TABLE I
EFFECT OF VARYING AMOUNTS OF THREE NATURAL AMINO ACIDS ON REVERSAL OF TOXICITY OF 1-AMINO-3-METHYLCYCLOPENTANECARBOXYLIC ACID (III)[a]

III, mg/5 ml	Control a b c	Nephelometer readings—Concn of amino acid, μg: 10^{-6} a b c	10^{-5} a b c	10^{-4} a b c	10^{-3} a b c	10^{-2} a b c	10^{-1} a b c	1 a b c	10 a b c	10^{2} a b c	10^{3} a b c
0.000	74 60 68	78 62 87	83 61 88	79 60 88	78 63 96	79 64 99	80 62 93	73 58 93	78 55 88	76 59 99	72 60 88
0.001											
0.002	81										
0.005	29 58 70	78 60 82	80 63 81		87						
0.01	20 26 39	73 41 40	76 47 79	60 79	78 60 79	73 60 83					
0.02	[0] [0] [0]	[0] 2 [0]	64 [1] 48	75 46 49	70 25 72	52 40 76	72 60	73 57	49		
0.05		0	[3] 0 [0]	[6] 7 [0]	[6] [6] 13	[4] [0] 51	16 [0] 84	19 [0]	75 41		
0.1			0	0 0	0 0 [0]	0 [0]	[0] 79	[9]	64 [1]		
0.2							51	0 90	33 [0]	71 50	
0.5							[0]	77	[3] 83	37 39	53
1								62	0 70	[0] [0] 81	72 40
2								24	43	63	49 [7] 72
5								[0]	12	24	12 [2] [58]
10									[0]	[0]	0 [4]

[a] a = L-valine, b = L-isoleucine, c = L-leucine.

TABLE II
CYCLOPENTYLAMINO ACIDS AND HYDANTOINS

Compd	Mp, °C	Yield, %	Formula[a]	R_f (pyridine-H_2O, 70:30)
ACPC	>300[b]	97	$C_6H_{11}NO_2$	0.77
Hydantoin of ACPC	204–206[c]	83	$C_7H_{10}N_2O_2$	
I	320–322	80	$C_8H_{15}NO_2$	0.83
Hydantoin of I	188–190	74	$C_9H_{14}N_2O_2$	
III	299–300[d]	97	$C_7H_{13}NO_2$	0.82
Hydantoin of III	224–225[e]	99	$C_8H_{12}N_2O_2$	

[a] All compounds were analyzed for N and were within ±0.4% of the theoretical values. [b] T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, 2119 (1960), reported mp 328–329°. [c] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 523 (1942), reported mp 204–205°. [d] N. Zelinsky and G. Stadnikoff, *Ber.*, **39**, 1722 (1906), reported mp 299–300°. [e] M. Tiffeneau, B. Tchoubar, Saislambert, and LeTellier-Dupré, *Bull. Soc. Chim. France*, 445 (1947), reported mp 226°.

TABLE III

mg/5 ml		mg/5 ml	
0.001		0.5	
0.002		1	
0.005	← III	2	
0.01		5	← ACPC
0.02		10	
0.05		20	
0.1		50	
0.2		100	← II

threonine, L-tryptophan, L-tyrosine, and L-valine. At 1 mg/5 ml, almost all of these substances caused a toxicity reversal. An investigation was thus carried out at 100 μg/5 ml to determine which substances at lower concentrations would reverse the toxicity. It was found that isoleucine, leucine, and valine were much more powerful reversal agents than the others and were examined further. Table I shows the results where tenfold concentration differences in these particular compounds were employed.

Work with Mice.—The comparative toxicity of the substances in Robidoux albino male mice (20 g) was examined in the following manner. Each of the four compounds was injected at 500 mg/kg; 0.2 ml of a saline solution of the compound at pH 7 was injected intraperitoneally in an aseptic manner once daily for 6 consecutive days; a minimum of six mice were employed for each compound. The animals were then allowed to rest for 8 days, following which they were sacrificed and a brief autopsy was performed. Figure 1 shows the results of the weight changes observed.

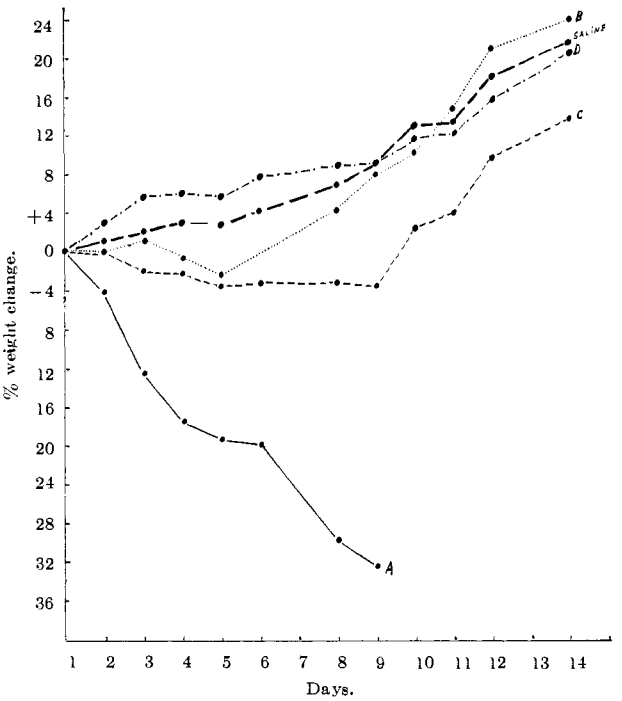

Figure 1.—Weight changes in mice following injections of compounds indicated: A = ACPC, B = compound II, C = compound III, and D = compound I.

Some Arylalkylamino Analogs of Acyclic Analgetics

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Replacement of N-methyl by N-phenethyl in analgetics where the nitrogen atom forms part of an alicyclic system (*e.g.*, morphine, and morphinan, benzomorphan, and 4-phenylpiperidine derivatives) invariably produces a compound of enhanced potency.[1] Data pertaining to the same structural modification in acyclic analgetics are sparse, however, the basic

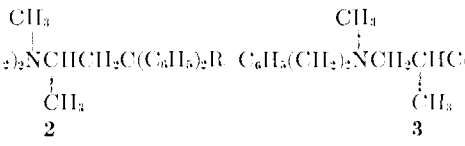
(1) A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **2**, 43 (1962).

$RCH(CH_3)CH_2N(COC_2H_5)C_6H_5$

1a, R = $N(CH_3)CH_2CH_2C_6H_5$
b, R = $N(CH_3)_2$
c, R = $N(CH_2C_6H_5)_2$

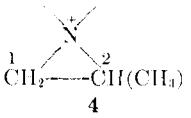
anilide **1a** (diampromid),[2] its thienyl analogs,[3] and 2-ethoxy-N-methyl-N-[2-(methylphenethylamino)ethyl]-2,2-diphenylacetamide[4] being the only examples of open-chain analgetics containing the N-phenethyl function. For this reason, and as part of a comparative study of structure–activity relationships in 3-amino-1,1-diphenylpropylamine and N-(2-aminopropyl)-propionanilide analgetics,[5] the synthesis of the N-phenethyl analogs of methadone and isomethadone was undertaken.

The standard procedure of alkylating diphenylacetonitrile with the appropriate 1-amino-2-chloropropane[6] gave a 1:1.5 mixture of the precursor nitriles (**2a** and **3a**) formed through the ethyleniminium ion intermediate **4**. Pmr characteristics of the two



2 **3**

a, R = CN
b, R = $C(NH)C_2H_5$
c, R = COC_2H_5



4

nitriles were compared with those of related isomeric pairs of known structure (Table I) and the major isomer was assigned the 2-methyl formula **3a** on the basis of its lower field *sec*-methyl and N-methyl signals (the relative chemical shifts of *sec*-methyl in 2- and 3-methyl derivatives reflects the greater proximity of 2-methyl to the deshielding cyano substituent).[7] The differing stabilities of the ketimines **2b** and **3b** formed by treating the nitriles with ethylmagnesium bromide (that from the major isomer required more drastic hydrolysis conditions) confirmed these structural assignments.[8]

TABLE I

PMR CHARACTERISTICS OF SOME 3-AMINO-1,1-DIPHENYLPROPYL CYANIDES IN $CDCl_3$[d]

$RCH(CH_3)CH(C(C_6H_5)_2CN)$ (3 = CH_3, 2 = CH)

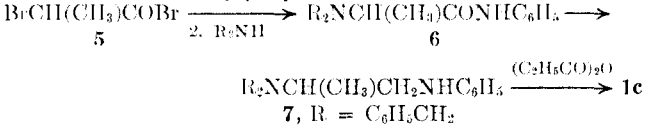
R	Methyl substituent	Chemical shift[a] *sec*-CH_3[b] Base	*sec*-CH_3[b] HCl	N-CH_3[c] Base	N-CH_3[c] HCl
$N(CH_3)_2$	2-	69	91	132	170
	3-	54	82	128	162
$N(CH_3)CH_2C_6H_5$	2-	70.5	90	129	176
	3-	60.5	87.5	124	167.5
	2-	67.5	Insol	...	...
	3-	54	81	...	...
	2-	69	Insol	...	...
	3-	57	81	...	...
$N(CH_3)CH_2CH_2C_6H_5$	2-	65	92	135	178
	3-	56	82	130	167

[a] In cps from TMS (60 Mc/sec). [b] Doublet, J = 6.5–7 cps. [c] Singlet (base); some signals due to salts are broadened or split into a doublet (J near 5 cps) through spin–spin coupling with the $^+$N–H proton. [d] See ref 7 and M. M. A. Hassan, Ph.D. Thesis, University of London, 1967.

The phenethylamino analogs of methadone (**2c**) and isomethadone (**3c**) were both devoid of activity when tested in mice by the hot-plate assay at dose levels of greater than 40 mg/kg (subcutaneous route),[9] results showing them to possess no significant analgetic properties. In comparison, hot-plate ED_{50} values for methadone and isomethadone in mice (measured in the same laboratory) are 5.2 and 7.9 mg/kg, respectively.[10] The relative analgetic activities of N-dimethyl and N-methylphenethyl derivatives of 6-amino-4,4-diphenylheptan-3-one are thus in sharp contrast with those of diampromid (**1a**) and its dimethylamino congener (**1b**) since, in the latter pair, the arylalkylamino member is by far the more potent compound.[5,6] These results substantiate the view, already advanced on the basis of differing stereospecificities and properties of N-benzylmethylamino analogs,[5,11] that 3-amino-1,1-diphenylpropyl and basic anilide analgetics differ in their modes of binding to the analgetic receptor.

A basic function containing an aryl group is a necessary feature for activity in diampromid and related analgetics, and it was thus of interest to examine the dibenzylamino analog **1c** in which two additional aromatic groups are potentially available for binding. This compound was prepared unambiguously from 2-bromopropionyl bromide by adapting the procedure of Wright, *et al.*[2] (**5** → **7** → **1c**) (Scheme I), and was also obtained by alkylating propionanilide with 2-chloro-1-dibenzylaminopropane. In the alkylation reaction, steric factors must govern opening of the ethyleniminium ion **4** since the anilide **1c**, obtained by nucleophilic attack at the less hindered C-1 position, was the exclusive product.

SCHEME I



5 **6** **7**, R = $C_6H_5CH_2$

The dibenzylaminoanilide **1c** proved to be inactive at dose levels greater than 40 mg/kg (hot-plate test in mice)[10] and possible reasons for the adverse effect of the additional phenyl group upon activity are its steric bulk (impeding binding to the receptor) and base-weakening influence (reducing the proportion of protonated species). The dibenzylamino anilide (pK_a' = 5.66) is significantly weaker a base than the an-

(2) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 476 (1961).
(3) N. Sugimoto, K. Okumura, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1061 (1962).
(4) J. J. Piala, J. P. High, and J. C. Burke, *Arch. Int. Pharmacodyn. Ther.*, **154**, 484 (1965).
(5) A. F. Casy and M. M. A. Hassan, *J. Pharm. Pharmacol.*, **19**, 17, 114 (1967).
(6) P. A. J. Janssen, "Synthetic Analgesics," Part 1, Diphenylpropylamines, Pergamon Press, Oxford, 1960, p 122.
(7) A. F. Casy, *J. Chem. Soc.*, *B*, 1157 (1966).
(8) L. C. Cheney, R. R. Smith, and S. B. Binkley, *J. Amer. Chem. Soc.*, **71**, 53 (1949).
(9) We thank Dr. Paul Janssen (Janssen Pharmaceutica) for this information.
(10) P. A. J. Janssen and A. H. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957).
(11) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).

algetically active benzylmethylamino congener **1** [R = $N(CH_3)CH_2C_6H_5$], pK_a' = 7.16 in 50% ethanol.

Experimental Section[12]

1-Methylphenethylamino-2-chloropropane.—Redistilled $SOCl_2$ (125 ml) in $CHCl_3$ (125 ml) was added to 1-methylphenethylamino-2-propanol[13] (99 g) in $CHCl_3$ (200 ml); the mixture was heated under reflux for 5 hr and then evaporated. The residue solidified after trituration with ether and was recrystallized from EtOH–Et_2O to give the chloroamine hydrochloride (102 g), mp 121–123°. *Anal.* ($C_{12}H_{19}Cl_2N$) C, H, N.

The derived base has bp 148° (20 mm). *Anal.* ($C_{12}H_{18}ClN$) C, H, N, equiv wt.

It formed a picrate, mp 111–113° from EtOH. *Anal.* ($C_{18}H_{21}ClN_4O_7$) C, H.

2- and 3-Methyl-3-methylphenethylamino-1,1-diphenylpropyl Cyanides (3a and 2a).—1-Methylphenethylamino-2-chloropropane (44.3 g) was added to a mixture of diphenylacetonitrile (42.5 g), C_6H_6 (120 ml), and $NaNH_2$ (10.3 g) which had previously been stirred at 30–40° for 30 min. The product was heated under reflux for 12 hr, then decomposed with H_2O and extracted with aqueous HCl. The base (70 g), recovered as usual, was a mixture of the cyanides **2a** and **3a** present in the ratio of 1.0:1.5, respectively (from integrals of the two N-methyl and *sec*-methyl pmr signals). Petroleum ether (bp 60–80°) was added to the mixture and the solid which separated was recrystallized from C_6H_6–petroleum ether to give the 3-methyl cyanide **2a** (28 g), mp 97–99°. *Anal.* ($C_{26}H_{28}N_2$) C, H, N, equiv wt.

The residues in the mother liquors gave a distillate, bp 198–200° (0.1 mm), which solidified on storage and was recrystallized from EtOH–Me_2CO to give the 2-methyl cyanide **3a** (30 g), mp 72–74°. *Anal.* ($C_{28}H_{28}N_2$) C, H, N, equiv wt.

4,4-Diphenyl-6-methylphenethylamino-3-heptanone.—The cyanide **2a** (9.25 g) in toluene (60 ml) was treated with EtMgBr, prepared from EtBr (8.4 g) and Mg (1.8 g), in the usual manner to give the amino ketimine **2b** (8.5 g), bp 202–205° (0.05 mm), ν_{max} 1710 (w) and 1632 cm^{-1} (m). It was heated with 10% HCl (50 ml) on a steam bath for 30 min and the recovered base was distilled to give the amino ketone **2c** (7.5 g), bp 188–190° (0.05 mm), ν_{max} 1710 cm^{-1} (s). *Anal.* ($C_{28}H_{33}NO$) C, H, N.

It gave a **hydrochloride dihydrate**, mp 108–110°, from Me_2CO–Et_2O, ν_{max} 3350 cm^{-1} (H_2O). *Anal.* ($C_{28}H_{34}ClNO\cdot 2H_2O$) C, H, N.

4,4-Diphenyl-5-methyl-6-methylphenethylamino-3-hexanone.—The cyanide **3a** (9.25 g), treated with EtMgBr as described above, gave the amino ketimine **3b** (9.5 g), ν_{max} 1720 (w) and 1631 $^{-1}$ (m), which was hydrolyzed by a 10-hr reflux period with concentrated HCl (60 ml). The recovered base was distilled to give the amino ketone **3c** (8.5 g), bp 192–194° (1 mm), ν_{max} 1710 cm^{-1} (s). *Anal.* ($C_{28}H_{33}NO$) C, H, N.

α-Dibenzylamino-N-phenylpropionamide (6).—A mixture of α-bromo-N-phenylpropionamide (22.8 g), dibenzylamine (19.7 g), K_2CO_3 (41 g), and Me_2CO was heated under reflux for 48 hr, then filtered, and the filtrate was evaporated. The residue was recrystallized from 70% EtOH to give the amino amide **6** (25.5 g), mp 80–82°. *Anal.* ($C_{23}H_{24}N_2O$) C, H, N, equiv wt.

N-[2-(Dibenzylamino)propyl]propionanilide (7).—The amino amide **6** (34.4 g) was reduced with LAH (7.6 g) by the procedure of Wright, *et al.*,[2] to give the diamine **7** (25 g), bp 190–192° (0.1 mm). *Anal.* ($C_{24}H_{26}N_2$) C, H, N, equiv wt.

It formed a **monohydrochloride monohydrate**, mp 90–92°, from EtOH–Et_2O, ν_{max} 3500 cm^{-1} (H_2O). *Anal.* ($C_{23}H_{27}ClN_2H_2O$) N, equiv wt.

The diamine **7** (3.5 g) with propionic anhydride (7 ml) gave the **basic anilide 1c** (3 g), bp 210–212° (0.1 mm). *Anal.* ($C_{26}H_{30}N_2O$) C, H, N, equiv wt.

It formed a **hydrochloride**, mp 170–171°, from EtOH–Et_2O. *Anal.* ($C_{26}H_{31}ClN_2O$) C, H, N, equiv wt.

Alkylation of propionanilide (3 g) with 2-chloro-1-dibenzylaminopropane[13] (5.8 g) by a reported methods also gave the basic anilide **1c** (3 g), hydrochloride mp and mmp 170–171°.

Pmr spectra were recorded on Varian A-60 and Perkin-Elmer R-10 instruments in $CDCl_3$ with TMS as standard. The pK_a' values of the basic anilides were measured in 50% EtOH–H_2O by Albert and Sergeants' method.[14]

(12) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(13) M. M. A. Hassan in footnote *d*, Table I.

(14) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.

Configurational Influences in Methadol and Normethadol Analgetics

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The greater analgetic potency of α-(−)-methadol compared with its *dextro* enantiomorph has long been an awkward anomaly in the study of configurational relationships among diphenylpropylamine analgetics, due to the fact that the more active α-methadol is derived from the weak analgetic *dextro* methadone rather than the potent *levo* form.[1,2] Evidence of the configuration of the secondary alcoholic center (C-3) of the methadols, lacking when attention was first drawn to this irregularity,[3] is now available[4,5] and it appears from these data (Table I) that the C-3 rather than the C-6 configuration is of prime importance respecting the activities of these alcohols. Thus the two most active methadols [α and β-(−)] both have the 3*S* configuration while the C-3 center of the most active isomethadol [β-(+)][6] belongs to the same steric series.[7] It was felt that support for this contention could be obtained by a study of methadol enantiomers lacking asymmetry at C-6 since it follows, from this view, that the *S* member of such a pair should be the more potent analgetic.

The required compounds **1b**, termed here normethadols in accord with the designation "normethadone" applied to the same analog of methadone[8] were obtained by reducing the norketone with LAH. Fractional crystallization of the (+)-tartrates gave the pure (+)-normethadol enantiomer while hydrochlorides of (±)- and (+)-normethadyl acetates were formed directly from the alcohols and acetyl chloride. Evidence for the configuration of (+)-normethadol was obtained by comparison of its ord spectrum with that of α-(+)-methadol (6*R*:3*R*). The latter compound has two asymmetric centers but it may reasonably be assumed that the center closer to the phenyl chromophore (*i.e.*, C-3) will largely determine the sign and fine structure of the Cotton effect. Hence ord characteristics should reflect C-3 stereochemistry in both compounds. It is to be noted that the two Cotton effects (Figure 1) not only have the same sign (positive) but also correspond closely in both peak positions and

(1) N. B. Eddy, E. L. May, and E. Mosettig, *J. Org. Chem.*, **17**, 321 (1952).

(2) As part of this study, α-(+)- and α-(±)-methadol were submitted to Dr. P. Janssen (Janssen Pharmaceutica) for hot-plate assay since it was felt desirable to confirm the original results. The new data (ED_{50} 30 mg/kg for α-(+)- and 22 mg/kg for α-(±)-methadol in mice, subcutaneous route) confirm that α-(−)-methadol is the more potent enantiomorph. Thanks are due to Dr. Janssen for these results.

(3) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

(4) P. S. Portoghese and D. A. Williams, *J. Pharm. Sci.*, **55**, 990 (1966).

(5) A. F. Casy and M. M. A. Hassan, *Tetrahedron*, **23**, 4075 (1967).

(6) E. L. May and N. B. Eddy, *J. Org. Chem.*, **17**, 1210 (1952).

(7) P. S. Portoghese and D. A. Williams, *Tetrahedron Letters*, 6299 (1966).

(8) Narcotic Drugs Under International Control, Multilingual List, United Nations, 1963.