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.* ($C_{26}H_{28}N_2$) 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.

TABLE I
HOT-PLATE ACTIVITIES IN MICE OF SOME METHADOLS AND NORMETHADOLS BY SUBCUTANEOUS ROUTE[a]
$(CH_3)_2NCH(R)CH_2C(C_6H_5)_2CH(OR')C_2H_5$
1a, R = CH_3
b, R = H

Precursor	Form	Configuration	ED_{50}, mg/kg: Methadols (R' = H)	ED_{50}, mg/kg: Acetylmethadols (R' = $COCH_3$)
(*R*)-(−)-Methadone (0.8)[b]	α-(+)-**1a**	6*R*:3*R*	24.7	0.3
	β-(−)-**1a**	6*R*:3*S*	7.6	0.4
(*S*)-(+)-Methadone (25.7)[b]	α-(−)-**1a**	6*S*:3*S*	3.5	1.8
	β-(+)-**1a**	6*S*:3*R*	63.7	4.1

Compd	Configuration	ED_{50}, mg/kg
(±)-Normethadol HCl	*RS*	9.88
(±)-Normethadol (±)-tartrate	*RS*	10.3
(+)-Normethadol (+)-tartrate	*R*	17.7
(±)-Acetylnormethadol HCl	*RS*	4.44
(+)-Acetylnormethadol HCl	*R*	2.7

[a] Methadol derivatives were tested in general purpose (GP) mice[1] and normethadols in the more sensitive Caesarian-delivered general purpose (CDGP) mice: A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965). [b] ED_{50} value.

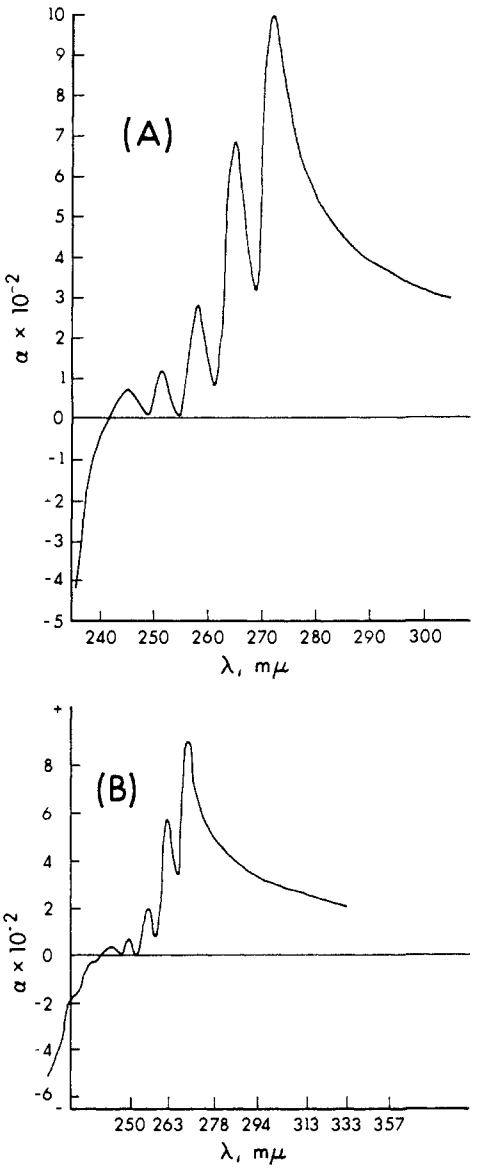

Figure 1.—Optical rotatory dispersion curves of (A) (+)-normethadol base in EtOH (*c* 10 mg/100 ml) and (B) α-(+)-methadol hydrochloride in H_2O (*c* 200 mg/100 ml).

molecular rotational values (Table II). On these grounds (+)-normethadol is assigned the *R* configuration.

TABLE II
PEAK POSITIONS AND MOLECULAR ROTATIONS [Φ] OF (+)-NORMETHADOL AND α-(+)-METHADOL[a]

Compd	λ_{max}, mμ	[Φ]
α-(+)-Methadol (HCl in H_2O)	270	32,350
	263	20,800
	256	9,050
	249	4,870
(+)-Normethadol (base in EtOH)	273	29,700
	266	20,790
	258	8,910
	252	3,560

[a] Methadol spectrum was measured with a Polarmatic 62, and normethadol spectrum with a Cary Model 60 photoelectric spectropolarimeter.

Hot-plate ED_{50} values for racemic and dextrorotatory normethadols and their acetate esters in mice are recorded in Table I. Thanks are due to Dr. E. L. May, National Institutes of Health, for arranging these tests. The greater ED_{50} value of *R*-(+)-normethadol compared with the racemic hydrochloride and tartrate demonstrates that this isomer is less potent than the corresponding *S*-(−) enantiomer. Hence the more active antipodes of α-methadol, β-methadol, and normethadol show configurational identity with respect to their alcoholic asymmetric centers, results which support the view that the C-3 geometry governs activity in these analgetics.

The relative activities of (+)- and (−)-α-methadol are reversed when the alcohols are acetylated (Table I), α-(+)-acetylmethadol derived from (−)-methadone being the more potent ester. This remarkable inversion of stereoselectivity may be interpreted in terms of the C-6 center reasserting its dominating role. Alternatively, however, it may be considered as due to esters requiring an *R* configurated C-3 center for optimal activity. From the present results the latter seems the more probable because the same stereochemical reversal is seen in the case of the normethadols and acetate esters, the less active *R*-normethadol yielding the more active antipodal form of the acetate (Table I). Of further significance, the more active antipodes of β-isomethadol and α-acetylisomethadol have *S* and *R* C-3 configurations, respectively.[6,7]

Methadone and diampromid (which also display stereoselective inversion) have been shown to differ

radically in their preferred conformations and it has been suggested that this fact may have a bearing upon their more active enantiomers (of formally alike asymmetry) differing in configuration.[9] Conformational differences between methadols and their acetates are also likely to be of importance in this context and a study of this nature is presently in hand.

Experimental Section[10]

α-(±)-Methadol, mp 100–102° (lit.[11] mp 100–101°), was obtained from (±)-methadone and LAH; α-(+)-methadol hydrochloride, mp 187–188°, $[\alpha]^{20}D$ +33.5° (*c* 0.2, H_2O) [lit.[12] mp 169–171°, $[\alpha]^{25}D$ +34° (*c* 0.26, H_2O)], was obtained from (−)-methadone and Na–PrOH[1] (LAH gave racemic material).

6-Dimethylamino-4,4-diphenylhexan-3-ol (Normethadol).—Normethadone (26.7 g) was reduced with LAH (1.7 g) in the usual way[1] to give the amino alcohol (21 g), mp 100–101°, from EtOH. It formed a **hydrochloride**, mp 140–142°, from Me_2Co–Et_2O. *Anal.* ($C_{20}H_{25}ClNO$) C, H, N. **Methiodide**, mp 183–185°, from EtOH–Et_2O. *Anal.* ($C_{21}H_{30}INO$) C, H, N. **Bitartrate** [using (±)-tartaric acid], mp 146–148°, from EtOH. *Anal.* ($C_{24}H_{33}NO_7$) C, H, N.

Normethadol (14.85 g) and (+)-tartaric acid (7.5 g) were dissolved in hot 96% EtOH (30 ml) and the solution was stored at room temperature. The solid which separated was crystallized twice from the same solvent to give (+)-normethadol (+)-tartrate (7.8 g), mp 144–146°, $[\alpha]^{27}D$ +20° (*c* 2, H_2O). *Anal.* ($C_{24}H_{33}NO_7$) C, H, N.

3-Acetoxy-6-dimethylamino-4,4-diphenylhexane Hydrochloride.—A mixture of (±)-normethadol (3.5 g), EtOAc (80 ml), and AcCl (3 ml) was heated under reflux for 2 hr and then cooled. The solid which separated was recrystallized from EtOH–Et_2O to give (±)-**normethadyl acetate hydrochloride**, mp 104–106°, as a monohydrate (ν_{max} 3350 cm^{-1}). *Anal.* ($C_{22}H_{30}ClNO_2 \cdot H_2O$) C, H, N.

Acetylation of (+)-normethadol gave the (+)-acetoxy ester hydrochloride, mp 163–165°, from EtOH–Et_2O, $[\alpha]^{26}D$ +22.5° (*c* 2, H_2O). *Anal.* ($C_{22}H_{30}ClNO_2$) C, H.

(9) A. F. Casy and M. M. A. Hassan, *J. Pharm. Pharmacol.*, **19**, 114 (1967).

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

(11) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(12) A. Pohland, F. J. Marshall, and T. P. Craney, *J. Am. Chem. Soc.*, **71**, 460 (1949).

7-Oxabicyclo[2.2.1]heptane-2,3-dicarboximides with Anticonvulsant Activity

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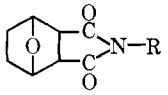
During an exploratory study of various derivatives of 7-oxabicyclo[2.2.1]heptane, we encountered marked anticonvulsant activity in the N-phenethyl-2,3-dicarboximide (I, R = phenethyl), a compound which may



I

be regarded as an elaborately substituted succinimide. Since its acute toxicity was relatively low, we undertook a study of the manner in which activity might be altered by variation of the R group.

Grogan and Rice[1] have described a number of imides of this sort. Some pharmacological testing was done, but revealed little significant activity. Beyond their work, only scattered examples of derivatives of this oxygen-bridged ring appear in the literature; it has been little used in the synthesis of potential drugs.

We prepared a series of imides (Table I) by heating primary amines with *exo,cis*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid or its anhydride, essentially according to published procedures.[1a] The products were considered to be *exo*, in conformity with the starting material. This assignment was confirmed by nmr examination in a number of instances; in no case was splitting of the signal for the protons at positions 2 and 3 of the cyclohexane ring by the protons at 1 and 4 observed ($J < 0.5$ cps).

Unexpectedly, two products, **46** and **47**, were obtained from 6-chloro-*o*-toluidine. Upon nmr examination, these were identified as rotationally isomeric forms of the expected imide, each containing 3–4% of the other rotamer. The signal for the protons at positions 2 and 3 was normally a single sharp line near δ 3.0. In the spectrum of **46**, it appeared as a pair of lines, a major one at 3.07 accompanied by a very small one at 3.02. For **47**, a similar but reversed pair appeared, the major line being at 3.05, the minor one at 3.09.

Confirmatory evidence of restricted rotation about the N-phenyl bond and consequent rotational isomerism among the phenylimides in general was afforded by the appearance of pairs of lines for the H-2,3 signal for those having only one *ortho* substituent, and for the protons of *o*-methyl groups, equal in size for the 2,6-xylylimide, unequal for *o*-tolylimides. Also, a small shift was seen between the two aromatic protons of the 2,4,6-trihalophenylimides, and in some cases two groups of lines could be seen for the protons at positions 1 and 4.

In pharmacological testing of the imides (Table II), considerable anticonvulsant activity was observed. Some of them showed potency in animal tests comparable to that of drugs currently used in therapy. Activity was essentially limited to compounds in which R was aryl or aralkyl with a one or two-carbon link between aryl group and imide N. Alkyl and heterocyclic imides had only feeble activity, if any.

Of the simple aralkyl derivatives, phenethyl (**4**) and benzyl (**3b**) were moderately active against both electroshock and pentylenetetrazole convulsions. β-Methylphenethyl (**8**) showed good activity in the electroshock test, but insertion of an α-methyl group (**6**, **7**) almost completely destroyed activity. Substitution on the phenyl ring tended to reduce potency.

The phenylimide (**3a**) was only feebly active. However, its monochloro derivatives were more active, and introduction of a second Cl or of an *o*-CH_3 substituent led to the most potent compounds of the series. The 2,3-dichlorophenylimide (**25**) showed the greatest overall activity. It was rivalled in potency against electroshock seizures by the 2,4- and 3,5-dichlorophenyl-, 3-chloro-*o*-tolyl-, and 2-chloro-5-trifluoromethylphenylimides (**26**, **30**, **48**, **52**) and against pentylenetetrazole seizures by the 2,5-dichlorophenyl- and 4-chloro-*o*-tolyl-

(1) (a) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963); (b) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953); (c) *ibid.*, **77**, 616 (1955).