Synthesis and Analgetic Activity of 1,2-Disubstituted 2-Phenethylamines

Arturo Donetti,* Ernesta Marazzi-Uberti, Silvano Casadio, and Camillo Bianchi

Research Laboratories of Istituto De Angeli, 20139 Milan, Italy. *Received December 6, 1971*

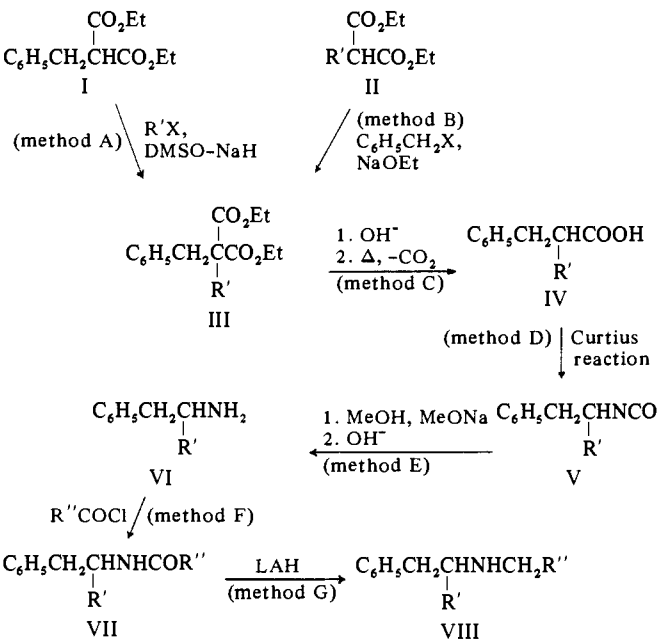
A series of 1,2-disubstituted 2-phenethylamines was prepared and assayed for analgetic activity in comparison with 1-benzyl-3-butenylamine. Some of these compounds showed analgetic activity, but at doses causing central stimulant effects.

It is known[1] that various aralkylamines possess analgetic activity, but none of them has yet found clinical utility mainly because of undesirable effects on the CNS. Recently, it has been reported[2] that 1-benzyl-3-butenylamine (aletamine) shows an analgetic effect at doses below those causing CNS stimulation; in addition it does not exhibit any of the pharmacological properties of narcotic analgetics.

This finding prompted us to extend the investigation to 2-phenethylamines bearing in the 1 position small-ring cycloalkylmethyl groups and isoprenoid radicals. Furthermore, two N-substituted derivatives of aletamine itself were prepared. All of the amines synthesized were investigated for analgetic activity with relationship to central stimulatory effects.

Chemistry. The methods employed (methods A-G) are illustrated by the synthetic pathway reported in Scheme I.

Scheme I



All of the compounds synthesized by methods A-C and E-G are listed in Tables I-III.

The diethyl disubstituted malonates III were obtained either by alkylation of diethyl aralkylmalonates I or by introduction of the aralkyl group into the diethyl alkylmalonates II. The diesters obtained were hydrolyzed and decarboxylated to form the phenylpropanoic acids IV.

These were converted to isocyanates V by reaction of their mixed anhydrides with NaN_3 and subsequent rearrangement of the resulting carboxazides.

The reaction of isocyanates V with MeONa-MeOH afforded the corresponding methyl carbamates which were converted to the primary amines VI by refluxing with KOH in aqueous EtOH.

While we applied the Hofmann rearrangement successfully to the prepn of 1-benzyl-3-butenylamine[3] (used as an intermediate in method F), the same procedure was far from satisfactory when applied to the synthesis of amines VI bearing geranyl, prenyl, cyclopropyl, and cyclobutyl groups. Because of the relative instability of these groups, the acid hydrolysis of the intermediate isocyanates V also failed to give good results. However, alkaline hydrolysis of the methyl carbamates proved to be the most successful procedure.

The acyl derivatives VII were prepared by acylation of the amines VI with the required acid chloride. The secondary amines VIII were prepared by reduction of the amides VII with LAH.

Pharmacology. Compds **11-15, 19-21** were screened for analgetic activity using aletamine as reference standard. The results in the hot plate test are included in Table IV in terms of relative potency in relation to the analgetic activity of aletamine which has been assigned the potency of 1.0. Compds **13** and **19**, when injected sc, and **11** and **19**, when administered orally, were more active than aletamine. The other compounds were found to be as active as or less active than the reference compound. No significant effect was observed when the compounds were tested by the tail pinch method in mice and by the pressure pain method in rats.

However, all of the compounds, unlike aletamine, showed CNS stimulation as indicated by hyperreflexia, irritability, and increase in spontaneous motor activity. In particular, **19** and **21**, which were further examined in chloral hydrate antagonism (Table V), approximated the stimulating effect of *d*-amphetamine.

Experimental Section

Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus. Ir spectra were run on a Perkin-Elmer 337 spectrophotometer, nmr spectra on a Varian A 60-A spectrometer (Me_4Si) (0.00 ppm). Ir and nmr spectra agreed in each case with the structural assignments. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.40% of the theoretical values.

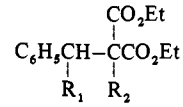
Biological Methods. All compds were administered sc or po dissolved in HCl soln. The vol administered was 0.2 ml/10 g of body wt for mice and 0.5 ml/100 g for rats. Ten animals were used for each dose level.

Analgetic activity was detd by 3 types of tests: (1) mouse hot plate test[4] (25 mg/kg sc, 50 mg/kg po), (2) tail pinch test in mice[5] (75 mg/kg po), (3) pressure pain test in rats (125 mg/kg po); this method was similar to that described by Randall and Selitto[6] with the difference that inflammation was not induced in the rat paw.

Chloral Hydrate Antagonism. Mice were injected ip with chloral hydrate (275 mg/kg) 15 min after oral administration of compds. The interval between loss and return of the righting reflex was recorded for each animal (sleeping time). The dose which caused 50% decrease in sleeping time was determined graphically from a dose–response curve.

Materials. Diethyl benzylmalonate,[7] diethyl 1-phenethylmalonate,[8] and diethyl geranylmalonate[9] were prepd by standard procedures as previously described. 1-Benzyl-3-butenylamine was prepd according to McCarty, *et al.*[3]

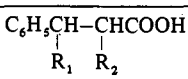
Table I. Diethyl 2,2-Disubstituted Malonates



No.	R_1	R_2	Method	% yield	Bp (mm), °C	Formula[a]
1	H		B	73	142–144 (0.5)	$C_{18}H_{24}O_4$
2	H		B	84	132–135 (0.2)	$C_{19}H_{26}O_4$
3	H	$CH_2=C(CH_3)CH_2$	A	87	128–130 (0.5)	$C_{18}H_{24}O_4$
4	CH_3	$(CH_3)_2C=CHCH_2$	A	79	135–137 (0.2)	$C_{20}H_{28}O_4$
5	H	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2$	B	62	167–170 (0.15)	$C_{24}H_{34}O_4$

[a] All analyses were for C, H.

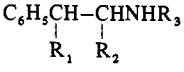
Table II. 2,3-Disubstituted 3-Phenylpropanoic Acids

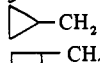
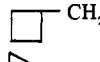


No.	R_1	R_2	Method	% yield	Bp (mm), °C	Formula[a]
6	H		C	60	120–122 (0.15)	$C_{13}H_{16}O_2$
7	H		C	75	140–142 (0.1)	$C_{14}H_{18}O_2$
8	H	$CH_2=C(CH_3)CH_2$	C	65	130–132 (0.5)	$C_{13}H_{16}O_2$
9	CH_3	$(CH_3)_2C=CHCH_2$	C	63	135–138 (0.2)	$C_{15}H_{20}O_2$
10	H	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2$	C	68	158–162 (0.02)	$C_{19}H_{26}O_2$

[a] All analyses were for C, H.

Table III. 1,2-Disubstituted 2-Phenethylamines



No.	R_1	R_2	R_3	Method	% yield	Bp (mm) or mp, °C	Formula[a]
11	H		H	E	79	68–70 (0.2)	$C_{12}H_{17}N$
12	H		H	E	64	85–87 (0.2)	$C_{13}H_{19}N$
13	H	$CH_2=C(CH_3)CH_2$	H	E	45	62 (0.2)	$C_{12}H_{17}N$
14	CH_3	$(CH_3)_2C=CHCH_2$	H	E	75	85 (0.2)	$C_{14}H_{21}N$
15	H	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2$	H	E	85	130 (0.2)	$C_{18}H_{27}N$
16	H	$CH_2=CHCH_2$		F	85	78–80[b]	$C_{15}H_{19}NO$
17	H	$CH_2=CHCH_2$		F	97	61–63[b]	$C_{16}H_{21}NO$
18	H	$CH_2=C(CH_3)CH_2$		F	75	83[b]	$C_{16}H_{21}NO$
19	H	$CH_2=CHCH_2$		G	64	85–87 (0.15)	$C_{15}H_{21}N$
20	H	$CH_2=CHCH_2$		G	70	102–104 (0.4)	$C_{16}H_{23}N$
21	H	$CH_2=C(CH_3)CH_2$		G	67	88 (0.1)	$C_{16}H_{23}N$

[a] All analyses were for C, H, N. [b] Crystd from petroleum ether (bp 40–70°).

Diethyl Cyclopropylmethylmalonate. Diethyl malonate (59 g, 0.37 mole) was added dropwise at 20–25° to a stirred suspension of 13.26 g (0.44 mole) of a 80% dispersion of NaH in mineral oil in 380 ml of DMF and 115 ml of PhH. The mixt was stirred at this temp until H_2 evolution was completed, then cyclopropylmethyl bromide[10] (54 g, 0.40 mole) was added slowly. The mixt was heated for 18 hr on the steam bath, cooled, poured into excess ice–H_2O and extd (Et_2O). The Et_2O layer was washed (H_2O) and dried ($MgSO_4$), and the soln was evapd to dryness. The residue was distd to give 54.6 g (69% yield) of a colorless oil, bp 130–132° (15 mm). *Anal.* ($C_{11}H_{18}O_4$) C, H.

Structure was confirmed by nmr. Typically, nmr (CCl_4) showed peaks at δ 0–0.25 (m, 2, cyclopropyl CH_2), 0.25–0.7 (m, 2, cyclopropyl CH_2), 0.6–1 (m, 1, cyclopropyl CH superimposed in part with the cyclopropyl CH_2), 1.22 (t, 6, CH_2CH_3), 1.72 [t, 2, $CH_2CH(CO_2Et)_2$], 3.28 [t, 1, $CH(CO_2Et)_2$], 4.1 (q, 4, CH_2CH_3).

Diethyl cyclobutylmethylmalonate was prepd similarly from cyclobutylmethyl bromide[10] and diethyl malonate (54% yield), bp 148–150° (15 mm). *Anal.* ($C_{12}H_{20}O_4$) C, H. Nmr (CCl_4) showed peaks at δ 1.22 (t, 6, CH_2CH_3), 1.5–2.5 (m, 9, cyclobutylmethyl H's), 3.1 [t, 1, $CH(CO_2Et)_2$], 4.12 (q, 4, CH_2CH_3).

General Methods. Method A. Diethyl 2,2-Disubstituted Malonates. A soln of 0.1 mole of diethyl benzylmalonate in 25 ml of DMSO was added dropwise at 20–25° to a stirred suspension of sodium methylsulfinylmethide[11] prepd *in situ* from 3.3 g (0.11 mole) of a 80% dispersion of NaH in mineral oil and 90 ml of DMSO. The mixt was stirred at room temp for 30 min and then 0.12 mole of the appropriate bromopropene in 50 ml of DMSO was added slowly. After 24-hr stirring at room temp the mixt was poured into ice–H_2O and extd (Et_2O). The Et_2O ext was washed

Table IV

Compd	Analgetic potency, mouse (hot plate test) sc	po
11	0.7	1.6
12	0.6	0.6
13	1.4	1.1
14	1.0	0.3
15	1.0	0.5
19	1.6	1.3
20	0.6	0.9
21	1.0	0.4
Aletamine	1.0	1.0

Table V

Compd	Chloral hydrate antagonism, mouse ED_{50}, mg/kg po
19	2.4
21	1.1
d-Amphetamine sulfate	1.8

(H_2O), dried ($MgSO_4$), and concd, and the residue was distd (Table I).

Method B. Diethyl 2,2-Disubstituted Malonates. A soln of 0.1 mole of the appropriate 2-substituted malonate in 30 ml of anhyd EtOH was added to a soln of 0.11 g-atom of Na in 80 ml of anhyd EtOH. The soln was refluxed for 30 min and then 0.12 mole of $PhCH_2Cl$ in 20 ml of anhyd EtOH was dropped in over 3 hr. The mixt was refluxed for 6 hr and then the EtOH soln was evapd to dryness. The residue was dissolved in Et_2O, washed (H_2O), and dried ($MgSO_4$). The solvent was evapd and the residue was distd (Table I).

Method C. 2,3-Disubstituted 3-Phenylpropanoic Acids. A mixt of 0.5 mole of the appropriate malonic ester, 2.5 moles of KOH, 500 ml of H_2O, and 500 ml of EtOH was refluxed 9 hr. EtOH was removed and the residue was dissolved in H_2O, cooled, and acidified with 10% HCl soln. The product was extd with Et_2O. The Et_2O ext was washed (H_2O), dried ($MgSO_4$), and evapd to dryness. The residue obtained was heated at 160–180° in the presence of catalytic amts of quinoline and Cu dust until CO_2 evoln was completed (4 hr). The product was purified by distn (Table II).

Method D. 1,2-Disubstituted 2-Phenethyl Isocyanates. To a soln of 0.1 mole of the appropriate acid in 100 ml of Me_2CO and 22 ml of H_2O at 0° was added slowly 0.15 mole of Et_3N in 250 ml of Me_2CO and then 0.15 mole of ethyl chloroformate in 60 ml of Me_2CO. After 30-min stirring at 0°, a soln of 0.2 mole of NaN_3 in 45 ml of H_2O was added dropwise. The mixt was stirred for 30 min, poured into excess H_2O, and extd (Et_2O). The Et_2O ext was washed (H_2O), dried ($MgSO_4$), and concd below 30°. The residual carboxazide was dissolved in 150 ml of toluene and heated cautiously until N_2 evoln was complete. Concn of the soln gave the crude isocyanate. These isocyanates were utilized without purification: 1-(2-methallyl)-2-phenethyl isocyanate and 1-geranyl-2-phenethyl isocyanate.

Boiling points (mm) and yields for distd isocyanates were: 1-cyclopropylmethyl-2-phenethyl isocyanate, 92–94° (0.4), 73%; 1-cyclobutylmethyl-2-phenethyl isocyanate, 95–98° (0.2), 83%; 1-(3,3-dimethylallyl)-2-methyl-2-phenethyl isocyanate, 94–96° (0.15), 60%.

Structure of these isocyanates was verified by the ir spectra, which showed the typical NCO absorption at 2260 cm^{-1}.

Method E. 1,2-Disubstituted 2-Phenethylamines. To a soln of 0.0035 mole of MeONa in 180 ml of anhyd MeOH, was added 0.1 mole of the appropriate isocyanate in 180 ml of anhyd MeOH and the soln was refluxed for 3 hr. After evapn of the solvent, the residue was dissolved in Et_2O, washed (H_2O), and dried ($MgSO_4$). The solvent was evapd to dryness to give the crude methyl carbamate which was converted directly to amine without purification.

To a soln of 0.1 mole of carbamate in 220 ml of EtOH was added 220 ml of 9 *N* KOH and the mixt was refluxed for 15 hr. The EtOH was removed and the residue was extd with Et_2O and H_2O. The Et_2O layer was washed (H_2O) and then extd with 10% HCl soln. The acid soln was made alkaline with 10% NaOH soln and the ppt worked up in the usual manner. These amines were purified by distn (Table III).

Method F. *N*-Acyl Derivatives of 1,2-Disubstituted 2-Phenethylamines. A mixt of 0.1 mole of the appropriate primary amine, 0.15 mole of Et_3N, and 80 ml of $CHCl_3$ was cooled to 5–10° and stirred, while 0.11 mole of the acid chloride was added dropwise. The reaction mixt was stirred at room temp for 13 hr and then dild with excess Et_2O. The organic soln was washed with 10% HCl soln, H_2O, $NaHCO_3$ soln, and then with H_2O. The organic layer was dried ($MgSO_4$) and concd, and the residue purified by crystn (Table III).

Method G. Reduction of *N*-Acyl Derivatives of 1,2-Disubstituted 2-Phenethylamines. To a stirred suspension of 0.3 mole of LAH in 300 ml of THF was added, dropwise, a soln of 0.1 mole of the appropriate amide in 180 ml of THF. The mixt was refluxed for 15 hr and cooled, and, in turn, moist Et_2O and H_2O were added. The sepd solid was washed (Et_2O), and the filtrate was dild with Et_2O and extd with 10% HCl soln. The acid soln was made alkaline with 50% NaOH soln and the basic material extd with Et_2O. The Et_2O ext was dried ($MgSO_4$) and concd, and the residue was distd (Table III).

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