8a	*o*-CH_3	74	87–90	Et_2O–SSB	$C_{15}H_{22}O_4S$
8b	*m*-CH_3	80	69–74	Et_2O–PE	$C_{15}H_{22}O_4S$
8c	*p*-CH_3	90	*a*		$C_{15}H_{22}O_4S$
8d	*p*-F	91	89–93	Et_2O–SSB	$C_{14}H_{19}FO_4S$
8e	*m*-CF_3	83	64–67	Me_2CO–SSB	$C_{15}H_{19}F_3O_4S$

[a] Noncrystalline; not analyzed.

Table VI. *cis*-4-Aryl-4-methoxycyclohexylamine Hydrochloride



Compd no.	X	Yield, %	Mp, °C	Formula
9a	*o*-CH_3	81	208–209	$C_{14}H_{22}ClNO$
9b	*m*-CH_3	65	163–165	$C_{14}H_{22}ClNO$
9c	*p*-CH_3	71	>300	$C_{14}H_{22}ClNO$
9d	*p*-F	81	195 dec	$C_{13}H_{19}ClFNO \cdot 0.5H_2O$[a]
9e	*m*-CF_3	61	184–186	$C_{14}H_{19}ClF_3NO$

[a] *Anal.* Calcd: C, 58.04; H, 7.50; N, 5.21. Found: C, 58.68; H, 7.29; N, 5.27.

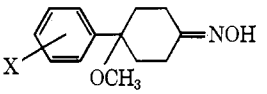
On larger scale, 5.51 g of ketone was reduced to 4.47 g (80%) of the equatorial alcohol, mp 57–60°.

4-Aryl-4-methoxycyclohexanols (Table IV). A mixture of 0.0225 mol of the ketone and 2.50 g of $NaBH_4$ in 100 ml of EtOH was stirred at room temperature for 4 hr. The solvent was removed *in vacuo* and the residue dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on silica gel (elution with 10% Me_2CO in CH_2Cl_2); the fractions were then combined on the basis of tlc to afford the product. The product, if crystalline, was then recrystallized.

***trans*-4-Aryl-4-methoxycyclohexanol Methanesulfonates (Table V).** To an ice-cooled solution of 0.026 mol of the alcohol in 30 ml of pyridine there was added 6 ml of CH_3SO_2Cl. Following 17 hr of standing in the cold the mixture was diluted with ice-H_2O. The precipitated gum was extracted with Et_2O. This extract was then washed with H_2O, ice-cold 2.5 *N* HCl, and brine. The solution was then taken to dryness to afford the product. This, if crystalline, was purified by recrystallization.

***cis*-4-Aryl-4-methoxycyclohexylamine Hydrochlorides (Table VI).** A mixture of 0.026 mol of the mesylate and an equal weight of NaN_3 in 80 ml of DMF was heated 17 hr at 90°. The solvent

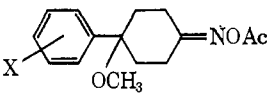
Table VII. 4-Aryl-4-methoxycyclohexanone Oximes



Compd no.	X	Yield, %	Mp, °C	Recrystn solvent	Formula
10a	*o*-CH_3	63	108–110	Et_2O–PE	$C_{14}H_{19}NO_2$
10b	*m*-CH_3	95	*a*		$C_{14}H_{19}NO_2$
10c	*p*-CH_3	95	114–115	Aqueous MeOH	$C_{14}H_{19}NO_2$
10d	*p*-OCH_3	87	177–179	Aqueous MeOH	$C_{14}H_{19}NO_3$
10e	*p*-Cl	79	148–151	EtOAc–C_6H_{12}	$C_{13}H_{16}ClNO_2$
10f	*p*-F	84	86–89	SSB	$C_{13}H_{16}FNO_2$
10g	*m*-CF_3	70	98–100	SSB	$C_{14}H_{16}F_3NO_2$

[a] Noncrystalline; not analyzed.

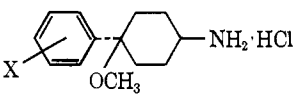
Table VIII. 4-Aryl-4-methoxycyclohexanone Oxime Acetates



Compd no.	X	Yield, %	Mp, °C	Recrystn solvent	Formula
11a	*o*-CH_3	99	96–98.5	Et_2O–PE	$C_{16}H_{21}NO_3$
11b	*m*-CH_3	72	*a*		$C_{16}H_{21}NO_3$
11c	*p*-CH_3	84	68–70	PE	$C_{16}H_{21}NO_3$
11d	*o*-OCH_3	82	82–85	SSB	$C_{16}H_{21}NO_4$
11e	*p*-Cl	92	87–89.5	Et_2O–PE	$C_{15}H_{18}ClNO_3$
11f	*p*-F	87	87–88	SSB	$C_{15}H_{18}FNO_3$
11g	*m*-CF_3	95	*b*		$C_{16}H_{18}F_3NO_3$

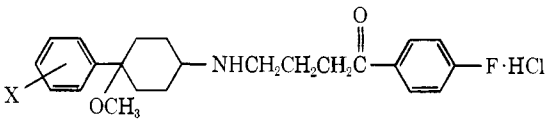
[a] Noncrystalline; purified by chromatography on silica gel; not analyzed. [b] Noncrystalline; not analyzed.

Table IX. *trans*-4-Aryl-4-methoxycyclohexylamine Hydrochlorides



Compd no.	X	Yield, %	Mp, °C	Formula
12a	*o*-CH_3	57	230–232	$C_{14}H_{22}ClNO$
12b	*m*-CH_3	45	176–178	$C_{14}H_{22}ClNO \cdot 0.5MeOH$
12c	*p*-CH_3	48	>300	$C_{14}H_{22}ClNO$
12d	*o*-OCH_3	54	191–193	$C_{14}H_{22}ClNO_2 \cdot 0.5H_2O$
12e	*p*-Cl	49	256–258	$C_{13}H_{19}Cl_2NO$
12f	*p*-F	49	264–266	$C_{13}H_{19}ClFNO$
12g	*m*-CF_3	31	202–203	$C_{14}H_{19}ClF_3NO$

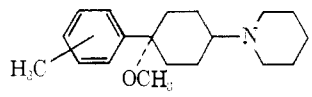
Table X. 4′-Fluoro-4-[(4-methoxy-4-arylcyclohexyl)amino]butyrophenone Hydrochlorides



Compd no.	X	Cis or trans	Yield, %	Mp, °C	Formula
13a	*o*-CH_3	Cis	58	192–193	$C_{24}H_{31}ClFNO_2$
14a	*o*-CH_3	Trans	45	163–166	$C_{24}H_{31}ClFNO_2 \cdot 0.5H_2O$
13b	*m*-CH_3	Cis	52	162–164	$C_{24}H_{31}ClFNO_2 \cdot 0.5H_2O$
14b	*m*-CH_3	Trans	42	167–170	$C_{24}H_{31}ClFNO_2$[c]
13c	*p*-CH_3	Cis	44	184–185	$C_{24}H_{31}ClFNO_2$
14c	*p*-CH_3	Trans	26	170–174	$C_{24}H_{31}ClFNO_2 \cdot 0.5H_2O$
14d	*o*-OCH_3	Trans	26	*a*	$C_{24}H_{31}ClFNO_3$
14e	*p*-Cl	Trans	52	185–188	$C_{23}H_{28}Cl_2FNO_2$[b]
13d	*p*-F	Cis	46	193–195	$C_{23}H_{28}ClF_2NO_2$
14f	*p*-F	Trans	36	176–178	$C_{23}H_{28}ClF_2NO_2$
13e	*m*-CF_3	Cis	46	176–178	$C_{24}H_{28}ClF_4NO_2$
14g	*m*-CF_3	Trans	44	189–191	$C_{24}H_{28}ClF_4NO_2$

[a] Amorphous. [b] *Anal.* Calcd: C, 62.73; H, 6.41; N, 3.18. Found: C, 62.19; H, 6.34; N, 3.17. [c] *Anal.* Calcd: C, 68.64; H, 7.44; N, 3.34. Found: C, 68.08; H, 7.39; N, 3.23.

Table XI. *cis*-1-(4-Methoxy-4-tolylcyclohexyl)piperidine *p*-Toluenesulfonates



Compd no.	Isomer	Yield, %	Mp, °C	Formula
15a	Ortho	56	171–172	$C_{28}H_{37}NO_4S$
15b	Meta	58	182–184	$C_{28}H_{37}NO_4S$
15c	Para	58	180–181	$C_{28}H_{37}NO_4S$

was then removed at oil pump vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A solution of the residual oil in 30 ml of THF was added with stirring over 40 min to 1.5 g of $LiAlH_4$ in 15 ml of THF. Following an additional 5 hr of stirring the mixture was cooled in ice and treated in turn with 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. This last residue was dissolved in Et_2O and treated with 1 equiv of 4.9 *N* HCl in Et_2O. The precipitated salt was purified by recrystallization (no heat) from MeOH–Et_2O.

4-Aryl-4-methoxycyclohexanone Oximes (Table VII). A mixture of 0.017 mol of the ketone, 3.75 g of NH_2OH·HCl, and 7.5 ml of 45% KOH in 70 ml of EtOH was heated at reflux for 4 hr. The solvent was removed *in vacuo* and the residue taken up in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was purified by recrystallization.

4-Aryl-4-methoxycyclohexanone Oxime Acetates (Table VIII). A solution of 0.017 mol of the oxime and 15 ml of Ac_2O in 30 ml of pyridine was allowed to stand at room temperature for 18 hr. The mixture was poured into ice–H_2O and the precipitated gum extracted with Et_2O. The organic layer was washed with ice-cold 2.5 *N* HCl, H_2O, $NaHCO_3$, and brine. The solid which remained when this solution was taken to dryness was purified by recrystallization.

***trans*-4-Aryl-4-methoxycyclohexylamine Hydrochlorides (Table IX).** To an ice-cold solution of 0.0156 mol of the oxime acetate in 20 ml of THF there was added dropwise with good stirring 46 ml of 1 *N* B_2H_6 in THF. Following 18 hr in the cold, 1 ml of H_2O was added dropwise. When effervescence ceased the solvent was removed *in vacuo*. The residue was stirred for 1 hr with 100 ml each of 0.5 *N* HCl and Et_2O. The organic layer was separated and extracted twice with 30 ml of 0.5 *N* HCl. The aqueous portions were combined and made strongly basic and the precipitate was extracted with Et_2O. The organic layer was washed with brine and concentrated. This last solution was treated with 2.0 ml of 4.9 *N* HCl in Et_2O and the precipitated solid collected on a filter. This last solution was purified by recrystallization (no heat) from MeOH–Et_2O.

4′-Fluoro-4-[(4-methoxy-4-arylcyclohexyl)amino]butyrophenone Hydrochlorides (Table X). To a solution of 9.7 mmol of the amine hydrochloride in 45 ml of DMF there was added 0.41 g of 57% NaH. Following 1 hr of stirring, 1.65 g of KI, 2.76 g of K_2CO_3, and 2.46 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene ketal was added. Following 17 hr of heating at 90°, the solvent was removed at oil pump vacuum. The residue was dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. To a solution of the residue in 30 ml of MeOH, there was added 15 ml of 2.5 *N* HCl. At the end of 1 hr the bulk of the solvent was removed *in vacuo* and the precipitated solid collected on a filter. This product was purified by recrystallization (no heat) from MeOH–Et_2O.

***cis*-1-(4-Methoxy-4-tolylcyclohexyl)piperidine *p*-Toluenesulfonates (Table XI).** To 6.7 mmol of the amine hydrochloride in 29 ml of EtOH there was added 1.7 ml of 4.18 *N* NaOMe in MeOH. Following 1 hr of stirring, 1.02 ml of 1,5-diiodopentane and 1.68 g of K_2CO_3 were added and the mixture was brought to reflux. At the end of 17 hr the solvent was removed *in vacuo* and the residue partitioned between H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. To a solution of the residue in Et_2O there was added 1 equiv of *p*-TSA in Et_2O. The resulting salt was recrystallized from CH_2Cl_2–EtOAc.

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Central Nervous System Depressants. 11. Benzodiazepines with Ureas in the 2 Position†

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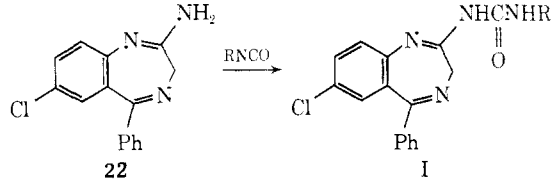
Twenty-one 2-ureidobenzodiazepines have been prepared. These included acyclic ureas with N′-Me, cyclopropyl, $COCH_3$, CH_2COOEt, COOEt, and CH_2CH_2Cl, cyclic ureas, [1,2-*a*]-*s*-triazinodiones, and 2-imidazolidinones. These were prepared from 2-amino-3*H*-1,4-benzodiazepines and isocyanates, followed by cyclization of the appropriate acyclic ureas. The acyclic ureas and imidazolidinones had a rather low order of CNS depressant activity but some of the triazinodiones (notably **12**) showed considerable interest.

In the preceding paper[1] we reported a series of 1,4-benzodiazepines with carbamoyl groups in the 1 position. Several were quite active anxiolytic agents. Since these are actually ureas, it seemed desirable to prepare benzodiazepines with ureas in other positions, especially the 2 position (I). These were prepared by the action of an isocyanate on a 2-amino-1,4-benzodiazepine.

Recently it came to our attention that workers at Takeda Chemical Industries[2] in Japan had made analogous compounds. Only one (I, R = CH_3) was identical with



22 I

ours. In our hands these open-chain ureas showed a rather low order of CNS activity. However, it was found that the carbethoxy ureas (I, R = COOEt) could be cyclized by heating to the triazinodiones (*e.g.*, **11**), which could be methylated in the 2, 4, and 5 positions. Some of these

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