(±)-*erythro*-**1-Benzenesulfonyl-2-(*p*-chloro-α-vinyloxybenzyl)piperidine** [(±)-**IVa**].—Treatment of 15 g of (±)-IIIa in Et_2O with 9 g of MeI afforded a quant yield methiodide which was dissolved in warm H_2O and treated with freshly prepd AgOH (from 17 g of $AgNO_3$). When the supernatant failed to give a pos I^- test ($NaNO_2$–H^+–starch) the mixt was filt and the H_2O was evapd. To the residue was added 800 ml of C_6H_6. This was slowly distd off as fresh dry C_6H_6 was added, until only a dry scum remained of the original residue. The C_6H_6 soln was evapd, and the residue was crystd from heptane to give 9.8 g (78%) of (±)-IVa: mp 132–133°; ir ($CHCl_3$) 1615 and 1635 cm^{-1} d (CH=CH_2). *Anal.* ($C_{20}H_{22}ClNO_3S$) C, H, N.

(±)-*erythro*-**Benzenesulfonyl-2-(*p*-chloro-α-hydroxybenzyl)piperidine** [(±)-**Va**].—To 7.84 g of (±)-IVa dissolved in 60 ml of warm 80% EtOH was added 2 ml of 12 *N* HCl. After 12 hr the solv was evapd, and the residue was crystd from heptane to give 5.5 g (75%) of (±)-Va: mp 116–117°; ir ($CHCl_3$) 3610 cm^{-1} (OH). *Anal.* ($C_{18}H_{20}ClNO_3S$) C, H, N.

(±)-*erythro*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(±)-**Vb**]. **A.**—Redn of 3.66 g of (±)-Va in 50 ml of EtOH in the presence of 3 g of 10% Pd/C gave 2.64 g (80%) of (±)-Vb after removal of the cat and solv and recrystn of the residue from heptane: mp 121–122°; ir ($CHCl_3$) 3610 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.65–7.25 (m, 10 H, Ph and $PhSO_2$), 5.07 (d, $J_{\alpha,2}$ = 7 Hz, H, OCH), 4.21 (unres 3-line m, *J* = 7 Hz, H, NCH), 3.9–3.1 (m, 2 H, NCH_2), 2.0–1.2 ppm (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

B.—To 0.95 g of (±)-*erythro*-2-(α-hydroxybenzyl)piperidine [(±)-Vc], prepd as descrd by Crook and McElvain,[9a] mp 141–142°, in 25 ml of Pyr was added dropwise over 1 hr, 0.88 g of $PhSO_2Cl$. The solv was evapd, and the residue was mixed with $CHCl_3$. The soln was washed with acid and with base, dried, filtd, and evapd to give an authentic sample of (±)-Vb from heptane–Et_2O: 0.5 g (30%); mp 122–123°; mmp with (±)-Vb obtd from (±)-Va, 121–122°; ir ($CHCl_3$) and nmr ($CDCl_3$) superimposable upon spectra of (±)-Vb obtd from (±)-Va. *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(±)-*threo*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(±)-**VIIb**].—When 0.48 g of (±)-*threo*-2-(α-hydroxybenzyl)-piperidine [(±)-VIIa], mp 171–172°, obtd as descrd by Crook and McElvain,[9a] mp 171–173°, was treated as in the prepn and work-up of (±)-Vb, there was obtd from heptane 0.33 g (40%) of (±)-VIIb: mp 94–95°; ir ($CHCl_3$) 3540 cm^{-1} (OH); nmr ($CDCl_3$) δ 8.2–7.2 (m, 10 H, Ph and $PhSO_2$), 4.91 (d, $J_{2\alpha}$ = 10 Hz, H, OCH), 4.3–2.9 (complex, 3 H, NCH_2 and NCH), 1.8–0.8 ppm (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(**2***R*,α*S*)-(+)-*erythro*-**1-Benzenesulfonyl-2-{α-[2′-(*N*,*N*-dimethylamino)ethoxy]benzyl}piperidine Methiodide** [(2*R*:α*S*)-(+)-**IIIb**].—After 55 g of the (−)-tartaric acid salt of (*S*)-(−)-Ia [(*S*)-(+)-carbinoxamine·bitartrate], mp 135–137° softens, clear liquid 181–182.5°, $[\alpha]_D$ (MeOH) +33.5 ± 1.5° (*c* 3.56) in 500 ml of 75% EtOH was redd as descrd for (±)-I, the cat was removed and replaced with 8 g of 10% Pd/C. Redn was contd until the free amine, isolable from the reaction mixt. was halogen free (Na fusion). The free amine was treated as descd in the prepn of (±)-IIIa to give 20 g (40%) of (2*R*,α*S*)-(+)-IIIb from Et_2O–pet ether (30–60°): mp 98–99°; $[\alpha]_D$ (MeOH) +61 ± 1.5° (*c* 1.89). *Anal.* ($C_{22}H_{30}N_2O_3S$) C, H, N.

The methiodide was obtained in quant yield in Et_2O and was recrystd from EtOH: mp 187–188°; $[\alpha]_D$ (MeOH) +43.4 ± 1.5° (*c* 2.19). *Anal.* ($C_{23}H_{33}IN_2O_3S$) C, H, N.

(**2***R*,α*S*)-(+)-*erythro*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(2*R*:α*S*)-(+)-**Vb**].—Subjection of 10.9 g of (2*R*:α*S*)-(+)-IIIb·methiodide to the conditions of the Hofmann elim descrd in the prepn of (±)-IVa afforded 3.6 g (50%) of opt act (2*R*,α*S*)-IVb: mp 102–103°; ir ($CHCl_3$) 1613 and 1633 cm^{-1}, d (CH=CH_2). *Anal.* ($C_{20}H_{23}NO_3S$) C, H, N. When subjected to the condns empld for the hydrol of (±)-IVa, 3.6 g of (2*R*,α*S*)-IVb afforded 2.0 g (60%) of (2*R*:α*S*)-(+)-Vb: mp 142–143°; $[\alpha]_D$ (EtOH) +45 ± 2° (*c* 0.82); ir ($CHCl_3$) and nmr ($CDCl_3$) identical with that of (±)-Vb. *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(*R*)-(−)-**1-Benzenesulfonyl-2-benzoylpiperidine** (**VI**).—To 0.1 g of (2*R*,α*S*)-(+)-Vb in 20 ml of Et_2O was added 1.5 ml of oxid soln prepd from 5 g of $Na_2Cr_2O_7 \cdot 2H_2O$, 3.75 ml of concd H_2SO_4 and H_2O to make 25 ml of soln. After stirring for 3 hr, the Et_2O was sepd, washed with H_2O and base, dried, clarified, filtd, and evapd to give a residue. This was crystd from heptane to afford 67 mg of (*R*)-(−)-VI: mp 103–103.5°, $[\alpha]_D$ (THF) −18 ± 3° (*c* 0.85); lit.[1c] mp 103°, $[\alpha]_D$ (THF) −20 ± 1°.

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Some Aryloxyalkylamines, *N*-Arylethylenediamines, and Related Compounds as Anorectic Agents

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The anorectic and stimulant properties of some 2-phenoxytriethylamines and related compounds have been compared. The effect of phenyl-ring substitution differs from that in the amphetamine series. A *p*-CN group is particularly effective in producing anorectic activity without stimulant effects.

Most anorectic drugs have associated undesirable properties such as CNS stimulation, euphoria, addictiveness, and hypertension.

A considerable number of modifications have been made to the amphetamine structure with a view to reducing its stimulant properties while retaining anorexigenic activity.[1] The most successful compound of this type is the *N*-ethyl-*m*-trifluoromethyl derivative, fenfluramine.[2] Some 1-phenoxy-2-propylamine derivatives are also claimed to have a favorable ratio of anorexigenic to stimulant activity.[3] We have observed anorexigenic activity in some tertiary phenoxyalkylamines (Table I) and find that substitution in this series has different effects on anorexigenic and central stimulant

(1) (a) "Amphetamines and Related Compounds," S. Garattini and E. Costa, Ed., Raven Press, New York, N. Y., 1969; (b) D. L. Marsh and D. A. Herring, *J. Pharmacol.*, **100**, 298 (1950); (c) G. F. Holland, C. J. Buck, and A. Weissman, *J. Med. Chem.*, **6**, 519 (1963).

(2) J. C. Le Douarec and H. Schmitt, *Therapie*, **19**, 831 (1964).

(3) Boehringer, Ingelheim, French Patent 1,529,480 (1967); *Chem. Abstr.*, **71**, 12806 (1969).

action, than in the amphetamine or phenoxypropylamine types.

As the origin of this investigation, anorectic activity in rats roughly equal to that of amphetamine was observed with 3-[4-(β-diethylaminoethoxy)phenyl]-sydnone (**2**). This compound reversed reserpine-induced hypothermia in mice at low dose levels and caused a behavioral change in cats consisting of stereotyped reactions which, in their most severe form, were suggestive of hallucinations. A detailed description is given in the Experimental Section. Amphetamine[4] also causes stereotyped reactions in cats and similar effects have been reported to occur in human beings suffering from an overdose of amphetamine[5] or phenmetrazine.[4] For this reason we used cat behavior to assess CNS stimulant properties.

In our chemical series there was good correlation between reserpine antagonism and intensity of CNS stimulation, and the reserpine test was therefore used as an initial, rapid method of screening for undesirable stimulant effects. Our objective was to separate these from the anorectic property. In contrast to the other standard anorectic drugs which we studied, fenfluramine did not reverse reserpine hypothermia and was slightly sedative in cats.

A series of 3-phenylsydnone derivatives showed that only the basic ethers had anorectic activity and since the meta-substituted derivative **6** was inactive, it seemed that the essential structure was a parasubstituted basic phenyl ether. Increasing the size of the alkyl groups on N, which increased liposolubility, caused a general decrease of activity, although the ratio of anorexigenic to antireserpine activity was improved. The possibility that the syndnone ring functions purely as an electron-withdrawing substituent is supported by the good activity of *p*-cyano- (**7**) and *p*-nitrodiethylaminoethoxybenzene (**8**), but is difficult to reconcile with the lack of activity of some other members of the series, notably the *p*-F_3C analog, **9**. The CN substituent is also remarkable in causing almost complete abolition of the antireserpine properties, but in contrast with substituted amphetamines,[1b] it is effective only when para to the basic side chain. A CN substituent on the Ph ring of some anorexigenic 2-alkylamino-1-phenoxypropanes has also been reported[3] to reduce stimulant activity, but, whereas other substituents, such as 3,4-methylenedioxy had a similar effect in that series, in the case of phenoxytriethylamines the 3,4-OCH_2O group gave an inactive compound (**28**). Another difference is exemplified by the 1-phenoxy-2-aminopropanes **47**, **48**, and **49**, of which only the primary amine has anorectic activity, whereas of 2-(*p*-cyanophenoxy) ethylamines **7**, **51**, and **50**, only the tertiary and secondary amines are active. Although *N*-phenyl- and *N*,*m*-chlorophenylpiperazine have anorectic activity,[6] results for **42**–**44** do not suggest any relationship with the present series.

Chain branching or increase in chain length (**62**, **63**, **65**, **46**, **66**) gave anorectic compounds but also caused an increase in the antireserpine activity. This includes the benzyloxy compound **46** which is a ring-opened analog of the phenmetrazine type of anorectic agent. Replacement of the ether O by CO, NH, or S (**38**–**41**) abolished the anorectic activity as did further substitution in the Ph ring (**31**–**33**). Compounds resulting from variation of the substituents in the tertiary amino group of structure **7** (**52**–**60**) were inferior to the parent compound in anorectic potency but the majority of this group were devoid of CNS-stimulant effects.

The introduction of CN or NO_2 into the para position of β-diethylaminoethoxybenzene gives rise to anorectic activity disproportionate to other central effects in an otherwise inactive molecule, whereas in the amphetamine or 1-phenoxy-2-propylamine series substituents reduce the stimulant component of active compounds. It is possible therefore, that the para substituent in active compounds of the present series has a specific binding property.

Compound **7** was convulsant in 1 cat at 100 mg/kg and in mice at 200 mg/kg and was therefore considered unsuitable for clinical use.

Experimental Section

Pharmacology.—Compds were administered by the oral route in aq soln or in 0.5% Tragacanth suspension, in the mouse and rat tests, control animals receiving the vehicle alone. In the cat behavior study the compds were given orally in a gelatine capsule. All doses are expressed as the free base.

Anorectic Activity.—Groups of male Wistar rats trained to daytime feeding were used at intervals over a 12-week period, the rat wt changing during this time from about 100 g to about 250 g.

Rats (48), in individual metabolism cages overnight, were dosed at random with the test compds. There were 8 or 12 rats per group. A weighed amount of food, 28–30 g, was given to each rat 1 hr after dosing and after a further 2 hr the food was removed, dried for 30 min at 60°, and reweighed. The food intake/100 g of body weight was calcd for each rat.

A standard dose of compd of 25 mg of base/kg was used and was followed by a detn of ED_{50} when necessary. Otherwise results are expressed as ++ or + indicating 25% or 10–25% reduction of food intake, respectively. *p* Values are calcd by Student's *t* test.

There was remarkably little variation in food intake between control rats, a typical result ± s.e. being 4.55 ± 0.177 g.

Antagonism of Reserpine Hypothermia.[7]—Room temp was 22°. Groups of 5 female CFW mice 18–20 g were given reserpine (2.5 mg/kg sc) 18 hr before test. The rectal temp after treatment was compared with the initial temp and a graph of percentage increase in temp against time constructed for each dose of compd. The area under the curve was measured and a dose–response curve obtained by plotting area against log dose. The results are expressed as ED_{50} in mg of base/kg.

Cat Behavior.—Adult cats, in groups of 6, were allowed to roam free, and were closely observed by a trained observer. The animals were thoroughly familiar with their surroundings and with each other before being placed on test. Cat behavior was noted for 5–6 hr after dosing. Stereotyped reactions consisted mainly of repetitive and seemingly purposeless movements of the ears and head. The ears alternated in movement and the head turned from side to side. This activity was occasionally combined with motor restlessness. During the severe stereotyped reaction the animal stared fixedly at an apparently empty point on the floor, cowering and backing violently away from it in apparent fear. Results were assessed as follows: +, nervousness; ++, stereotyped reaction; +++ severe stereotyped reaction.

Chemistry.—Melting points were measured in capillary tubes in a Büchi apparatus and are corrected. Chromatog materials used were alumina type H (Spence) deactivated by addn of 5% w/w of 10% HOAc and silica for chromatog 0.2–0.5 mm (Merck). Solvent exts of aq mixts were washed (H_2O), dried ($MgSO_4$), and evapd at 40–50° (*ca.* 20 mm) using a rotary evaporator unless

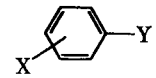
(4) A. Randrup and I. Munkvad., *Psychopharmacologia*, **11**, 300 (1967).

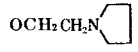
(5) P. H. Connell, "Amphetamine Psychosis," Maudsley Monograph No. 5, Chapman and Hall, London, 1958.

(6) American Cyanamid Co., U. S. Patent 3,253,989 (1966); *Chem. Abstr.*, **65**, 5311 (1966).

(7) B. M. Askew, *Life Sci.*, **10**, 725 (1963).

TABLE I



No.	X	Y	Method[a]	Salt	Mp or bp (mm) of compound and/or salt, °C	Yield, %	Recryst solvent	Formula[b]	Anorectic[c]	Reserpine[d]	Cat[e] Dose	Cat[e] Intensity
1	4-(3-Sydnonyl)	$OCH_2CH_2NMe_2$	D		95.0–95.5	42	EtOAc–petr ether (bp 60–80°)	$C_{12}H_{15}N_3O_3$	++, $P < 0.001$	50		
2	4-(3-Sydnonyl)	$OCH_2CH_2NEt_2$	D		77.5–78.0	54	EtOAc–petr ether (bp 60–80°)	$C_{14}H_{19}N_3O_3$	5	2.5	50	+++
3	4-(3-Sydnonyl)	$OCH_2CH_2NBu_2$	D		54.5–55.0	18	Petr ether (bp 40–60°)	$C_{18}H_{27}N_3O_3$	6.3	33	25	++
4	4-(3-Sydnonyl)	$OCH_2CH_2NAm_2$	D		54–55	4	Petr ether (bp 60–80°)	$C_{20}H_{31}N_3O_3$	++, $P < 0.001$	50		
5	4-(3-Sydnonyl)		D		86.0–86.5	41	EtOAc–petr ether (bp 60–80°)	$C_{14}H_{17}N_3O_3$	7.0	10		
6	3-(3-Sydnonyl)	$OCH_2CH_2NEt_2$	D		42–43	15	i-Pr_2O	$C_{14}H_{19}N_3O_3$	i	50–100		
7	4-CN	$OCH_2CH_2NEt_2$	j	Citrate	149–150 dec		EtOH	$C_{19}H_{26}N_2O_8$	23.5	>100	50 100	i ++
8	4-NO_2	$OCH_2CH_2NEt_2$	k	HCl					10.8	>25	50	+
9	4-CF_3	$OCH_2CH_2NEt_2$	C	Citrate	133–134	42	EtOH	$C_{19}H_{26}F_3NO_8$	i	i		
10	4-MeS	$OCH_2CH_2NEt_2$	B_1	HCl	110–112	50	$CHCl_3$–EtOAc	$C_{13}H_{22}ClNOS$	i	i		
11	4-MeSO	$OCH_2CH_2NEt_2$	B_1	Citrate	86–88	18	EtOH	$C_{19}H_{29}NO_9S$	i	i		
12	4-$MeSO_2$	$OCH_2CH_2NEt_2$	B_1	Citrate	133–135	28	EtOH	$C_{19}H_{29}NO_{10}S$	i, ns.	i		
13	4-NCS (iso)	$OCH_2CH_2NEt_2$	D, l	HCl	175.0–175.5	95	$CHCl_3$–hexane	$C_{13}H_{19}ClN_2OS$	i	25		
14	4-SCN	$OCH_2CH_2NEt_2$	D	Citrate	120.5–121.5	3	EtOH	$C_{19}H_{26}N_2O_8S \cdot 0.5H_2O$	+, $P < 0.01$	i		
15	4-Ph	$OCH_2CH_2NEt_2$	m						+, $P < 0.05$	i		
16	4-p-$NO_2C_6H_4$	$OCH_2CH_2NEt_2$	n						+, $P < 0.05$	30	20	+
17	4-CO_2H	$OCH_2CH_2NEt_2$	D		119–121		MeCOEt	$C_{13}H_{19}NO_3$	i	i		
18	4-CO_2Me	$OCH_2CH_2NEt_2$	o						i	>100		
19	4-CHO	$OCH_2CH_2NEt_2$	p						i	i		
20	4-CH=NOH	$OCH_2CH_2NEt_2$	p						++, $P < 0.001$	24.5		
21	4-CH=N·NHCONH$_2$	$OCH_2CH_2NEt_2$	D		188–188.5	63	EtOH–H_2O	$C_{14}H_{22}N_4O_2$	i	42		
22	4-COMe	$OCH_2CH_2NEt_2$	q						i	>100		
23	4-C(Me)=NOH	$OCH_2CH_2NEt_2$	D		92–93	94	C_6H_6–petr ether (bp 60–80°)	$C_{14}H_{22}N_2O_2$	+, $P < 0.05$	45		
24	4-CH=$CHCO_2Me$	$OCH_2CH_2NEt_2$	A_3		168–169 (11)	70						
				HCl	185–186			$C_{16}H_{24}ClNO_3$	i	>100		
25	4-CH=CHCN	$OCH_2CH_2NEt_2$	D	Citrate	115–116	1	EtOH–Et_2O	$C_{21}H_{28}N_2O_8$	i			
26	4-CH=$CHCO_2H$	$OCH_2CH_2NEt_2$	D		110–111	85		$C_{15}H_{21}NO_3$	i	i		
27	4-$CSNH_2$	$OCH_2CH_2NEt_2$	D		90–91	65	EtOAc–petr ether (bp 60–80)°	$C_{13}H_{20}N_2OS$	i	i	25	++
28	3,4-CH_2O_2	$OCH_2CH_2NEt_2$	A[f]	Citrate	125–126	60	EtOH	$C_{19}H_{27}NO_{10}$	i	>100		
29	4-Me_2N	$OCH_2CH_2NEt_2$	r	Bis(p-toluene-sulfonate)	95–96		EtOH–EtOAc	$C_{28}H_{40}N_2O_7S_2 \cdot H_2O$	i	>100	50	+
30	2,4-$(NO_2)_2$	$OCH_2CH_2NEt_2$	A_3	Citrate	85–87	43	EtOH	$C_{18}H_{25}N_3O_{12}$	+, $P < 0.05$	50		
31	2-OH, 4-NO_2	$OCH_2CH_2NEt_2$	A_2	HCl	225–226	45	2-Methoxyethanol	$C_{12}H_{19}ClN_2O_4$	i	>100		
32	3-Me, 4-NO_2	$OCH_2CH_2NEt_2$	A_3	Citrate	149–150		MeOH	$C_{19}H_{28}N_2O_{10}$	i	i		

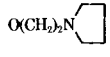
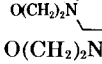
33	2-Cl, 4-NO_2	$OCH_2CH_2NEt_2$	*s*	Citrate	134–135		MeOH–EtOH	$C_{18}H_{25}ClN_2O_{10}$	i	20–25		
34	3-CF_3	$OCH_2CH_2NEt_2$	A_1		143–146 (26)	72			i	i		
				HCl	132–133		EtOAc	$C_{13}H_{19}ClF_3NO$	i	i		
35	3-CH=NOH	$OCH_2CH_2NEt_2$	D		72–73	70	EtOAc–petr ether (bp 60–80°)	$C_{13}H_{20}N_2O_2$	i	i		
36	3-CN	$OCH_2CH_2NEt_2$	D		120–126 (0.05)	80			i	i		
				HCl	158–159		EtOH–EtOAc	$C_{13}H_{19}ClN_2O$				
37	3-NO_2	$OCH_2CH_2NEt_2$	E	HCl	146–147	14	MeOH–EtOAc	$C_{12}H_{19}ClN_2O_3$	i	i		
38	4-NO_2	$COCH_2CH_2NEt_2$	*t*						i	31	50	++
39	4-NO_2	$SCH_2CH_2NEt_2$	*u*						i	25–50		
40	4-NO_2	$NHCH_2CH_2NEt_2$	*v*	Citrate	143–144		MeOH	$C_{18}H_{27}N_3O_9$	+, ns	28		
41	4-CN	$NHCH_2CH_2NEt_2$	E	Citrate	137–138	22	MeOH	$C_{19}H_{27}N_3O_7$	+, $P < 0.05$	25–50		
42	4-NO_2		*w*						++, $P < 0.05$	25		
43	4-NO_2		*x*						+, $P < 0.01$	25–50		
44	4-CN		E		112.5–113.5	14	Petr ether (bp 100–120°)	$C_{12}H_{15}N_3$	i	i		
45	4-NO_2	$(CH_2)_3NEt_2$	E, *u*		130–131 (0.6)	87						
				Citrate	129–130		EtOH	$C_{19}H_{28}N_2O_9$	5	2.8	40	+++
46	4-CN	$CH_2O(CH_2)_2NEt_2$	C	Citrate	120–121	76	EtOH	$C_{20}H_{28}N_2O_8$	25	7.8	50	+++
47	4-H	$OCH_2CH(Me)NH_2$	E, *y*		130–135 (17)	87						
				Phosphate	167–168		MeOH–EtOAc	$C_9H_{16}NO_5P$	++, $P < 0.05$	4.8	30	i[h]
48	4-H	$OCH_2CH(Me)NHEt$	E, *z*		120 (23)	35						
				HCl	143–144		EtOH–EtOAc		i	50–100	30	i
49	4-H	$OCH_2CH(Me)NEt_2$	B, *z*	Citrate	99–100	5	EtOH–EtOAc	$C_{19}H_{29}NO_8$	i	i	20	i
50	4-CN	$O(CH_2)_2NH_2$	E	HCl	274–275 dec	31	MeOH–EtOAc	$C_9H_{11}ClN_2O$	i	50–100		
51	4-CN	OCH_2CH_2NHEt	B	Citrate	114–116	29	EtOH	$C_{17}H_{22}N_2O_8$	++, $P < 0.05$	i		
52	4-CN	$OCH_2CH_2NMe_2$	*aa*	Citrate	126–127 dec		EtOH	$C_{17}H_{22}N_2O_8$	i	i		
53	4-CN	$OCH_2CH_2NPr_2$	B	Citrate	125–126 dec	68	EtOH	$C_{21}H_{30}N_2O_8$	+, $P < 0.01$	i		
54	4-CN	$OCH_2CH_2NBu_2$	B	Citrate	97–99	35	EtOH	$C_{23}H_{34}N_2O_8$	+, $P < 0.05$	i		
55	4-CN	$OCH_2CH_2NAm_2$	B		150–154 (0.02)							
				p-Toluene-sulfonate	99.0–99.5	37	EtOAc–Et_2O	$C_{26}H_{38}N_2O_4S$	i	i		
56	4-CN		B	Citrate	120–121 dec	68	EtOH	$C_{19}H_{24}N_2O_8$	+, $P < 0.01$	19		
57	4-CN		B	Citrate	96–98	89	EtOH	$C_{20}H_{26}N_2O_8$	+, ns	5–10		
58	4-CN		B		89–90	63	Petr ether (bp 100–120°)	$C_{13}H_{16}N_2O_2$	+, $P < 0.05$	i		
59	4-CN		B		72–73	29	Petr ether (bp 80–100°)	$C_{14}H_{19}N_3O$	i	i		
60	4-CN	$O(CH_2)_2N(Et)CH_2CH_2OH$	B	Citrate	115–117 dec	67	EtOH	$C_{19}H_{26}N_2O_9$	i	20–50		
61	4-NO_2	$OCH(Me)CH_2NEt_2$	*bb*						++, $P < 0.001$	i		
62	4-CN	$OCH(Me)CH_2NEt_2$	C	Citrate	120–122	5	EtOH–EtOAc	$C_{20}H_{28}N_2O_8$	+, $P < 0.001$	i		
63	4-CN	$OCH_2CH(Me)NEt_2$	B_2	*p*-Toluene-sulfonate	109–110	14	EtOH–Et_2O	$C_{21}H_{28}N_2O_4S$	5	6.25	10	+
64	2-Cl	$OCH_2CH(Me)NHMe$	*cc*	HCl					+, $P < 0.02$	16.5		

TABLE I (*Continued*)

No.	X	Y	Method[a]	Salt	Mp or bp (mm) of compound and/or salt, °C	Yield, %	Recryst solvent	Formula[b]	Anorectic[c]	Reserpine[d]	Cat[e] Dose	Cat[e] Intensity
65	4-CN	$O(CH_2)_3NEt_2$	A	Citrate	141.5–142.0	72	EtOH	$C_{20}H_{28}N_2O_8$	21	2.1	50	++
66	4-CN	$O(CH_2)_4NEt_2$	B	Citrate	106–108	93	EtOH	$C_{22}H_{32}N_2O_8$	+, ns	3.6	50	+++
67	4-Diethylaminoethoxypyridine		E, *dd*		100–103 (0.2)	38						
				2 HCl	170–171		MeOH–EtOAc	$C_{11}H_{26}Cl_2N_2O^w$	+, $P < 0.05$	>100		
	Amphetamine								6.9	0.6	5	+++
	Diethylpropion								19	1.5	20	++
	Fenfluramine								5	i	10	i[i]
	Methyl phenidate								30	5–10	16	++
	Pipradol								25	2.5	25	+++

[a] Where only a literature reference is given, the compound was prepared by the literature method, but the formula is given for a previously undescribed salt. Letters refer to methods described under Chemistry; if a literature reference is also given the compound has been made previously by a different method. [b] Analyses (C, H, N) of compounds whose formulas are given were within 0.4% of the calculated values. [c] Figures denote ED_{50} in mg/kg; (+) more than 25% reduction of food intake at 25 mg/kg dose; (+) 10–25% reduction; (i) less than 10% reduction; *P* values by Student's *t* test; ns = not significant. [d] ED_{50} in mg/kg; i, inactive at 100 mg/kg. [e] +, nervousness; ++, stereotyped reactions; +++, severe stereotyped reaction (defined under Experimental Section. [f] Previously reported [M. A. Fahmy and H. T. Gordon, *J. Econ. Entomol.*, **58**, 451 (1965)] without physical constants. [g] This compound was too hygroscopic for analysis. [h] Marked hypertensive and sedative effect. [i] Sedative effect. [j] F. C. Copp and G. C. Coker, Wellcome Foundation Ltd., British Patent 924,961 (1963); *Chem. Abstr.*, **59**, 9883 (1963). [k] See ref 10. [l] I. Utsumi, T. Ida, T. Kiguchi, and M. Tsunoka, *Yakugaku Zasshi*, **74**, 238 (1954). [m] L. Bauer, J. Cyerman, and W. J. Sheldon, *J. Chem. Soc.*, 2342 (1951). [n] F. L. Bach, J. C. Barclay, F. Kende, and E. Cohen, *J. Med. Chem.*, **11**, 987 (1968). [o] M. B. Moore and M. Vernsten, *J. Amer. Chem. Soc.*, **78**, 5633 (1956). [p] H. D. Cossey, C. J. Sharpe, and F. F. Stephens, *J. Chem. Soc.*, 4322 (1963). [q] V. A. Zasovov, E. I. Metel'kova, and S. N. Milovanova, *Zh. Obshch. Khim.*, **26**, 2499 (1956). [r] J. Fakstorp and J. Christiansen, *Acta Chem. Scand.*, **11**, 1698 (1957). [s] H. Najer and P. Mabille, *Bull. Soc. Chim. Fr.*, 645 (1958). [t] L. W. Nobles and J. H. Burckhalter, *J. Amer. Pharm. Ass. Sc. Ed.*, **67**, 77 (1958). [u] See ref 20. [v] See ref 11. [w] R. L. Bent, J. C. Dessloch, E. C. Duennebier, D. W. Fassett, D. B. Glass, J. H. James, D. B. Julian, W. R. Ruby, J. M. Snell, J. H. Sterner, J. H. Therle, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **73**, 3100 (1951). [x] H. Loewe, H. Mieth, and J. Urbanietz, *Arzneim.-Forsch.*, **16**, 1306 (1966). [y] C. D. Hurd and P. Perletz, *J. Amer. Chem. Soc.*, **68**, 38 (1946). [z] M. Palonovski, M. Pesson, and J. Bededuc, *C.R. Acad. Sci.*, **233**, 1120 (1951). [aa] See ref 1. [bb] American Cyanamid Co., Netherlands Patent 6,410,914 (1964); *Chem. Abstr.*, **62**, 14692 (1965). [cc] See ref 3. [dd] See ref 12.

stated otherwise. Microanalyses were carried out by Mr. R. J. Clark of these Laboratories using a Perkin-Elmer 240 elemental analyzer and are within 0.4% of the theoretical values unless quoted in full.

General Methods of Preparation. A.—A soln of the dialkylaminoalkyl chloride in PhH (prepared from 1.1 equiv of the hydrochloride) was added to a soln of the Na salt of the phenol in EtOH, and the mixt was heated under reflux for 5 hr. The cooled mixt was filtered and evapd, the residue was partitioned between Et_2O and H_2O, and the Et_2O was washed (1 *N* NaOH, H_2O), dried ($MgSO_4$), and evapd. The products were purified further if necessary by chromatog on alumina using PhH or Et_2O as eluant.

A_1.—A soln of the Na salt of the phenol in PhH was treated similarly.

A_2.—A soln of the Na salt of the phenol in DMF was treated similarly (in the case of the product obtained from 4-nitrocatechol the wash with NaOH was omitted).

A_3.—A soln of the dialkylaminoalkyl chloride (1.1 equiv) in PhH was added to a mixt of anhyd K_2CO_3 and the phenol in Me_2CO, and the mixt was stirred and boiled under reflux for 5 hr and worked up as in A (in the case of the product obtd from 2,4-dinitrophenol the wash with NaOH was omitted).

B.—The appropriate aryloxyalkyl bromide reacted with amines under the following condns: with $EtNH_2$ in EtOH soln or Et_2NH and a trace of NaI in Me_2CO soln, by heating at 100° for 16 hr in a sealed tube; with other amines by heating at 100° using excess of amine as solvent. After evapn of solvent and unreacted amine at 60–70° under reduced pressure, the residue was partitioned between 2 *N* HCl and Et_2O, the aq layer was basified (40% NaOH soln), and the crude base was isolated by Et_2O extn. Salts were prepd from the crude bases except in the case of 4-(2-di-*n*-amylaminoethoxy)benzonitrile which was first purified by distn, bp 150–154° (0.02 mm).

B_1.—An aryloxyalkyl chloride was employed in method B. 4-(2-Diethylaminoethoxy)phenyl methyl sulfoxide (**11**), which was H_2O sol, was isolated by treating the reaction mixt with an excess of Na_2CO_3, evapg to dryness, and extg the residue with *i*-PrOH.

B_2.—An aryloxyalkyl tosylate was used in method B.

C.—A reactive halogen compd (*e.g.*, *p*-trifluoromethylbromobenzene, *p*-chlorobenzonitrile, or *p*-cyanobenzyl bromide) was added to a soln of the Na salt of the dialkylamino alcohol in excess dialkylamino alcohol and heated at 130° for 16 hr. The soln was evapd at 70° (15 mm), and the residue was partitioned between Et_2O and 2 *N* HCl. The aq layer was basified (40% NaOH), and the product was isolated by Et_2O extn.

D. Modification of Compds Contg the Diethylaminoethoxyphenyl Moiety. 4-(2-Diethylaminoethoxy)phenyl Isothiocyanate (13).—EtOH (55 ml), NH_4OH (d = 0.88, 20 ml), and CS_2 (10 ml) were stirred at 0° during addn of a soln of 4-(2-diethylaminoethoxy)aniline (20.8 g) in EtOH (20 ml). After 2 hr at 0°, the *N*-(*p*-diethylaminoethoxyphenyl)dithiocarbamic acid was filtered off and washed with Me_2CO, (95%, mp 143–144°). *Anal.* ($C_{13}H_{20}N_2OS_2$) C, H, N. The dithiocarbamic acid (12.7 g), $CHCl_3$ (200 ml), and Et_3N (7 ml) were stirred at 0° and ethyl chloroformate (5.1 ml) was added in 10 min. After 1 hr the soln was washed (H_2O, 2 *N* HCl) and the $CHCl_3$ was evapd to give the isothiocyanate·HCl.

4-(2-Diethylaminoethoxy)phenyl Thiocyanate (14) was prepd from 4-(2-diethylaminoethoxy)aniline as described for 4-methoxyphenyl thiocyanate[8] and was purified by chromatog on alumina with PhH.

4-(2-Diethylaminoethoxy)cinnamonitrile (25).—4-(2-Diethylaminoethoxy)benzaldehyde (8.8 g), cyanoacetic acid (3.8 g), pyridine (20 ml), and piperidine (1 ml) were heated at 100° for 9 hr. The soln was evapd, and the residue was dissolved in Et_2O, washed (1 *N* NaOH, $NaHSO_3$ soln, H_2O), dried ($MgSO_4$), and evapd to give the base (0.2 g).

4-(2-Diethylaminoethoxy)benzoic Acid (17).—Methyl 4-(2-diethylaminoethoxy)benzoate was hydrolyzed,[9] the resulting hydrochloride was treated with Zeo-Karb 225, the resin was eluted with NH_4OH, and the eluate was evapd.

4-(2-Diethylaminoethoxy)cinnamic acid (26) was obtained by hydrolysis of the Me ester with 2 *N* NaOH (1.1 moles) in MeOH at 20° for 16 hr. Zeo-Karb 225 (H^+) was added to pH 7, the

(8) J. W. Dienske, *Rec. Trav. Chim. Pays-Bas*, **50**, 167, 407 (1931).

(9) R. Fusio, S. Chiavarelli, G. Palazzo, and D. Bovet, *Gazz. Chim. Ital.*, **78**, 951 (1948).

mixt was filtered, the filtrate was evapd, and the residue was collected with Et_2O.

4-(2-Diethylaminoethoxy)thiobenzamide (27).—H_2S was passed into a mixt of 4-(2-diethylaminoethoxy)benzonitrile (21.8 g), pyridine (100 ml), and Et_3N (42 ml) for 6 hr. The mixt was evapd, and the residue was purified by chromatog on alumina with EtOAc.

3-(2-Diethylaminoethoxy)benzaldoxime and 3-(2-Diethylaminoethoxy)benzonitrile (35, 36).—$NH_2OH \cdot HCl$ (1.2 moles) was added to a stirred mixt of 4-(2-diethylaminoethoxy)benzaldehyde (1 mole) and 1 *N* NaOH (1.2 moles) over 10 min. After 30 min excess Na_2CO_3 was added, and the product was isolated by extn with Et_2O followed by chromatog on alumina with $CHCl_3$. The oxime was boiled under reflux for 5 hr with excess Ac_2O, the soln was evapd, and the product was isolated by addn of Na_2CO_3 soln and Et_2O extn.

Sydnones were generally prepd from *N*-4-(2-dialkylaminoethoxy)phenylglycines *via* the *N*-nitrosoglycines. The *N*-substituted glycine·2HCl (Table II) was dissolved in H_2O, and 3 equiv of 2 *N* NaOH was added, followed by 1.1 equiv of $NaNO_2$ soln. The soln was stirred at −5° and concd HCl was added in 30 min to give pH 2. After another 30 min the soln was evapd at 50° *in vacuo*. The residue was extd several times with hot MeOH, which was evapd. The residue was heated at 100° with excess Ac_2O for 1 hr, the soln was evapd, ice and excess Na_2CO_3 soln were added, and the oil was isolated by Et_2O extn. The residue was purified by chromatog on silica with Me_2CO. 3-(*m*-Diethylaminoethoxyphenyl)sydnone was prepd *via* *N*-(*m*-diethylaminoethoxyphenyl)glycine ethyl ester. The ester was hydrolyzed by heating with 2 equiv of 2 *N* NaOH for 1 hr, and the soln was nitrosated *etc.*, as above.

E. Miscellaneous Preparations. 3-(2-Diethylaminoethoxy)-nitrobenzene·HCl (37) was prepd in the same way as the para isomer.[10]

***N*-*p*-Cyanophenyl-*N'N'*-diethylethylenediamine (41)** was prepd from *p*-aminobenzonitrile by the method described for the *p*-nitro analog[11] and was purified first on a silica column by clearing with PhH–EtOAc and eluting with Me_2CO to give a product which was purified further on alumina using PhH.

1-(*p*-Cyanophenyl)-4-methylpiperazine (44).—*N*-Methylpiperazine (12 g) and *p*-chlorobenzonitrile (8.25 g) were heated at 120° for 16 hr. The mixt was evapd, the residue was partitioned between 1 *N* HCl and EtOAc, and the aq layer was basified; the product obtd by Et_2O extn was purified by chromatog on silica using Me_2CO and on alumina using Et_2O.

4-(3-Diethylaminopropyl)nitrobenzene (45) was prepd by the reaction of 3-(*p*-nitrophenyl)propyl chloride with Et_2NH in Me_2CO as described in method B.

2-*p*-Cyanophenoxyethylamine (50).—2-*p*-Cyanophenoxyethyl bromide (0.02 mole) and potassium phthalimide (0.02 mole) in DMF (20 ml) were heated at 100° for 2 hr and dild with H_2O to ppt *N*-(2-*p*-cyanophenoxyethyl)phthalimide (62%, mp 186.5–187° from EtOAc). *Anal.* ($C_{17}H_{12}N_2O_3$) C, H, N. An EtOH soln of the phthalimide derivative was decompd by boiling with $N_2H_4 \cdot H_2O$ for 2 hr. The EtOH was evapd, 2 *N* HCl was added, and the solid was filtered off. The filtrate was basified (NaOH soln), and the amine was isolated by Et_2O extn.

4-(2-Diethylaminoethoxy)pyridine (67).—A soln of 4-pyridone (0.05 mole) in 2 *N* NaOH (25 ml) was treated with aq $AgNO_3$ (0.02 mole), and the Ag salt was washed (H_2O, EtOH, Et_2O) and air-dried. This was boiled for 2 hr under reflux with a soln of diethylaminoethyl chloride (0.02 mole) in PhMe and filtered, the PhMe was evapd, and the product was distd (85%): bp 100–103° (0.2 mm); [lit.[12] bp 95° (0.03 mm)]; λ_{max} uv (EtOH) 222 mμ (pH 7); 238 mμ (pH 2) consistent with a 4-alkoxypyridine.[13] The hydrochloride was too hygroscopic for anal.

2-Amino-1-phenoxypropane (47).—2-Bromo-1-phenoxypropane (0.02 mole) and potassium phthalimide (0.02 mole) in DMF (20 ml) at 120° for 5 hr gave *N*-(1-methyl-2-phenoxyethyl)-phthalimide (46%, mp 69–70° from petr ether, bp 60–80°, *Anal.* ($C_{17}H_{15}NO_3$) C, H, N), which, on boiling with $N_2H_4H_2O$ in EtOH for 2 hr, gave the amine by the usual procedure.[14]

2-Ethylamino-1-phenoxypropane (48) was obtained by reduction of crude 2-acetamido-1-phenoxypropane (7 g) in PhMe (20 ml) with 70% $Na(MeOCH_2CH_2O)_2AlH_2$ (2.25 moles) in PhMe[15] at 80° for 2 hr.

Intermediates. *N*-Arylglycine·2HCl (Table II) was obtd by hydrogenation of a soln of equimolar amts of the appropriate *p*-dialkylaminoethoxyaniline and glyoxylic acid hydrate in 2 *N* HCl at 1 atm over 10% Pd/C until no more H_2 was absorbed (1–8 hr). The filtered soln was evapd at reduced pressure, and the residue was recrystd.

TABLE II

p-$XCH_2CH_2OC_6H_4NHCH_2CO_2H \cdot 2HCl$

X	Mp, °C dec	Recrystn solvent	% yield	Formula[a]
MNe_2N	210–213	EtOH	75	$C_{12}H_{18}N_2O_3 \cdot 2HCl$[b]
Et_2N	174–176	EtOH	52	$C_{14}H_{22}N_2O_3 \cdot 2HCl$
Bu_2N	151–152	EtOH–EtOAc	51	$C_{18}H_{30}N_2O_3 \cdot 2HCl$[c]
Am_2N	133–135	MeOH–Et_2O	12	$C_{20}H_{34}N_2O_3 \cdot 2HCl$[d]
	180–182	MeOH–EtOAc	66	$C_{14}H_{20}N_2O_3 \cdot 2HCl$

[a] All compds were analyzed for C, H, N. [b] C: calcd, 46.3; found, 45.8. [c] C: calcd, 54.7; found, 54.2. [d] C: calcd, 56.7; found, 56.2.

***p*-Dialkylaminoethoxyanilines.**—4-(β-Hydroxyethoxy)acetanilide[16] in pyridine was treated with TsCl below 20°. After 3 hr the mixt was added to ice water, and the solid was recrystd from EtOH to give β-(4-acetamidophenoxy)ethyl toluene-*p*-sulfonate (90%), mp 142–143.5°. *Anal.* ($C_{17}H_{19}NO_5S$) C, H, N. The tosyl deriv was heated in an oil bath at 100° for 3 hr with excess R_2NH, the mixt was evapd, and the residue was heated under reflux for 3 hr with 6 *N* HCl. The soln was basified (40% NaOH) and extd with Et_2O to give *p*-$XCH_2CH_2OC_6H_4NH_2$: X = Bu_2N, 78% yield, bp 163–165° (0.2 mm), dihydrochloride mp 205–206.5° dec (EtOH), *Anal.* ($C_{16}H_{30}Cl_2N_2O$) C, H, N; X = Am_2N, 92% yield, bp 145–147° (0.02 mm), *Anal.* ($C_{18}H_{32}N_2O$) C, H, N: X = pyrrolidino,[17] 81% yield, bp 130–135° (0.01 mm).

4-(2-Dimethylaminoethoxy)aniline[16] and 4-(2-diethylaminoethoxy)aniline[16] were prepd by alkylation of 4-acetamidophenol in NaOEt–EtOH with the appropriate dialkylaminoalkyl chloride in the usual way and hydrolysis of the product for 2 hr with boiling 6 *N* HCl.

3-(2-Diethylaminoethoxy)aniline was prepd similarly from *m*-acetamidophenol: yield, 55%, bp 120° (0.25 mm). *Anal.* ($C_{12}H_{20}N_2O$) C, H, N.

***N*-(*m*-Diethylaminoethoxyphenyl)glycine Ethyl Ester.**—3-(2-Diethylaminoethoxy)aniline, ethyl bromoacetate, NaOAc (0.1 mole each), and EtOH (20 ml) were heated at 120° under reflux for 5 hr. The mixt was evapd, and the residue was partitioned between Et_2O and 2 *N* HCl. The ester was isolated by basification and ether extn and distd, 50%, bp 146–152° (0.02 mm). *Anal.* ($C_{16}H_{26}N_2O_3$) C, H, N.

***p*-Methylthiophenoxyethyl Chloride and 4-(2-Chloroethoxy)-phenyl Methyl Sulfoxide and Sulfone.**—*p*-Methylthiophenoxyethanol[18] (10 g) and TsCl (20 g) in pyridine (100 ml) heated for 15 min at 100° and dild with H_2O gave *p*-methylthiophenoxyethyl chloride (67%), mp 66–67° (petr ether, bp 80–100°). *Anal.* ($C_9H_{11}ClOS$) C, H. H_2O_2 (30% 4.56 g) was added to a soln of *p*-methylthiophenoxyethyl chloride (3.38 g) in HOAc (10 ml) so that the temp was maintd at 55–65°. After 3 days the soln was dild with H_2O and neutralized (Na_2CO_3), and the solid obtd by PhH extn was chromatogd on alumina with PhH to give the sulfone (0.76 g), mp 86.5–87° (aq MeOH). *Anal.* ($C_9H_{11}ClO_2S$) C, H. Further eln of the column with EtOAc gave the sulfoxide (1.6 g), mp 83.5–84° (PhH). *Anal.* ($C_9H_{11}ClO_2S$) C, H.

4-(*p*-Cyanophenoxy)butyl bromide was prepd in 54% yield from 1,4-dibromobutane by the process described for 2-(*p*-cyanophen-

(10) H. J. Engelbrecht, British Patent 961,275 (1964); *Chem. Abstr.*, **61**, 6958 (1964).

(11) M. A. Stahann and A. C. Cope, *J. Amer. Chem. Soc.*, **68**, 2494 (1946).

(12) K. Miescher and E. Urech, U. S. Patent 1,881,236 (1933); *Chem. Abstr.*, **27**, 1096 (1933).

(13) A. I. Scott, "Interpretation of the Ultra-Violet Spectra of Natural Products," Pergamon Press, Elmsford, N. Y., 1964, p 180.

(14) H. R. Ing and R. F. H. Manske, *J. Chem. Soc.*, 2348 (1926).

(15) As supplied by Exico, Chemical Division, London, W.C.1, *cf.* M. Cerny, J. Malek, M. Capka, and V. Chvalovsky, *Collect. Czech. Commun.*, **34**, 1033 (1969), and previous papers.

(16) R. M. Herbst and J. V. Simonian, *J. Org. Chem.*, **17**, 595 (1952).

(17) I. A. Kaye, W. J. Burlant, and L. Price, *ibid.*, **16**, 1421 (1951).

(18) D. J. Drain, J. G. B. Howes, R. Lazare, G. M. Salaman, R. Shadbolt, and H. W. R. Williams, *J. Med. Chem.*, **6**, 63 (1963).

oxy)ethyl bromide,[19] mp 45–46° (petr ether, bp 100–120°). *Anal.* ($C_{11}H_{12}BrNO$) C, H.

1-(*p*-Cyanophenoxy)-2-(toluene-*p*-sulfonyloxy)propane.—*p*-Cyanophenol (23.8 g) was treated with propylene oxide (15.5 ml) under the described conditions[18] and an Et_2O soln of the crude 1-(*p*-cyanophenoxy)-2-propanol was washed (1 *N* NaOH, H_2O), dried ($MgSO_4$), and evapd. An ice-cooled soln of the residue in pyridine (100 ml) was treated with TsCl (40 g) and after 2 hr was dild with H_2O (1 l.) and extd with Et_2O which was washed (1 *N* HCl, H_2O), dried ($MgSO_4$), and evapd. The oil was chromatogd on silica with Et_2O to obtain, as the first component, an oil, which was crystd from MeOH to give the tosylate (12.8 g), mp 107–109°. *Anal.* ($C_{17}H_{17}NO_4S$) C, H, N.

(19) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *J. Chem. Soc.*, 103 (1942).

3-(*p*-Nitrophenyl)propyl Chloride.—Nitration of 3-phenylpropyl chloride[20] gave a product which was shown to contain 2 major components in approx equal amts by glpc (apiezon celite at 150°). The prod (59.6 g) distd at 0.5 mm through a spinning-band column (108 × 2 cm) giving fractions of bp 129–130° (16.3 g) and 148–149° (19.8 g). Chromatog of the 2-fractions on alumina using petr ether (60–80°) gave homogeneous products. The lower boiling isomer absorbed (ir) at 1530, 1350, and 790 cm^{-1} (ortho) and the higher boiling isomer at 1505, 1335, and 840 cm^{-1} (para).[21]

(20) J. Buchi, J. Enezian, G. Enezian, G. Valette, and C. Pattani, *Helv. Chim. Acta*, **43**, 1971 (1960).

(21) *Cf.* C. P. Conduit, *J. Chem. Soc.*, 3273 (1959).

Microbiological and Chemical Modification of *N*-Benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (*N*-Benzoylmecamylamine)

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The metabolic transformation of the *N*-Bz derivative of the ganglionic blocking agent mecamylamine [*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**1**)] by *Sporotrichum sulfurescens* results in oxygenation at positions 6 and 7 to give the hydroxylamides **2** and **3**. Several mecamylamine analogs (**4–7** and **10–21**) were prepared from the microbial metabolites.

The chemical preparations and structure–activity relationships of *N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (mecamylamine) and analogs as ganglionic blocking agents have been well documented.[1] Our interest in the microbial oxygenation of the title compound (**1**) was 2-fold; *viz.*, to compare the stereochemistry and relationship of the enzymic hydroxylation site of the products with related biotransformations,[2] and to observe the effects of the products and their analogs on hypertension.

Fermentation of *N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine with *Sporotrichum sulfurescens* produced a complex mixture of hydroxylated products from which it was possible to isolate a major component in 21% yield; if the mixture was oxidized before undertaking isolations, 2 major ketonic products could be obtained, one of mp 82°, in 24% yield and the other, of mp 136–138°, in 29% yield. It was further determined that oxidation of the originally isolated OH compd led to the ketone melting at 82°. Examination of the nmr spectrum of the ketoamides cast some light on their structures. There are only 3 possibilities for ketone attachment to the substrate (**1**), *i.e.*, at C_5, C_6, or C_7. The spectrum of *N*-benzoylmecamylamine (**1**) showed a sharp signal, 3 H, at δ 2.92 ppm for the NCH_3 protons. A medium broad signal, 1 H, with no discernable splitting pattern, at δ 2.48 ppm, was assigned to the tertiary proton at C_1. The remainder of the spectrum, aside from the Ph protons, was in the range between δ 0.80 and 2.10 ppm with sharp signals at δ 1.20, 1.24, and 1.53 ppm for the 3 CCH_3 groups. The spectrum of both ketones showed the signal for the tertiary proton at C_1 downfield, as a shoulder at the base of the NCH_3 signals; the NCH_3 plus the shoulders now integrated for 4 protons. This downfield shift of protons at C_1 is very likely caused by the C=O attachments being α to the C_1H, *i.e.*, at C_6 and at C_7. The ketones of mp 82° and mp 136–138° were reduced with $NaBH_4$ to give two hydroxyamides, both of which were not present in the original biotransformation mixture.

The structure of the alcohol isolated directly from the fermentation was shown to be *exo*-6-hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**2**) by solvolytic fragmentation. Grob and coworkers[3] have shown in their studies on 1-methyl-4-, -5-, and -7-decahydroquinolyl tosylates that if a C–OTs bond and the free electron pair on N are in an antiperiplanar position with respect to the intermediate transfer bond, these compds undergo quantitative stereospecific fragmentation. Compound **2** was reduced with LAH to a hydroxybenzylamine (**6**) and then converted to its tosyl ester (**7**). This compd, upon heating in 80% aq EtOH, was converted exclusively to its fragmentation products, *N*-methylbenzylamine salt (**9**) and 3-methyl-3-(3-cyclopentenyl)-2-butanone (**8**). The ketone **8** was identified by its nmr and ir spectra and by analysis as a 2,4-dinitrophenylhydrazone. The nmr spectrum showed 2 equivalent olefinic protons, with a coupling constant approaching zero, as a singlet at δ 5.67 ppm. It should

(1) C. A. Stone, M. L. Torchiana, K. L. Meckelnherd, J. Stavorski, M. Sletzinger, G. A. Stein, W. V. Rugle, D. F. Reinhold, W. A. Gaines, H. Arnold, and K. Pfister, III, *J. Med. Pharm. Chem.*, **5**, 665 (1962); (b) K. Pfister, III, and G. A. Stein, U. S. Patent 2,831,027 (April 15, 1958); (c) G. A. Stein, M. Sletzinger, H. Arnold, D. Reinhold, W. Gaines, K. Pfister, III, *J. Amer. Chem. Soc.*, **78**, 1514 (1956); (d) Z. J. Vejlelek and M. Provita, *Collect. Czech. Chem. Commun.*, **24**, 2614 (1959); (e) N. D. Edge, S. J. Corne, G. E. Lee, and W. R. Wragg, *Brit. J. Pharmacol. Chemother.*, **15**, 207 (1950).

(2) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967); (b) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **35**, 622 (1970), and ref cited therein.

(3) (a) C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkins, *Helv. Chim. Acta*, **50**, 416 (1967); (b) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3207 (1968), have applied this principle in their structure studies of benzoyl-*trans*-decahydroquinolinol; one of them (R. A. Johnson) suggested the applicability to this work.