H. Oliver for the microanalyses, Miss E. M. Tanner for the optical rotations, and Mrs. P. Varner, Mr. M. D. Stephens, and Miss J. Wax for participation in the biological work.

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New Compounds

Synthesis of New Glycido Derivatives. 2-Dimethylaminoethyl Triphenylglycidate and 2-Dimethylaminoethyl 2,3,3-Triphenylglycidyl Ether

Arturo Donetti* and Bruno Lumachi

Research Laboratories of Istituto De Angeli, 20139 Milan, Italy.
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Some time ago[1] one of us described the synthesis of triphenylglycidonitrile and derivatives (**1a–d**). Since many basic alkyl esters of diarylhydroxyacetic acid and many basic alkyl diaryl ethers are endowed with interesting biological activity, it seemed of interest to us to prepare **2** and **3** and to test them for antispasmodic, anticonvulsant, antitussive, analgetic, and antiinflammatory activities.

$(C_6H_5)_2CN_2 + C_6H_5COCN \longrightarrow (C_6H_5)_2C\!\!<\!\!\overset{O}{}\!\!>\!\!CRC_6H_5$

1a, R = CN
b, R = $CONH_2$
c, R = COOH
d, R = $COOCH_3$
e, R = CH_2OH

2, R = $CH_2OCH_2CH_2N(CH_3)_2$
3, R = $COOCH_2CH_2N(CH_3)_2$

The title compounds revealed a good antiinflammatory activity not accompanied, however, by an equally good analgetic action. None of the other actions investigated showed anything of interest.

Experimental Section†

Triphenylglycidonitrile (1a), triphenylglycidamide (1b), triphenylglycidic acid (1c), and **methyl triphenylglycidate (1d)** were prepared as previously described.[1]

2,3,3-Triphenylglycidol (1e). MeOH (10.6 g, 0.33 mole) was added dropwise at −5° into a stirred suspension of LAH (4.4 g, 0.11 mole) in anhyd THF (250 ml). After 15-min stirring, methyl triphenylglycidate (**1d**) (9.1 g, 0.027 mole) was added portionwise. The mixt was stirred at room temp for 3 hr and then moist Et_2O and H_2O were added cautiously. The sepd solid was washed (Et_2O) and the aqueous layer was extd with Et_2O. The combined organic solns were washed (H_2O), dried, and evapd to dryness. The residue was recrystd from ligroin (bp 90–100°) to give **1e** (7.3 g, 87.6% yield) as colorless crystals, mp 104°. *Anal.* ($C_{21}H_{18}O_2$) C, H.

2-Dimethylaminoethyl 2,3,3-Triphenylglycidyl Ether·HCl (2). Finely powdered $NaNH_2$ (1.35 g, 0.34 mole) was added to a soln of **1e** (9.5 g, 0.031 mole) in PhH (95 ml) and the mixt was refluxed for 1 hr with stirring. After cooling to room temp, an 8.77% soln of dimethylaminoethyl bromide (0.04 mole) in PhH was added dropwise. After an addl 1-hr stirring, the mixt was dild with excess Et_2O and then extd with 10% HCl soln. The oil which sepd from the acid soln was extd with $CHCl_3$. The $CHCl_3$ soln was evapd to dryness and the residue was taken up with Et_2O and filtered to give **2** (5.3 g, 41% yield) as a colorless solid, mp 159° dec. *Anal.* ($C_{25}H_{28}ClNO_2$) C, H, Cl, N.

2-Dimethylaminoethyl Triphenylglycidate·HCl (3). Compound **1c** (10 g, 0.031 mole) and dimethylaminoethyl chloride (5.6 g, 0.052 mole) were dissolved in Me_2CHOH (95 ml) and the soln was refluxed for 3 hr. After cooling to room temp, excess H_2O was added to the mixt. The resulting aqueous soln was basified with 10% NaOH soln and the basic material was extd with Et_2O. The Et_2O ext was washed (H_2O) and evapd to dryness to give a waxy product which was converted to a cryst solid by addition of 10% HCl soln. The solid was filtered and recrystd from EtOH–Et_2O to give 3 (6.3 g, 47% yield) as a colorless solid, mp 203° dec. *Anal.* ($C_{25}H_{26}ClNO_3$) C, H, Cl, N.

†Melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical value.

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Alkyl Derivatives of Tetrahydroisoquinoline, 1-Phenylpiperazine, and 4-Diphenylmethylpiperidine

W. J. Irwin,* D. L. Wheeler, and N. J. Harper

Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B47ET, England.
Received November 5, 1971

Many useful medicinal compounds[1,2] are based upon the isoquinoline, piperazine,[3,4] and piperidine[5-7] ring systems. As part of a general screening program we have prepared[8] some cyclopropylmethyl and cyclobutylmethyl derivatives of these systems[9] by reduction of the corresponding amides. These compounds show an increasing separation of the aromatic portion of the molecule from the *N*-cycloalkyl group.

Some preliminary screening results on mice, which also include 4-diphenylmethylpiperidine (**3g**, R = H), are presented in Table II. The diphenylmethylpiperidines and phenylpiperazines were found to have a CNS depressant action

Table I

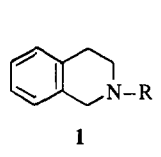
Compound	R	Acylation time, hr	Mp, °C	Yield, %	Solvent	Formula[a]
1a·HCl	 CH$_2$(A)	4	210–212	76	EtOH–Et$_2$O	$C_{13}H_{18}ClN$
1b·HCl	 CH$_2$ (B)	12	193–194	73	EtOH–Et$_2$O	$C_{14}H_{20}ClN$
1c·HCl	$(CH_3)_2CHCH_2$	3	200–201	70	EtOH–Et$_2$O	$C_{14}H_{20}ClN$
2a·HCl	 CO (C)	18	190–191	79	MeOH–Et$_2$O	$C_{14}H_{19}ClN_2O$
2b·2HCl	A		187–188 dec	64	MeOH–Et$_2$O	$C_{14}H_{22}Cl_2N_2$
2c	 CO (D)	4	102–103	48	Petr ether	$C_{15}H_{20}N_2O$
2d·HCl	B		218–219 dec	67	EtOH–Et$_2$O	$C_{15}H_{23}ClN_2$
2e[b]	C	18	86–87	55	Petr ether	$C_{14}H_{17}ClN_2O$
3a·HCl	A	3	234–235	79	EtOH–Et$_2$O	$C_{22}H_{28}ClN$
3b	D	4	121–122	62	Me$_2$CO–petr ether	$C_{23}H_{27}NO$
3c·HCl	B		248–249	62	EtOH–Et$_2$O	$C_{23}H_{30}ClN$
3d	$(CH_3)_3CCO$	18	140–141	68	Me$_2$CO–petr ether	$C_{23}H_{29}NO$
3e·HCl	$(CH_3)_3CCH_2$		271–273	71	MeOH–Et$_2$O	$C_{23}H_{32}ClN$
3f[c]	$(CH_2)_3COC_6H_4F$-*p*	66	130–131	69	EtOH	$C_{28}H_{30}FNO$

[a] All compds were analyzed for C, H, and N and were within ±0.4% of the theoretical values except for **2d** (C: calcd, 67.6; found, 68.1%). [b] Deriv of 1-(*o*-chlorophenyl)piperazine. [c] Prepd from 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxalane.[10]

Table II

			Phenylquinone-induced[b] writhing			Neuropharmacological tests[b]					
Compd	Dose, mg/kg	LD_{50},[a] mg/kg	% inhibition	ED_{50}, mg/kg	Pento-barbitone potentiation,[b] %	Mydriasis, %	Rotating rod, %	Grip strength, %	Hot plate, %	Tonic extension (leptazol), %	Death (leptazol), %
1a	30	100–300	26		0	0	0	0	20	0	0
1b	100	100–300		49.5	20	−24	20	20	20	0	0
1c	30	100–300	21		10[c]	0	40	20	20	0	0
2a	30	100–300		11	0	−10	20	0	40	0	0
2b	30	100–300		8.5	20	0	0	40	100	0	0
2c	100	>300	68		0	−11.5	0	0	0	0	0
3a	10	30–100		5.4	20[d]	25	0	0	0	80	30
3b	100	>300	12		0	10	0	60	60	20	20
3c	10	30–100		17.5	10[d]	46	0	0	0	40	40
3d	100	>300	46		0	0	0	0	0	20	0
3e	100	>300	36		0	−5	0	0	20	0	0
3g	30	30–100	36		30	53	40	0	0	0	0

[a] Ip. [b] Sc. [c] Dose level, 100 mg/kg. [d] Dose level, 30 mg/kg.



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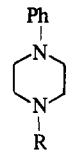

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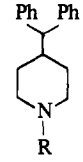

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at low dosage levels and stimulant activity with increased doses. The derivatives **(2b, 3a, 3c, 3g)** appeared to have a membrane-stabilizing effect and, in addition, 1-cyclopropylmethyl-4-phenylpiperazine **(2b)** was found to possess a neuroleptic activity similar to that of chlorpromazine.

Experimental Section

General Acylation Procedure. The acid chloride (0.05 mole) in dry C_6H_6 (15 ml) was added slowly to a mixt of the amine (0.045 mole) and $NaHCO_3$ (7 g) in dry C_6H_6 (15 ml) and the mixt was then heated under reflux for the stated time. The filtrate from the cooled mixt was dild with twice its own vol of Et_2O and washed with 1 *N* HCl and then H_2O. Evapn of the dried ($MgSO_4$) Et_2O soln yielded the amide which was usually suitable for further reaction without purification.

General Reduction Procedure. The amide (0.02 mole) in dry Et_2O (50 ml) was added slowly to a stirred suspension of LAH (1.5 g) in dry Et_2O (50 ml) and the mixt was heated under reflux for 18 hr. To the cooled mixt was added slowly successive quantities of H_2O (4 ml), NaOH (3 ml, 30%), and H_2O (10 ml) to produce a granular ppt. The ethereal mixt was filtered, dried ($MgSO_4$), and evapd to yield the tertiary amine which was usually converted into the HCl salt with dry HCl gas.

2-(3,3-Dimethylallyl)-1,2,3,4-tetrahydroisoquinoline (1c). 1-Chloro-3-methylbut-2-ene (6.25 g) in DMF (20 ml) was added slowly to a stirred mixt of 1,2,3,4-tetrahydroisoquinoline (6.65 g) and $NaHCO_3$ (6 g) in DMF (20 ml) and the mixt was heated under reflux for 3 hr. Filtration and evapn yielded an oil which was washed (H_2O) to remove the last traces of DMF and converted into a hydrochloride **(1c)**.

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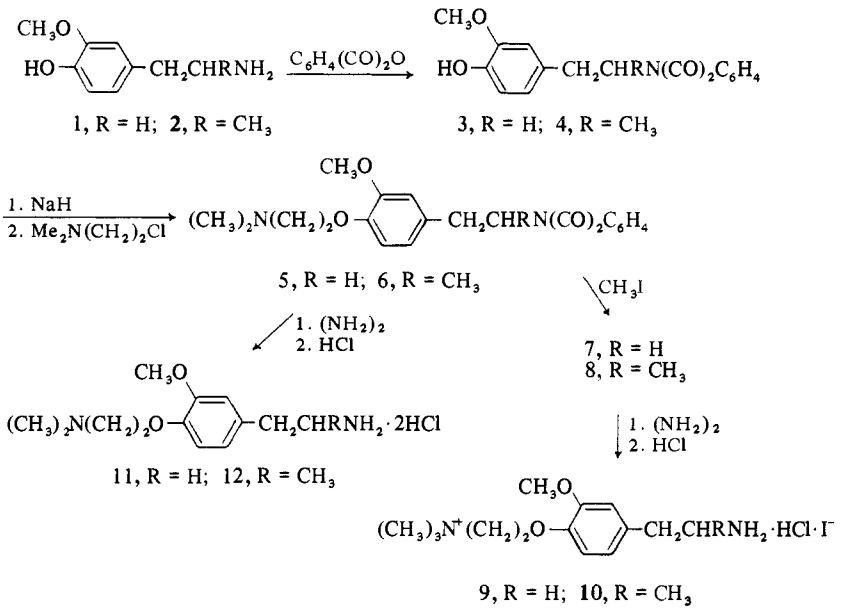
1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-aminoalkanes†

Martha Ann Colombini‡ and Alfred Burger*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901. *Received November 9, 1971*

Compounds which contain both β-aminoalkyl ("adrenergic") and choline ether groups attached to the same aromatic ring have not been reported previously. We are describing here the synthesis of 4-dimethylaminoethoxy-3-methoxyphenethylamine and 1-(4-dimethylaminoethoxy-3-methoxyphenyl)-2-aminopropane and their trimethylammonium ions, derived from the tertiary amine functions. Since the effects of divergent pharmacophores in the same molecule are usually not complementary, it was not too surprising to find that none of these compounds exhibited any noteworthy activities in mouse dose-range tests.



Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses, performed by Galbraith Laboratories, Knoxville, Tenn., gave values within 0.25% of those calcd. Ir spectra (Perkin-Elmer spectrophotometer Model 337) were detd in KBr pellets for solids, and NaCl disks for liquids (neat); nmr spectra were measured on a Hitachi-Perkin-Elmer spectrometer, Model R-20 [Me_4Si or 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O)]. Mass spectra of amines were detd on a Model RMU-6E mass spectrometer; all spectra were as expected. Removal of solvents was carried out using a Rinco rotary evaporator.

4-Hydroxy-3-methoxyphenethylamine·HCl (1). Modifying the procedure of Ramirez and Burger,[1] a mixt of 27.5 g (0.14 mole) of 1-(4-hydroxy-3-methoxyphenyl)-2-nitroethene and 400 ml of dry THF was added dropwise to a stirred refluxing mixt of 26.5 g (0.7 mole) of LAH in 1 l. of abs Et_2O over 3.5 hr. After an addl 60 hr of good stirring and refluxing the mixt was cooled to 5°, excess LAH was decompd with pieces of ice followed by 1.5 l. of 1.5 *N* H_2SO_4 at 0°. The aqueous layer was sepd, Li_2CO_3 was added to pH 6, and the mixt was filtered while hot. To this hot soln 35 g (0.15 mole) of picric acid was added, and after *ca.* 16 hr 45 g (*ca.* 80%) of orange cryst picrate, mp 195–198°, was filtered off. The crystals were placed in 1.2 l. of boiling H_2O and 210 ml of 37% HCl was added. Upon cooling, picric acid was collected, the filtrate was extd twice with $PhNO_2$ (150 ml) and 3 times with Et_2O. The aqueous layer was evapd. The residual beige crystals weighed 20.9 g (73.6%), mp 212–213° dec.

1-(4-Hydroxy-3-methoxyphenyl)-2-aminopropane·HCl (2) was obtd similarly from 1-(4-hydroxy-3-methoxyphenyl)-2-nitro-1-propene in 58.6% yield as almost colorless crystals, mp 258–259° dec (lit.[2] mp 251° dec).

1-(4-Hydroxy-3-methoxyphenyl)-2-phthalimidoethane (3). Toluene (125 ml) was added to a mixt of 10.2 g (0.05 mole) of 1, 7.5 g (0.05 mole) of phthalic anhydride, and 9 ml of Et_3N. The mixt was refluxed under a Dean–Stark trap for 2 hr and then stirred overnight. A yellow solid settled out. It was filtered and washed with 3 × 17 ml of H_2O; yield 16.7 g, mp 145–148°. Recrystn from 300 ml of EtOH produced iridescent greenish yellow crystals, mp 148.5–150°. Addl material from the H_2O–PhMe filtrate gave a total of 12.05 g (81.1%). *Anal.* ($C_{17}H_{15}NO_4$) C, H, N; *m/e* 297 (M^+).

1-(4-Hydroxy-3-methoxyphenyl)-2-phthalimidopropane (4) was prepd similarly from 2. It took 8 hr to form the calcd amt of H_2O. The crude material was dark brown, yield of pure 4, 77.1%, mp 153–154°. *Anal.* ($C_{18}H_{17}NO_4$) C, H, N.

1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-phthalimidoethane·HCl (5). NAH [50% in mineral oil, 1.5 g (33 mmoles)] was added to a soln of 8.91 g (30 mmoles) of 3 in 35 ml of dry PhMe. The mixt was refluxed under N_2 for 8 hr and cooled, and 33 mmoles of dimethylaminoethyl chloride was added. After refluxing overnight, another 16 mmoles of $Me_2N(CH_2)_2Cl$ was added, and refluxing contd for 5 hr. The milky brownish mixt was treated with ice, acidified (HCl), and extd with 3 × 35 ml of Et_2O. A white ppt forming in the aqueous layer was salted out with NaCl, filtered off, and recrystd from abs EtOH and a little acetone, yield 11.1 g (91.4%), mp 175–175.5°. *Anal.* ($C_{21}H_{25}ClN_2O_4 \cdot H_2O$) C, H, N.

1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-phthalimidopropane (6) was prepd analogously from 4. The hygroscopic HCl salt could not be crystd but the base, liberated at pH 12 at 0°, was triturated with dry Et_2O and crystd after several days. Recrystn from abs EtOH afforded colorless crystals (8.2 g, 65.2%), mp 64–65°. *Anal.* ($C_{22}H_{26}N_2O_4$) C, H, N; *m/e* 382 (M^+).

1-(3-Methoxy-4-trimethylammoniumethoxyphenyl)-2-phthal-

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