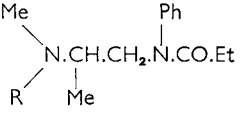
J. Pharm. Pharmac., 1967, **19**, 17–24 Received May 26, 1966

Analgesically active basic anilides: stereospecificity and structure of the basic group

A. F. CASY* AND M. M. A. HASSAN

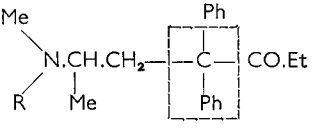
The synthesis of (*RS*)-, (*R*)- and (*S*)-*N*-(2-dimethylaminopropyl)propionanilide and the benzylmethylamino- analogues of methadone and isomethadone is described. The hot-plate activities in mice of the (*S*)- enantiomorphs of both the dimethylamino- and benzylmethylaminopropionanilides are greater than those of the corresponding (*RS*)- and (*R*)- forms, while the methadone and isomethadone analogues are inactive in the same test. These results support the view that 3-amino-1,1-diphenylpropyl- and basic anilide - analgesics differ in their modes of binding to the analgesic receptor site.

IN 1959 some analgesically active basic anilides (I) were reported which were regarded as analogues of methadone because they are formally derived from (II; R = Me) by replacing one phenyl group and its attached quaternary carbon atom with nitrogen (Wright, Brabander & Hardy, 1959). The enantiomorphic forms of diampromid (Ia) (the most active



(I)

R = a)Ph.[CH₂]₂ b)Ph.CH₂; c)Me.



(II)

methadone (R = Me)

member of the series) and its *N*-benzyl analogue (Ib) differ in their analgesic activities (Table 1), in common with (+)- and (−)-methadone and related enantiomorphic pairs. The more active enantiomorphs of several analgesics [including (−)-methadone] containing the structural feature >N·CH(Me)·R, are related to *R*-(−)-alanine (Beckett & Casy, 1965 and refs there cited). The more active forms of the anilides (Ia and b), which contain the same type of asymmetric centre as methadone are, however, related to *S*-(+)-alanine (Portoghese & Larson, 1964). This reversal of optical specificity is not without precedent in analgesics related to methadone [ethyl (+)-2,2-diphenyl-4-dimethylaminopentanoate and α-(−)-methadol, both derived from (+)-methadone, are more active in mice than their respective enantiomorphs (Eddy, Halbach & Braenden, 1956)], but in all other classes studied, groups of analgesics with related asymmetric centres have identical configurations (Beckett & Casy, 1965).

In analgesics based on the 4-phenylpiperidine skeleton it is well known that derivatives carrying *N*-2-arylethyl substituents are more active than corresponding *N*-methyl derivatives; *N*-benzyl derivatives, however, have either very low potencies or are inactive (Beckett & Casy, 1965 and refs there cited). In acyclic analgesics, such as methadone, optimum

From the Department of Pharmacy, Chelsea College of Science and Technology (University of London), Manresa Road, London, S.W.3.

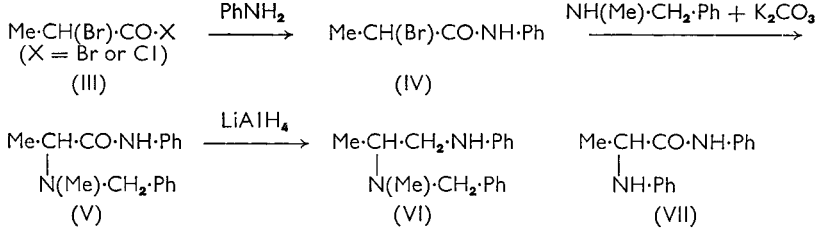
* Present address: Faculty of Pharmacy, University of Alberta, Edmonton, Alberta.

activity is obtained with a dimethylamino-group or with a five- or six-membered alicyclic basic group, activity falling when larger basic substituents are employed. Thus the basic functions of the anilides (Ia and b) are of a type unusual to acyclic analgesics, the benzyl group of (Ib) being, in addition, unusual even to analgesics of greater molecular rigidity.

These observations may be related to the fact that the basic anilides (Ia and b) do not conform to the configurational requirements established for methadone and related compounds, and the aim of this work was to obtain data regarding such a correlation. Two approaches were adopted: determination of (i) the stereospecificity of the basic anilide (Ic), containing the "normal" basic dimethylamino-function of acyclic analgesics, and (ii) the effect of replacing the *N*-methyl group in methadone and isomethadone by the *N*-benzyl group, a group, present in the basic anilide (Ib), a compound which has significant analgesic potency.

CHEMISTRY

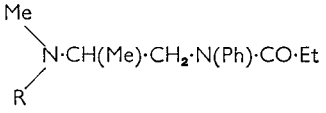
(±)-*N*-[2-(Benzylmethylamino)propyl]aniline (VI), the key intermediate in this work, was prepared from an α-bromopropionyl halide (III) by a reported method (see III–VI) (Wright, Brabander & Hardy, 1961). The need to use an excess of methylbenzylamine in the conversion of the bromanilide (IV) to the basic anilide (V) was avoided by



including potassium carbonate (as acid adsorbent) in the reaction mixture. Pyridine was a less satisfactory adduct in this respect, in one experiment the α-anilino-anilide (VII) (structure confirmed by nmr spectroscopy) being isolated rather than the desired anilide (V). [Pyridine presumably displaces aniline from the anilide (IV), the latter base then reacting with unchanged substrate to give (VII)]. Catalytic debenzylation of *N*-[2-(benzylmethylamino)propyl]propionanilide (Ib), derived from the diamine (VI), in the presence of formaldehyde, gave the dimethylamino-anilide (Ic); the corresponding (+)- and (−)-enantiomorphs were obtained when the optically active propionanilides (Ib) were used in this reaction. The configurational relationships of enantiomorphic forms of the dimethylamino-, benzylmethylamino- and methylphenethylamino-anilides (I) are shown in Table 1, all (+)-bases [≡(−)-base salts] in this series having identical configurations.

The racemic dimethylamino-anilide (Ic) was also prepared by alkylation of the sodio-derivative of propionanilide with 2-chloro-*NN*-dimethylpropylamine. This reaction involves a rearrangement and probably

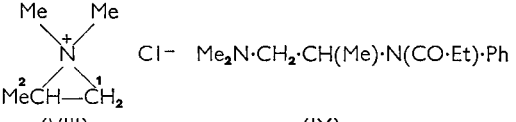
TABLE 1. OPTICAL AND ANALGESIC ACTIVITIES OF SOME *N*-(2-AMINOPROPYL)-PROPIONANILIDES



R	$[\alpha]_D^{22-25°}$ in EtOH		Configuration	Pharmacological activity (mg/kg)	
	Base	Salt[1]		AD50 (tail flick)[2]	ED50 (hot plate)[3]
Ph·CH_2	Racemic form		—	8	15
	+41·9	−23·5	*S*	4·3	12
	−41·9	+23·0	*R*	inactive (50)	⩾ 40
Ph$[CH_2]_2$	Racemic form		—	3·7	—
	+25·2[4]	—	*S*	3·6	—
	−25·9	—	*R*	11·7	—
Me	Racemic form		—	—	50
	+17·0	−40·9	*S*	—	35
	−17·7	+41·5	R	—	⩾ 40
Pethidine				11	23

[1] Hydrochloride (R = Ph·CH_2), nitrate (R = Me).
[2] in rats by subcutaneous injection (Wright & Hardy, 1963).
[3] in mice by subcutaneous injection (Janssen & Jageneau, 1957).
[4] Wright & Hardy (1963).

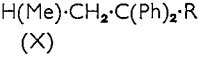
proceeds via the ethyleneimonium ion (VIII) (Schultz & Sprague, 1948). It appears that steric factors govern the direction of nucleophilic attack



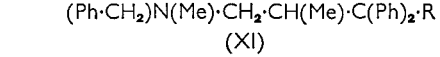
(VIII) (IX)

upon this intermediate since the propionanilide (Ic) [which must result from attack at the less hindered C-1 atom of the ion (VIII)] was isolated in high yield, while the close similarity of the nmr spectra of the total alkylation product and the pure anilide (Ic) showed that little of the isomeric anilide (IX) (characterized by a *N*-methyl singlet at 132 c/sec and a methine multiplet centred at 306 c/sec) is formed in this reaction.

In contrast, alkylation of diphenylacetonitrile with *N*-(2-chloropropyl)-*N*-methylbenzylamine resulted in a 1 : 1·5 mixture of the isomeric cyanides (X and XI; R = CN) as was clearly apparent from the nmr spectrum of the total alkylation product. These cyanides, with ethyl magnesium



(X)



(XI)

bromide, gave the ketones (X and XI; R = CO.Et), the benzylmethyl-amino-analogues of methadone and isomethadone respectively; in the case of the cyanide (XI; R = CN), the hydrocarbon (XI; R = H) was isolated as a by-product of this reaction.

PHARMACOLOGY AND DISCUSSION

The analgesic activities of the racemic (*RS*)-, (*R*)-, and (*S*)-forms of the basic anilides (Ib and c) (Table 1), and of the benzylmethylamino-ketones (X and XI; R = CO.Et) were determined in mice after subcutaneous injection, using the hot-plate method (Janssen & Jageneau, 1957). The (*S*)-benzylmethylamino-anilide produced morphine-like excitation in mice and had twice the hot-plate activity of pethidine; the (*R*)-enantiomorph was much less active in this test and caused no Straub tail response. These results parallel the activities of the same isomers in rats by a tail-pressure method (Wright & Hardy, 1963).* The (*RS*)-dimethylamino-anilide was about half as active as pethidine and had morphine-like effects. The corresponding (*S*)-isomer was more potent but produced no Straub reaction, while the (*R*)-isomer was inactive; neither isomer gave behavioural effects.

Because of the low order of potency of the (*RS*)- and (*S*)- forms of the dimethylamino-anilide, and the doubts about their morphine-like action, a clear decision on the influence of basic group structure upon stereospecificity is not possible. However, accepting these limitations, it does appear that stereospecificity in the dimethylamino-anilide is the same as that found in the anilides (Ia and b), the (*S*)-isomer being the more active form in all instances. Thus, stereospecificity in diampromid and its *N*-benzyl analogue does not appear to be directly linked with the presence of an arylalkylamino-substituent in the molecule.

Pharmacological results with the benzylmethylamino-analogues of methadone and isomethadone emphasize the unusual structural requirements for activity, relating to the basic group, in the amino-anilides (I), the *N*-benzylmethadone (X; R = CO·Et) and isomethadone (XI; R = CO·Et) analogues being virtually devoid of activity in the hot-plate test.

It appears likely, therefore, that 3-amino-1,1-diphenylpropyl and basic anilide analgesics differ in their modes of binding to the analgesic receptor site, as recently proposed by Portoghese (1965). Possible reasons for binding differences will be discussed elsewhere in terms of probable conformations of the analgesic molecules.

Experimental

α-Benzylmethylamino-N-*phenyl-propionamide* (V). A mixture of α-bromo-*N*-phenyl-propionamide (22·8 g, 0·1 mole), methylbenzylamine (12·1 g, 0·1 mole), anhydrous potassium carbonate (41·4 g, 3 mole) and acetone (200 ml) was heated under reflux for 12 hr. The reaction mixture was filtered, the filtrate evaporated, and the solid residue crystallized from ethanol to give the basic anilide (V) (24·6 g, 92% yield), m.p. 72–73° (Wright & others, 1961, give for this a m.p. 72–74°). When potassium carbonate was replaced by pyridine (15 ml) in the above procedure,

* In rats the (*S*)/(*RS*) potency ratio was almost 2 [a value indicating the (*R*)-isomer was inactive and without influence upon the (*S*)-isomer], whereas in mice the ratio was 1·25 [indicating the (*R*)-isomer to have some activity and/or to potentiate the action of its enantiomorph]. (*S*)/(*RS*) potency ratios of just above unity have also been reported for related anilides in rats (Portoghese & Riley, 1965).

α-anilinopropionanilide (VII) (12 g), m.p. 126–128° from ethanol, was isolated (Found: C, 74·75; H, 6·65; N, 11·7; equiv. wt 246. $C_{15}H_{16}N_2O$ requires: C, 75·0; H, 6·7; N, 11·7%; equiv. wt 240). It gave a *hydrochloride*, m.p. 201–203° from ethanol-ether (Found: C, 65·0, H, 6·0; N, 10·0; equiv. wt 275. $C_{15}H_{17}ClN_2O$ requires: C, 65·1; H, 6·2; N, 10·1%; equiv. wt 277). The α-anilino-anilide (VII) had the following nmr characteristics (c/sec from TMS in $CDCl_3$): 448, 434, 404, main peaks of multiplet (10 aryl protons); 243, broad singlet (N–H); 234, centre of multiplet (C–H); 93, doublet J7 (sec-Me). The N–H signal was absent and the C–H multiplet was a 1:3:3:1 quartet (233, J7) in $CDCl_3$–D_2O.

(±)-N-[2-(*Benzylmethylamino*)*propyl*]*aniline* (*VI*) *and its resolution.* α-Benzylmethylamino-*N*-phenyl-propionamide (53·6 g) was reduced with lithium aluminium hydride (15·2 g) by the procedure of Wright & others (1961) to give the diamine (VI) (46 g), m.p. 43–44° from aqueous ethanol (Portoghese & Larson, 1962, report m.p. 42–44°). The (±)-diamine (VI) (52 g) and (+)-tartaric acid (30·8 g) in 95% ethanol (525 ml) deposited a salt (on storage at 25°) which was recrystallized four times from the same solvent to give the (+)-diamine (+)-tartrate (26·5 g), m.p. 102–103°, $[\alpha]_D^{22}$ −11·5 (*c*, 2% in H_2O) [Portoghese & Larson, 1964, report m.p. 101–103°, $[\alpha]_D^{27}$ −16·0° (*c*, 5% in H_2O)]. This salt (26 g) gave the free (+)-*diamine* (VI) (15·5 g), m.p. 60–61° from ethanol, $[\alpha]_D^{22}$ + 34·9° (*c*, 0·75% in ethanol) [Portoghese & Larson, 1964, give m.p. 59–61°, $[\alpha]_D^{27}$ + 31·2 (*c*, 5% in ethanol)]. The salt which deposited from the combined mother liquors of the above resolution (after concentration and storage at 25° for 12 hr) was recrystallized four times from water to give the (−)-diamine (+)-tartrate (12·3 g), m.p. 82–84°, $[\alpha]_D^{22}$ + 30° (*c*, 2% in H_2O) [Portoghese & Larson, 1964, give m.p. 82–84°, $[\alpha]_D^{25}$ + 30° (*c*, 2% in water)]. This salt (12 g) gave the (−)-diamine (VI) (6·8 g), m.p. 59–61°, $[\alpha]_D^{22}$ − 34° (*c*, 0·75% in ethanol) [Portoghese & Larson, 1964, give m.p. 59–60°, $[\alpha]_D^{30}$ − 30·8 (*c*, 5% in ethanol)].

(±)-, (+)- *and* (−)-N-[2-(*Benzylmethylamino*)*propyl*]*propionanilide* (*Ib*). The (±)-diamine (VI), with propionic anhydride, gave the (±)-propionanilide (Ib), b.p. 166–170°/0·4 mm, hydrochloride, m.p. 152–153° from acetone (Wright & others, 1961, give b.p. 166–170°/0·4 mm, hydrochloride, m.p. 150–151°). It formed a *methiodide*, m.p. 176·5–178·5° from ethanol-acetone (Found: C, 55·8; H, 6·85; N, 6·3; equiv. wt 450. $C_{21}H_{29}IN_2O$ requires: C, 55·75; H, 6·5; N, 6·2%; equiv. wt 452). The (+)-diamine gave the (−)-propionanilide, b.p. 178°/0·6 mm, $[\alpha]_D^{22}$ −41·9° (*c*, 5% in ethanol) [Portoghese & Larson, 1964, give b.p. 152–157°/0·3 mm, $[\alpha]_D^{32}$ −45·7 (*c*, 5% in ethanol); Wright & Hardy, 1963, give $[\alpha]_D^{25}$ −37·6° (*c*, 3–4% in ethanol)]. It formed a hydrochloride, m.p. 141–142° from acetone-ether, $[\alpha]_D^{22}$ + 23° (*c*, 1% in ethanol) [Wright & Hardy, 1963, give m.p. 141–142°, $[\alpha]_D^{25}$ + 13·8 (*c*, 3–4% in ethanol)]. The (−)-diamine gave the (+)-propionanilide, b.p. 186–188°/1 mm, $[\alpha]_D^{22}$ + 41·9° (*c*, 5% in ethanol), hydrochloride, m.p. 141–142°, $[\alpha]_D^{22}$ −23°5° (*c*, 1% in ethanol) [Wright & Hardy, 1963, give m.p. 141–142°, $[\alpha]_D^{25}$ −14·5 (*c*, 3–4% in ethanol)].

(±)-, (+)- *and* (−)-N-(2-*Dimethylaminopropyl*)*propionanilide* (*Ic*). A mixture of the (±)-benzylmethylamino-anilide (Ib) (3·1 g), formaldehyde (3·5 ml, 40% solution in water), palladized charcoal (1 g, 10%) and 90% ethanol (100 ml) was shaken with hydrogen at 60° until the theoretical volume of gas had been absorbed. The mixture was filtered, the filtrate evaporated and the residue dissolved in N HCl (30 ml) and extracted with ether. The aqueous phase was made alkaline with aqueous sodium hydroxide solution, extracted with ether and the dried (Na_2SO_4) extract evaporated to yield the (±)-dimethylamino-anilide (Ic) (2 g). A mixture of this base (2 g) in ethanol and nitric acid (4·5 ml, 10%) was evaporated under reduced pressure and the residue dried by azeotropic distillation with ethanol-benzene. The oily product solidified when triturated with dry ether and was crystallized from ethanol-ether to give a nitrate, m.p. 134–136° (Wright & others, 1961, by a different route, give m.p. 134–136°). The (−)-benzylmethylamino-anilide (6·2 g), treated as above, gave the (−)-dimethylamino-anilide (4 g), $[\alpha]_D^{22}$ −17·75° (*c*, 2% in ethanol). It formed a (+)-*nitrate*, m.p. 120–121° from ethanol-ether, $[\alpha]_D^{23}$ + 41·5 (*c*, 1% in H_2O) (Found: C, 56·1; H, 7·8; N, 14·3; equiv. wt 295. $C_{14}H_{23}N_3O_4$ requires: C, 56·5; H, 7·8; N, 14·1%; equiv. wt 297). The (−)-anilide (Ic) with hydrogen bromide, gave N-(2-*dimethylaminopropyl*)*aniline dihydrobromide*, m.p. 203–206° (Found: C, 39·6; H, 6·05; N, 8·6. $C_{11}H_{20}Br_2N_2$ requires: C, 38·85; H, 5·9; N, 8·2%). The (+)-benzylmethylamino-anilide gave the (+)-dimethylamino-anilide, $[\alpha]_D^{23}$ + 17° (*c*, 2% in ethanol). It formed a (−)-*nitrate monohydrate*, m.p. 120–121° from ethanol-ether, $[\alpha]_D^{23}$ −40·9 (*c*, 1% in H_2O) (Found: C, 53·3; H, 8·0; equiv. wt 315. $C_{14}H_{23}O_4.H_2O$ requires: C, 54·0; H, 7·9%; equiv. wt 315) ν_{max} 3300 cm^{-1} (H_2O, broad band). The (±)-dimethylamino-anilide was also obtained as follows: A stirred mixture of propionanilide (74·5 g), sodium hydride (24 g, 50% in oil) and xylene (one litre) was heated at 110–120° (oil-bath) for 3 hr whereupon the sodium propionanilide separated. 2-Chloro-*NN*-dimethylpropylamine (66·8 g freshly liberated from the hydrochloride salt) in xylene (400 ml) was added and the mixture heated at 120–130° for 10 hr with stirring. The cold reaction mixture was filtered, the residue washed with xylene, and the combined filtrate and washings extracted with 10% hydrochloric acid. The extract was made alkaline with aqueous ammonia and extracted with ether; the organic phase was dried (Na_2SO_4), evaporated and the residue distilled to give base A (82 g), b.p. 120–122°/0·1 mm, which formed the nitrate (Ic) (60·5 g), m.p. and mixed m.p. 135·5–137·5°. The base from this salt had the following nmr characteristics (c/sec from TMS in CCl_4): 439, main peak of multiplet (5 aromatic protons); 232, quartet J gem 14 J vic 8·5, 203, quartet J gem 14 J vic 6 (methylene protons); 128, singlet (NMe_2); 117, quartet J7 ($CO.\underline{CH_2}.Me$); 57·5; triplet J7 ($CO{\cdot}CH_2{\cdot}\underline{Me}$); 49, doublet J 6·5 (sec-Me). The nmr spectra of the pure propionanilide (Ic) and the total alkylation product (base A, above) were very similar; the latter displayed a small peak at 132 c/sec (NMe_2) characteristic of the isomeric anilide (IX). The latter, prepared by the method of Wright & others, 1961), was isolated as a *hydrochloride*,

m.p. 169–171° (from ethanol-ether) (Found: C, 58·5; H, 8·7. $C_{14}H_{25}ClN_2O_2$ requires: C, 58·2; H, 8·7%).

Reaction of N-(2-*chloropropyl*)-N-*methylbenzylamine with diphenylacetonitrile.* *N*-(2-Chloropropyl-*N*-methylbenzylamine (61 g) (Wilson, 1952) in benzene (60 ml) was added to a mixture of diphenylacetonitrile (60 g), sodamide (14·6 g) and benzene (200 ml) which had previously been stirred at 30–40° for 1 hr, and the product heated under reflux for 18 hr. The benzene solution was then washed with water and concentrated to give a crude mixture of cyanides (X and XI, R = CN) (103 g), present in the ratio of 1·5 (XI) to 1·0 (X) [from integrals of the two *N*-Me (129 and 124) and sec-Me (70·5 and 60·5 c/sec from TMS in $CDCl_3$) nmr signals]. Light petroleum (b.p. 60–80°) was added to the mixture and the solid which separated (47 g) recrystallized from benzene-light petroleum b.p. 40–60° to give the 2-methylpropyl cyanide (XI) (40 g), m.p. 106·5–107·5° (Wilson, 1952, gives the same m.p.). The mother liquors were concentrated and the residue acidified with methanolic hydrogen chloride, whereupon the butyl cyanide (X) hydrochloride (21 g), m.p. 210·5–212·5° from ethanol-ether, separated (Wilson, 1952, gives m.p. 206)°. The higher field chemical shifts of the *N*-Me and sec-Me groups, given above, correspond with the butyl cyanide (X), and the lower field with the isomer (XI).

6-*Benzylmethylamino*-4,4-*diphenylheptan*-3-*one.* The butyl cyanide (X) (7·1 g) in toluene (50 ml) was added to ethyl magnesium bromide in ether (40 ml) prepared from ethyl bromide (6·5 g) and magnesium (1·4 g). The ether was removed by distillation, the mixture heated under reflux for 5 hr, and then added to ice and concentrated hydrochloric acid (35 ml). The base (6 g), recovered from the aqueous phase, with hydrogen bromide gave the *ketone* (X, R = CO·Et) *hydrobromide*, m.p. 96–98° from ethanol (Found: C, 68·85; H, 7·2; N, 3·2; equiv. wt 462. $C_{27}H_{32}BrNO$ requires: C, 69·3; H, 6·9; N, 3·0%; equiv. wt 466).

6-*Benzylmethylamino*-5-*methyl*-4,4-*diphenylhexan*-3-*one.* The 2-methylpropyl cyanide (XI, R = CN) (7·1 g), treated with ethyl magnesium bromide as described above, gave the amino-ketimine (XI, R = C(NH)Et) (7·2 g), which was heated under reflux with concentrated hydrochloric acid (40 ml) and ethanol (5 ml) for 12 hr to yield the *ketone* (XI, R = CO·Et), isolated as a *hydrobromide*, m.p. 205–206° from ethanol-ether (Found: C, 69·1; H, 7·0; equiv. wt 464).

In one reaction the hydrocarbon (XI, R = H) was isolated from the crude ketimine. It gave a *maleate*, m.p. 174–176° from ethanol-ether (Found: C, 75·8; H, 7·2; N, 3·15. $C_{28}H_{31}NO_4$ requires: C, 75·5; H, 7·0; N, 3·15%). The infrared spectrum of the free base showed no significant absorption in the region 1600–1800 cm^{-1}.

The nmr spectra were recorded on a 60 Mc Varian A–60 instrument in $CDCl_3$ or CCl_4 with TMS as internal standard. We thank Miss J. Lovenack, School of Pharmacy, University of London, for carrying out these measurements, and Dr. P. Janssen for the pharmacological results.

References

Beckett, A. H. & Casy, A. F. (1965). *Progress in Medicinal Chemistry*, Vol. 4, p. 171, editors Ellis, G. P. & West, G. B. London: Butterworths.
Eddy, N. B., Halbach, H. & Braenden, O. J. (1956). *Bull. World Hlth Org.*, **14**, 353–402.
Janssen, P. A. J. & Jageneau, A. H. M. (1957). *J. Pharm. Pharmac.*, **9**, 381–400.
Portoghese, P. S. (1965). *J. mednl Chem.*, **8**, 609–616.
Portoghese, P. S. & Larson, D. L. (1964). *J. pharm. Sci.*, **53**, 302–305.
Portoghese, P. S. & Riley, T. N. (1965). *Ibid.*, **54**, 1831–1833.
Schultz, E. M. & Sprague, J. M. (1948). *J. Am. chem. Soc.*, **70**, 48–52.
Wilson, W. (1952). *J. chem. Soc.*, 3524–3529.
Wright, W. B., Brabander, H. J. & Hardy, R. A. (1959). *J. Am. chem. Soc.*, **81**, 1518.
Wright, W. B., Brabander, H. J. & Hardy, R. A. (1961). *J. org. Chem.*, **26**, 476–485.
Wright, W. B. & Hardy, R. A. (1963). *J. mednl Chem.*, **6**, 128–130.