Alpha- and Beta-Prodine Type Compounds

A. H. Beckett, A. F. Casy, and G. Kirk

J. Med. Chem., **1958**, 1 (1), 37-58 • DOI: 10.1021/jm50002a004

Journal of Medicinal and Pharmaceutical Chemistry

VOL. I, NO. 1 (1959)

Alpha- and Beta-Prodine Type Compounds

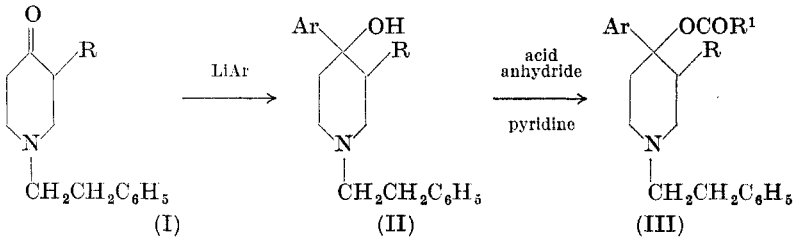
A. H. BECKETT, A. F. CASY and G. KIRK

School of Pharmacy, Chelsea College of Science and Technology, London S.W.3.

Introduction

The relative configurations of alpha- and beta-prodine have been discussed in a number of papers. Recently, ZIERING, MOTCHANE and LEE[1] have published an interpretation of the infra-red absorption spectra of the derived alcohols which they consider supports their original assignments,[2] viz., *cis* methyl/phenyl for alpha- and *trans* methyl/phenyl for beta-prodine. BECKETT, CASY and WALKER,[3,4] on the other hand, were led to advance the reverse configurations on the basis of conformational analysis and hydrolysis rates. Further evidence in favour of the assignments of Beckett and co-workers has been provided by the determination of the isomeric compositions of tertiary alcohols obtained by the addition of lithium aryls to 1,3-dimethyl-4-piperidone.[5] It has been shown, from considerations of the stereochemistry of addition to ketones, that this information is of value in assigning configurations to the various stereoisomers. This present work reports the extension of addition studies to a series of N-2′-phenylethyl-4-piperidones with the object of providing further evidence for the assignment of configurations to alpha- and beta-prodine type compounds. It has the further object of producing compounds of known configuration for analgesic tests to provide information about the stereochemical requirements of analgesics and the analgesic receptor site.

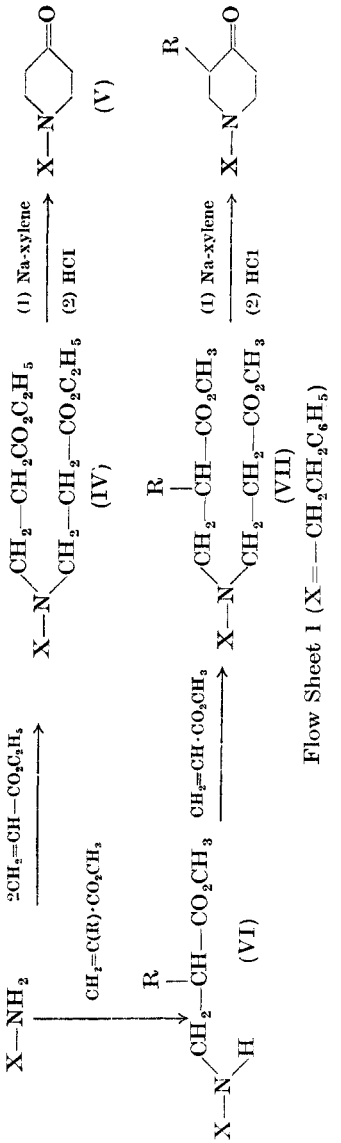
The key intermediates in the synthesis of the tertiary alcohols and esters reported in this present work were 4-piperidones of general formula (I, R = H or alkyl). Reaction of the ketone (I) with a lithium aryl and subsequent acylation of the resultant tertiary alcohol (II) gave the 'reversed ester' (III, R^1 = lower alkyl). The synthesis of the 4-piperidones (I, R = H, CH_3 and



(I) (II) (III)

C_2H_5) is outlined in Flow Sheet 1. The diester (IV) was obtained in almost quantitative yield by refluxing 2-phenylethylamine with excess of ethyl acrylate for 48 h. Cyclization of the diester was achieved by a Dieckmann type condensation, using sodium-shot in xylene; decarboxylation of the resultant β-keto ester gave the piperidone (V). Treatment of the base with ethanolic hydrochloric acid led to the ethyl ketal instead of the expected piperidone hydrochloride. The free ketone, derived by acid hydrolysis, showed the characteristic carbonyl stretching frequency (1,725 cm^{-1}), absent in the ketal. The low chlorine analysis reported by BOLYARD and MCELVAIN[6] for N-2′-phenylethyl-4-piperidone hydrochloride is explained if their product was in fact the ketal hydrochloride (found: Cl, 11·49; calc.: 14·79 for piperidone; 11·31 for ketal hydrochloride). Recently, BROOKS and WALKER[7] have shown the products reported by Bolyard and McElvain as 1-benzyl and 1-butyl-4-piperidone hydrochloride to be the corresponding ketal hydrochlorides. The failure of 4-piperidones substituted in the 3-position by alkyl groups to give ketals readily [e.g. 1,3-dimethyl-4-piperidone (HOWTON)[8] and the ketones (I, R = CH_3, C_2H_5 and n C_3H_7)] cannot be attributed simply to steric effects since ketal formation has been reported in the cases of 2,5-dimethyl-4-piperidone[9] and 1-methyl-3-(2′-carbethoxyethyl)-4-piperidone.[10] Treatment of N-2′-phenylethyl-4-piperidone with lithium phenyl gave N-2′-phenylethyl-4-phenyl-4-piperidinol. This alcohol was also prepared from N-2-phenylethylamine, formaldehyde and α-methylstyrene following SCHMIDLE and MANSFIELD'S process[11] for the synthesis of the corresponding N-methyl analogue.

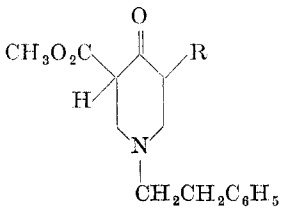
The piperidones (I, R = CH_3 and C_2H_5) were prepared by an adaptation of Howton's synthesis of 1,3-dimethyl-4-piperidone[8]. The secondary base (VI) was obtained in high yield by allowing



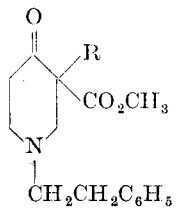
Flow Sheet 1 (X = $-CH_2CH_2C_6H_5$)

the reactants to stand at room temperature for several weeks; a higher reaction temperature gave a much reduced yield. Treatment of the secondary base (VI) with methyl acrylate at the

reflux temperature gave the tertiary base (VII). Attempts to prepare this base by the reverse process, i.e. addition of methyl methacrylate to the secondary base (VI, R = H), were unsuccessful. The cyclized product may be formulated in two ways, (VIII) and (IX), the former being the more likely (see ROYALS[12]). Presence of the form (VIII), which alone is capable of enolization under

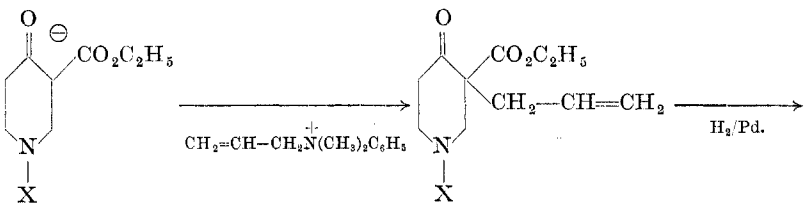


(VIII)

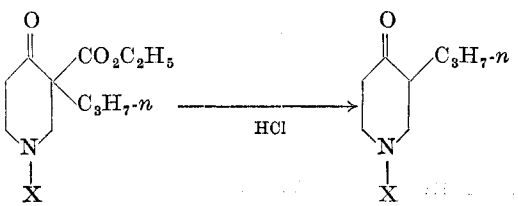


(IX)

mild conditions, was detected by the intense coloration that the product gave with ferric chloride; absence of this colour reaction gave indication of the completion of decarboxylation. The piperidone (I, R = C_2H_5) was made by an analogous series of reactions starting from ethyl 1-ethylacrylate prepared by the method of MANNICH and RITSERT.[13] Synthesis of the 3-*n*-propyl ketone (I, R = *n*-C_3H_7) is shown in Flow Sheet 2 and follows a method due



(X) (XI)

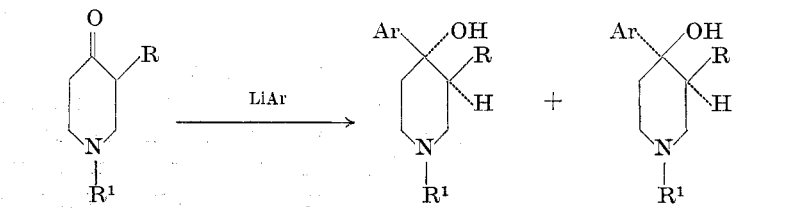


(XII)

Flow Sheet 2 (X=—$CH_2CH_2C_6H_5$)

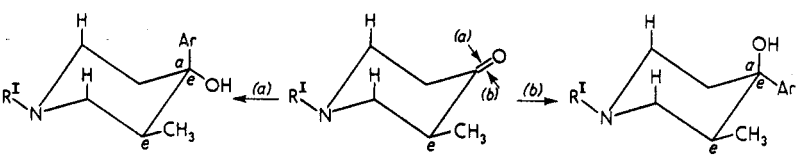
to McELVAIN and BARNETT[14] for the corresponding N-methyl ketone. C-Allylation of the sodio-derivative (X) was achieved by reaction with allyldimethylanilinium bromide. (Note: treatment with an alkyl halide would be expected to lead to N-, rather than C-substitution.) Decarboxylation was not attempted at the next stage since McELVAIN and BARNETT[14] have shown that acid treatment of the corresponding N-methyl compound gives a cyclic hemiacetal. The keto-ester (XII), obtained by hydrogenation of the allyl compound (XI), gave no coloration with ferric chloride since enolization is precluded (*cf.* the corresponding 3-alkyl keto-esters derived by cyclization reactions).

The addition of lithium aryls to 3-substituted 4-piperidones can give two diastereoisomeric alcohols (XIII and XIV) which differ in the *cis–trans* relationship of the 3-alkyl and 4-aryl groups. BECKETT, CASY, KIRK and WALKER,[5] from arguments based upon



Ar/R *cis* (XIII) Ar/R *trans* (XIV)

the stereochemistry of addition to ketones, consider that the *trans*-isomer should be formed in major amount and that the preponderance of this isomer should increase with increasing size of the aryl addendum in the vicinity of the reaction centre (see formula (XV); attack from the least hindered side (*b*), giving the *trans*-isomer (XVI), is favoured if the piperidone reacts in the chair conformation with the 3-methyl group equatorial).



cis (CH_3/Ar) isomer (XVII) (XV) *trans* (CH_3/Ar) isomer (XVI)

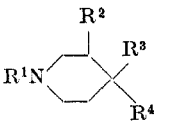
These conclusions were supported by examination of the isomeric compositions of tertiary alcohol mixtures derived from 1,3-dimethyl-4-piperidone. With the alcohols (XIII and XIV, R and $R^1 = CH_3$, $Ar = C_6H_5$), an isomeric ratio of 3 : 1 (as the propionic ester hydrochlorides) was obtained, and with the *m*- and *p*-tolyl alcohols, one isomer predominated. The *o*-tolyl and *o*-methoxyphenyl alcohols were obtained in one, sensibly exclusive, form.

In the present work, treatment of 3-methyl-1-2′-phenylethyl-4-piperidone with lithium phenyl gave an isomeric mixture from which only one product could be separated in a pure condition. This isomer represented at least 60 per cent of the mixture. Absorption chromatographic separation was unsuccessful as in the case of the corresponding N-methyl compounds. A small quantity of a second isomer was obtained by fractional crystallization of the propionoxy ester hydrochlorides from ether-ethanol. The major component of the product derived from lithium *m*-tolyl consisted of one isomer having a sharp melting point. Further crops melted over a wide range indicating the presence of a second isomer. A similar result was obtained in the case of the lithium *p*-tolyl product. With lithium *o*-tolyl, *o*-methoxyphenyl and 2,6-dimethylphenyl, addition to the piperidone gave a product which was recovered in high yield, upon recrystallization, with little change in melting point. If isomers are formed in these latter additions they represent only a very small fraction of the reaction product.

Evidence for the configurational identity of the isomers (type A, see Table I) formed in major amount on the addition of lithium aryls to 1,3-disubstituted-4-piperidones is provided by infra-red absorption measurements. These isomers reveal a consistent pattern in the regions 990–1,010 cm^{-1} and 1,350–1,385 cm^{-1}, which is different from that shown by the isomers (type B) formed in minor amount.

Type B isomers have their strongest absorption in the region 1,040–1,055 cm^{-1} which may be characteristic of the C–O stretching mode. With type A isomers no one absorption peak is consistently maximum in the region 1,000–1,150 cm^{-1} and it is not yet possible to make C–O stretching frequency assignments. The pattern found, however, differs from that of type B isomers

Table I. Characteristics of infra-red absorption of 1,3-disubstituted 4-aryl-4-substituted piperidines



R^1	R^2	R^3	R^4	Isomer	Absorption peaks of characteristic frequency (cm^{-1}) region A (990–1,010 cm^{-1})	region B (1,350–1,385 cm^{-1})
CH_3	CH_3	C_6H_5	OH	A*	1,000	1,355 1,383
,,	,,	o-$OCH_3.C_6H_4$	,,	A	1,001	1,357 1,380
,,	,,	o-$OCH_3.C_6H_4$	$OCOCH_3$	A	1,001	1,365 1,380
,,	,,	o-$CH_3.C_6H_4$	OH	A	1,001	1,352 1,376
,,	,,	m-$CH_3C_6H_4$	,,	A	1,000	1,355 1,383
,,	,,	p-$CH_3.C_6H_4$	,,	A	1,002	1,354 1,382
,,	,,	2,6-$(CH_3)_2C_6H_3$	,,	A	1,002	1,360 1,385
,,	,,	C_6H_5	,,	B†	no peak	1,372 1,380
,,	,,	m-$CH_3.C_6H_4$	,,	B	no peak	1,376 1,383
,,	,,	p-$CH_3.C_6H_4$	,,	B	no peak	1,372 1,383
$(CH_2)_2C_6H_5$	,,	C_6H_5	,,	A	1,004	1,351 1,376
,,	,,	o-$CH_3.C_6H_4$	,,	A	1,003	1,351 1,376
,,	,,	m-$CH_3.C_6H_4$	,,	A	1,007	1,353 1,376
,,	,,	p-$CH_3.C_6H_4$	,,	A	1,003	1,354 1,377
,,	,,	2,6-$(CH_3)_2C_6H_3$	,,	A	1,000	1,355 1,380
,,	C_2H_5	o-$CH_3.C_6H_4$	,,	A	1,001	1,354 1,377
,,	n-C_3H_7	C_6H_5	,,	A	992	1,355 1,380

* Alcohol from alphaprodine.
† Alcohol from betaprodine.

and may be attributed, in part, to an axial hydroxyl group since it is similar to that shown by 4-piperidinols bearing bulky 4-substituents (no 3-substituent). In the latter compounds the piperidine ring is concluded to be in a chair conformation with the bulky group equatorial and the hydroxyl, consequently, axial.

Additional evidence for the *trans* configuration of Type A isomers is derived from hydrolysis studies upon the corresponding propionoxy esters. The results obtained in the case of alpha- and beta-prodine have already been reported by Beckett and Walker,[4] who found that betaprodine hydrolysed more rapidly

than alphaprodine. These studies have now been extended to the corresponding N-2′-phenylethyl compounds prepared in this present work (III, $R = CH_3$; $R^1 = C_2H_5$) and show that the type B hydrolyses more rapidly than the type A isomer (see Table II for

Table II. Comparative Hydrolysis Studies of N-2′-Phenylethyl-3-methyl-4-propionoxy-piperidines*

Initial concn. of ester, mole	Initial concn. of NaOH, mole	Time after mixing, h	Percentage hydrolysis	
			type A isomer	type B isomer
0·014	0·11	4	3·2	19·4
,,	,,	17	18·1	37·5
,,	,,	26	32·3	51·7
,,	,,	49	54·3	73·7
,,	,,	72	62·0	82·7

* See BECKETT and WALKER[4] for experimental procedure.

details). These results indicate that type A esters possess an axial and type B esters an equatorial propionoxy group and are consistent with the assigned configurations. The differences in hydrolysis rates of type A and type B esters, although small, are consistent in direction. Archer[22] considers alpha- and beta-prodine to differ in 3-methyl rather than 4-propionoxy conformation and interprets the observed hydrolysis rate differences in terms of these structures. The latter explanation, however, does not explain the bulk of the observations recorded in this present paper.

It is to be noted that the hydrolytic evidence and infra-red spectra interpretations bearing on the stereochemistry of tertiary alcohols described in this work relate to establishing the conformations of the hydroxy and aryl groups. Once these have been determined, assignment of *cis*- and *trans*-configurations rests upon the assumption that the 3-methyl substituent of the piperidine ring is equatorially placed. In this we have applied the precepts of conformational analysis which require, in the absence of strong

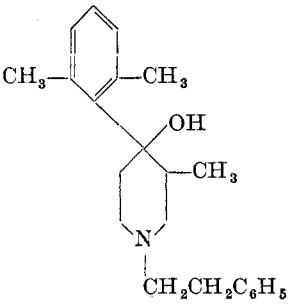
electrostatic interactions and exceptionally large groups, that six-membered cyclic structures have a maximum number of equatorial substituents. Similarly, the configurations derived from consideration of the stereochemistry of addition to ketones are valid only if it be accepted that the 4-piperidones react in the chair conformation with the 3-methyl group equatorial.

Direct confirmation of the *configuration* of type A isomers is provided by considering all the possible conformations of the tertiary alcohol (XVIII) bearing the very bulky 2,6-dimethylphenyl group in the 4-position of the piperidine ring (see Table III).

Table III. Conformations of the tertiary alcohol (XVIII)

	Configuration (CH_3/Ar)	CH_3	2,6-$(CH_3)_2C_6H_3$
(1)	*trans* (Chair)	*e.*	*e.*
(2)	*trans* (Chair)	*a.*	*a.*
(3)	*trans* (Boat)	*be.*	*bs.*
(4)	*trans* (Boat)	*ba.*	*fp.*
(5)	*cis* (Chair)	*e.*	*a.*
(6)	*cis* (Chair)	*a.*	*e.*
(7)	*cis* (Boat)	*be.*	*fp.*
(8)	*cis* (Boat)	*ba.*	*bs.*

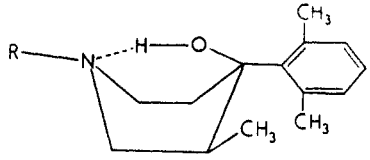
When attempts are made to construct these structures from Courtauld models it proves possible to make only forms 1 and 3



(XVIII)

without introducing strain, both of which have the *trans*-configuration with respect to the methyl and aryl groups. While it

is not intended to imply that failure to make a particular conformation is any indication that it cannot exist, it is reasonable to conclude that conformations capable of construction involving least strain will, at least, constitute the major components of any isomeric mixture. In fact, the product obtained by reacting



(XIX)

N-2′-phenylethyl-3-methyl-4-piperidone with lithium 2,6-dimethylphenyl proves to be, sensibly, one pure isomer and must have, therefore, the *trans* (methyl/aryl) configuration. It remains to discriminate between the chair and boat forms. Hydrogen bonding of type (XIX), i.e. intramolecular, would be expected if the compound has the boat conformation but would be absent if the chair is the prevailing form. Examination of the infra-red absorption spectrum of the alcohol (XVIII) shows that the band characteristic of bonded OH disappears on dilution, indicating the absence of intramolecular hydrogen bonding.*

Chemical Structure and Analgesic Activity

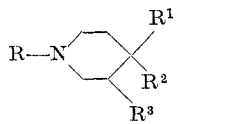
The analgesic activities of the tertiary alcohols and esters reported in this paper were determined in mice by subcutaneous injection, using an adaptation of the 'hot plate' method as described by JANSSEN and JAGENAU.[16] Our thanks are due to Dr. Paul Janssen for carrying out the pharmacological tests. The activities, calculated from the ED50 values, are expressed relative to morphine for convenience. However, the hot plate method does not distinguish between morphine-type analgesics and other compounds which increase reaction time.

* Since the submission of this paper, Dr. W. H. Barnes of the National Research Council, Ottawa, Canada, has informed us (3 February 1959) that X-ray crystallographic studies using (±)—alphaprodine hydrochloride have demonstrated a *trans* methyl/phenyl configuration. The conformation (solid state) is a chair for the piperidine ring with the phenyl group equatorial and the propionoxy axial. This configuration and conformation is an agreement with those assigned in the present and previous papers by Beckett *et al* [3, 4, 5, 17].

With this limitation, certain aspects of the influence of chemical structure upon analgesic potency are discussed. In the assessment of structure–activity relationships, type A isomers have been compared with alpha-prodine, and type B with beta-prodine.

Replacement of the N-methyl group by N-2′-phenylethyl. The basic centres of potent analgesics normally bear at least one

Table IV. Effect of replacing N-CH_3 by N-$CH_2CH_2C_6H_5$



R^1	R^2	R^3	Configuration Me/Ar	Analgesic activity (morphine = 100) R = —CH_3	R = —$(CH_2)_2C_6H_5$
C_6H_5	$OCOCH_3$	H	—	9†	633*
,,	$OCOC_2H_5$	,,	—	260†	346*
,,	$OCOC_3H_7$-*n*	,,	—	44†	107
,,	$OCOC_2H_5$	CH_3	*cis*	870	2,195
			trans	200	450
o-$CH_3C_6H_4$	OH	,,	,,	20	77
,,	$OCOCH_3$	,,	,,	75	1,325
,,	$OCOC_2H_5$	,,	,,	85	259
m-$CH_3C_6H_4$	OH	,,	,,	<20	80
,,	$OCOCH_3$	,,	,,	<20	179
,,	$OCOC_2H_5$	,,	,,	50	39
p-$CH_3C_6H_4$	OH	,,	,,	<15	97
,,	$OCOCH_3$	,,	,,	30	88
,,	$OCOC_2H_5$	,,	,,	150	17
o-$OCH_3C_6H_4$	OH	,,	,,	<20	46
,,	$OCOCH_3$	,,	,,	30	407

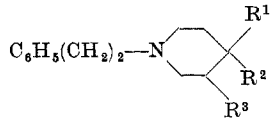
* ELPERN *et al.*,[19] have recently reported the activities of these compounds to be 340 (acetoxy) and 860 (propionoxy).
† Reference 18

methyl group. It is now well established that replacement of this group by the N-2′-phenylethyl and related groups results in a substantial increase in analgesic activity.[17] Pharmacological results confirm, in most cases, the expected increase in activity of the N-2′-phenylethyl compounds prepared in this present work over the corresponding N-methyl compounds (see Table IV).

Alkyl substitution in the 3-position of the piperidine ring. Although the results available do not form a complete series for

comparison, the values recorded in Table V indicate that, with few exceptions, optimum activity in respect to 3-alkyl substitution is afforded by a methyl group. ZIERING, MOTCHANE and LEE[1] have reported that alpha-prodine and its 3-ethyl analogue have similar activities, while the same increase in size of the 3-substituent in the case of beta-prodine leads to a considerable fall in potency. The same workers[1] find that 3-allyl substitution results in enhanced activity, the alpha-isomer being the more active. Until the configurations of the 3-ethyl and 3-allyl prodine

Table V. Effect of 3-alkyl substitution in the piperidine ring*



R1	R2	Analgesic activity (morphine=100) R3=H	R3=CH3	R3=C2H5	R3-n-C3H7
C_6H_5	OH	35	70	—	33
,,	$OCOCH_3$	633	385	—	456
,,	$OCOC_2H_5$	346	430	—	—
o-$CH_3C_6H_4$	OH	—	77	41	—
,,	$OCOCH_3$	—	1,325	760	—
,,	$OCOC_2H_5$	—	259	142	—
m-$CH_3C_6H_4$	OH	62	80	—	—
,,	$OCOCH_3$	117	179	—	—

* All results results refer to type A isomers where applicable.

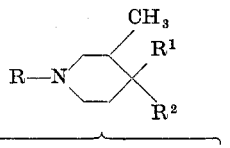
analogues have been established, the significance of these results, in terms of the proposed analgesic receptor site,[3] cannot be assessed.

Structural changes within the 4-aryl group. The effects on analgesic activity that result from modification of the 4-aryl group are summarized in Table VI; the activities of the corresponding N-methyl compounds[5] are also included. It is clear that the activities of the alcohols and esters do not follow the same sequence and that, furthermore, the effects in the N-2′-phenylethyl compounds are not paralleled by the corresponding N-methyl alcohols and esters. Variation in the size of the 4-aryl group has little influence upon the analgesic properties of the N-2′-phenylethyl-3-methyl alcohols (note also the 2,6-dimethylphenyl alcohol,

activity = 80). In the case of the 4-tolyl compounds, the *ortho* isomer represents the most active form in four of the six series. The acetoxy ester of N-2′-phenylethyl-3-methyl-4-*o*-tolyl-piperidinol is particularly active and has been selected for detailed pharmacological study.

Influence of configuration. RANDALL and LEHMAN[20] have shown betaprodine to be approximately six times as active as alphaprodine in rats. JANSSEN,[5] working with mice, reports a similar potency ratio. The N-2′-phenylethyl analogues prepared in this present work exhibit parallel differences in activities.

Table VI. Effect of 4-aryl substitution in type A isomers



R	R^1	Analgesic activity (morphine = 100)				
		$R^2 \equiv C_6H_5$	$R^2 = o\text{-}CH_3C_6H_4$	$R^2 = m\text{-}CH_3C_6H_4$	$R^2 = p\text{-}CH_3C_6H_4$	$R^2 = o\text{-}OCH_3C_6H_4$
CH_3	OH	—	20	<20	<15	<20
$(CH_2)_2C_6H_5$	,,	70	77	80	97	46
CH_3	$OCOCH_3$	—	75	<20	30	30
$(CH_2)_2C_6H_5$	,,	385	1,325	179	88	407
CH_3	$OCOC_2H_5$	200	85	50	150	—
$(CH_2)_4C_6H_5$	,,	430	259	39	17	—

Thus *cis*-N-2′-phenylethyl-3-methyl-4-phenyl-4-propionoxypiperidine is almost five times as active as the *trans*-isomer. The configurational identity of the more active isomers is consistent with the proposals advanced by BECKETT and CASY[3] for the structural requirements of analgesics and the analgesic receptor site.

The 4-acyloxy group. In unsubstituted reversed esters of pethidine, the propionoxy esters represent the most active compounds. Similarly, in the case of esters prepared from 4-aryl analogues of the prodine alcohols, the propionoxy ester is invariably superior in activity to the acetoxy ester.[5] However, the reverse is found with the corresponding N-2′-phenylethyl compounds, the acetoxy esters being the more potent (see Table IV, and the 3-ethyl compounds of Table V).

Experimental * †

N-Di-(2-carbethoxyethyl)-2′-phenylethylamine. Ethyl acrylate (300 g) was added with stirring to 2-phenylethylamine (121 g) in dry ethanol (200 ml) and the mixture refluxed for 48 h. The product was fractionally distilled under reduced pressure to give N-di-(2-carbethoxyethyl)-2′-phenylethylamine (303 g) as a colourless oil, b.p. 166–168° (0·3 mm), n_D^{20} 1·4986. (Calcd. for $C_{18}H_{27}O_4N$: equiv., 321. Found: equiv., 320; THAYER AND MCELVAIN[21] give b.p. 190–193° (2 mm), n_D^{20} 1·4990.)

N-2′-phenylethyl-4-piperidone ethylketal. N-Di-(2-carbethoxyethyl)-2′-phenylethylamine (70 g) was added to a stirred suspension of bird shot sodium (10·8 g) in xylene (250 ml) and the mixture, protected from moisture, warmed to 50° to initiate the reaction. A further quantity of base was then added drop-wise at a rate sufficient to maintain the reaction. Stirring was continued for 3 h after addition of the base, the mixture cooled, and water (250 ml) added drop-wise. The aqueous phase was separated, washed with ether (2 × 100 ml), and acidified with concentrated hydrochloric acid (congo red). The solution was saturated with anhydrous potassium carbonate and the yellow oil which separated extracted with ether (600 ml). After drying (K_2CO_3), the ether was evaporated to give crude N-2′-phenylethyl-3-carbethoxy-4-piperidone (103 g). (Found: equiv., 282; calcd. for $C_{16}H_{21}O_3N$ equiv., 275.) The ketone was refluxed with aqueous 20 per cent hydrochloric acid (450 ml) for 3·5 h (negative reaction with ferric chloride). The product was evaporated to dryness under reduced pressure, the free base liberated with aqueous 25 per cent sodium hydroxide and extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue treated with excess of alcoholic 10 per cent hydrochloric acid. The crystals (42 g) which separated were collected, the free base liberated with aqueous ammonia and extracted with ether. The ether was dried (Na_2SO_4) and the ether evaporated to give *N-2′-phenylethyl-4-piperidone ethylketal* (35 g) as a pale yellow oil which could not be distilled. Found: equiv., 279; calcd. for

* Melting points are uncorrected.

† Analyses are by Mr. G. S. Crouch, School of Pharmacy, University of London; equivalent weights of bases and salts were determined by titration in non-aqueous media.

$C_{17}H_{27}O_2N$ equiv., 277). It gave a *hydrochloride*, needles from ethanol, m.p. 178–179° dec.

Anal. Calcd. for $C_{17}H_{23}O_2NCl$: C, 65·0; H, 9·0; N, 4·8; equiv., 314. Found: C, 64·3; H, 8·9; N, 4·8; equiv., 317. The ketal gave a *picrate*, needles from ethanol, m.p. 136–137° dec.

Anal. Calcd. for $C_{23}H_{32}O_9N_4$: C, 54·5: H, 6·0; N, 11·1; OC_2H_5, 17·8; equiv., 506. Found: C, 54·3; H, 6·0; N, 11·4; OC_2H_5, 17·5; equiv., 506.

N-2′-phenylethyl-4-piperidone. A mixture of N-2′-phenylethyl-4-piperidone ethylketal (20 g) and dilute aqueous hydrochloric acid (150 ml) was refluxed for 2 h, cooled and washed with ether. The free base was liberated with aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue (13·0 g) crystallized from light petroleum (b.p. 80–100°) to give *N-2′-phenylethyl-4-piperidone* (12·1 g), needles, m.p. 60·5–61·5°.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 76·9; H, 8·4; N, 6·9; equiv., 203. Found: C, 76·3; H, 8·15; N, 7·0; equiv., 204.

*2-Carbomethoxy-*n*-propyl-2′-phenylethylamine.* A solution of methyl methacrylate (226·5 g) in dry methanol (100 ml) was added to 2-phenylethylamine (180 g) and the mixture left for 42 days at room temperature. The product was fractionally distilled under reduced pressure to give (*2-carbomethoxy-*n*-propyl*)-*2′-phenylethylamine* (265·0 g) as a colourless oil, b.p. 116–118° (0·6 mm). (Found: equiv., 225. Calcd. for $C_{13}H_{19}O_2N$ equiv., 221.) It gave a picrate, yellow prisms from ethanol, m.p. 96·5°.

Anal. Calcd. for $C_{19}H_{22}O_9N_4$: C, 50·7; H, 4·9; equiv., 450. Found: C, 51·0; H, 5·2; equiv., 451.

(*2-Carbomethoxyethyl*) - (*2′-carbomethoxy-*n*-propyl*) - *phenylethylamine.* A mixture of (2-carbomethoxy-*n*-propyl)-phenylethylamine (185 g) and methyl acrylate (147 g) was refluxed for 48 h. The product was fractionally distilled under reduced pressure to give (*2-carbomethoxyethyl*)-(*2′-carbomethoxy-*n*-propyl*)-*phenylethylamine* (148·0 g) as a colourless oil, b.p. 155–157° (0·25 mm), n_D^{20} 1·4892.

Anal. Calcd. for $C_{17}H_{25}O_4N$: C, 66·4; H, 8·2; N, 4·6; equiv., 307. Found: C, 66·0; H, 8·1; N, 4·65; equiv., 303·5.

N-2′-Phenylethyl-3-methyl-4-piperidone. (2-Carbomethoxy-*n*-

propyl)-phenylethylamine (70 g) was added to a stirred suspension of bird shot sodium (11·3 g) in xylene (250 ml) and the mixture, protected from moisture, warmed at 60° to start the reaction. A further quantity of the tertiary amine (80 g) was then added dropwise at a rate sufficient to maintain the reaction. The mixture was refluxed for 2 h after addition of the base, the product cooled and added to water (300 ml). The aqueous phase was separated, washed with ether (3 × 100 ml), and acidified with concentrated hydrochloric acid (congo red). The product was saturated with anhydrous potassium carbonate and the yellow oil which separated was extracted with ether (4 × 150 ml). After drying (Na_2SO_4), the ether was evaporated to give a viscous, amber-coloured oil (80 g) which was refluxed for 1 h with aqueous 20 per cent hydrochloric acid (350 ml) (negative reaction with ferric chloride). The product was evaporated to dryness under reduced pressure, the residue dissolved in the minimum quantity of hot alcohol and ether added to the warm solution until a faint permanent cloudiness was apparent. The crystals which separated were collected, the free base liberated with aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue distilled under reduced pressure to give *N-2'-phenylethyl-3-methyl-4-piperidone* (34·9 g), b.p. 123–125° (0·3 mm), n_D^{19} 1·5309. (Found: equiv., 218. Calcd. for $C_{14}H_{19}ON$ equiv., 217.) It gave a *picrate*, yellow needles from ethanol, m.p. 169·5–170·5° dec.

Anal. Calcd. for $C_{20}H_{22}O_8N_4$: C, 53·8; H, 5·0; N, 12·5; equiv., 446. Found: C, 53·7; H, 5·1; N, 12·0; equiv., 445.

(*2-Carbethoxy*-n-*butyl*)-*phenylethylamine.* Ethyl 2-ethylacrylate (b.p. 138°; Mannich and Ritsert give b.p. 138°) (143 g) in alcohol (70 ml) was added to 2-phenylethylamine (90 g) and the mixture left for 50 days at room temperature. The product was fractionally distilled under reduced pressure to give (*2-carbethoxy*-n-*butyl*)-*phenylethylamine*) (131·0 g) as a colourless oil, b.p. 123–125° (0·3 mm) n_D^{20} 1·4947.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72·2; H, 9·3; N, 5·6; equiv., 249. Found: C, 72·2; H, 9·1; N, 5·8; equiv., 249.

(*2-Carbethoxyethyl*)-(*2'-carbethoxy*-n-*butyl*)-*phenylethylamine.* A mixture of (2-carbethoxy-*n*-butyl)-phenylethylamine (125·0 g) and ethyl acrylate (150 g) was refluxed for 48 h. The product

was fractionally distilled under reduced pressure *to give* (2-*carbethoxyethyl*)-(2′-*carbethoxy*-n-*butyl*)-*phenylethylamine* (70 g) as a colourless oil, b.p. 168–170° (0·2 mm), n_D^{20} 1·4871.

Anal. Calcd. for $C_{20}H_{31}O_4N$: C, 68·75; H, 8·9; N, 4·0; equiv., 347. Found: C, 69·6; H, 8·9; N, 4·1; equiv., 347.

N-2′-*phenylethyl*-3-*ethyl*-4-*piperidone.* (2-Carbethoxy-*n*-butyl)-(2′-carbethoxyethyl)-phenylethylamine (60 g) was added to a stirred suspension of bird shot sodium (8·0 g) in xylene (220 ml) and the mixture heated to 60° to start the reaction. A further quantity of base (60 g) was then added drop-wise at a rate just sufficient to maintain the reaction. After all the base had been added the mixture was heated at 70° for 3 h, the product cooled and added to ice water (300 ml). The xylene phase was evaporated almost to dryness under reduced pressure and the residue acidified with aqueous 20 per cent hydrochloric acid (40 ml). The solution was extracted with ether (2 × 100 ml), to remove traces of xylene, a further quantity of aqueous 20 per cent hydrochloric acid (240 ml) added and the solution heated on a steam bath for 7 h (negative ferric chloride test). The product was evaporated to dryness under reduced pressure, the residue made alkaline with strong aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue distilled under reduced pressure to give *N*-2′-*phenylethyl*-3-*ethyl*-4-*piperidone* (46·2 g) as a colourless oil, b.p. 138° (0·25 mm), n_D^{19} 1·5271. Found: equiv., 235. Calcd. for $C_{15}H_{21}ON$ equiv., 231.) It gave a *picrate*, yellow needles from acetone, m.p. 176–178° dec.

Anal. Calcd. for $C_{21}H_{24}O_8N_4$: C, 54·8; H, 5·3; N, 12·2; equiv., 460. Found: C, 55·6; H, 5·5; N, 12·4; equiv., 465.

N-2′-*Phenylethyl*-3-*carbethoxy*-3′-*allyl*-4-*piperidone.* N-2′-Phenylethyl-3-carbethoxy-4-piperidone (103 g) prepared as previously described from 2,2′(di-carbethoxyethyl)-phenylethylamine (150 g) in dry benzene (100 ml) was added drop-wise to a vigorously stirred suspension of sodium hydride (9·17 g) in dry benzene (250 ml). When the initial reaction had subsided the mixture was refluxed for 4 h, cooled to room temperature and allyldimethylanilinium bromide (92·5 g) added. The mixture was stirred and refluxed for 48 h, cooled and added to water (250 ml). The benzene layer was separated, washed with water (4 × 100 ml) and dried (K_2CO_3). The solvent was evaporated and the residue

fractionally distilled under reduced pressure to give dimethylaniline (42 g), b.p. 90–92° (25 mm) (McElvain and Barnett give b.p. 88–90° (25 mm)) and *N-2′-phenylethyl-3-allyl-3′-carbethoxy-4-piperidone* (39·5 g) as a pale yellow oil, b.p. 100° (0·7 mm), 190° (1·7 mm). (Found: equiv., 313. Calcd. for $C_{18}H_{25}O_3N$ equiv., 304.) It gave a *hydrochloride*, needles from ether-ethanol, m.p. 180–181°.

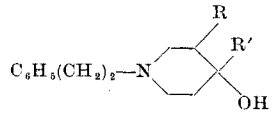
Anal. Calcd. for $C_{18}H_{26}O_3NCl$: C, 63·6; H, 7·7; N, 4·1; equiv., 340. Found: C, 64·8; H, 7·55; N, 3·9; equiv., 346.

N-2′-Phenylethyl-3-n-propyl-4-piperidone. A solution of N-2′-phenylethyl-3-carbethoxy-3′-allyl-4-piperidone hydrochloride (34·0 g) in absolute ethanol (300 ml) was shaken with hydrogen at room temperature and pressure in the presence of 5 per cent palladized charcoal (5·0 g). After 20 min the theoretical amount of hydrogen was absorbed, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residual yellow oil (34·0 g) was dissolved in 20 per cent hydrochloric acid (120 ml), the solution refluxed for 24 h, cooled, and evaporated to dryness under reduced pressure. The residue was slurried with water (25 c.c.) and excess of anhydrous potassium carbonate and extracted with ether (4 × 50 ml). After drying (Na_2SO_4), the ether was evaporated and the residue (16·5 g) distilled under reduced pressure to give *N-2′-phenylethyl-3-n-propyl-4-piperidone* (12·0 g) as a colourless oil, b.p. 140–144° (0·5 mm), n_D^{20} 1·5264. (Found: equiv., 240. Calcd. for $C_{16}H_{23}ON$ equiv., 245.) It gave a *picrate*, yellow needles from ethanol, m.p. 153–154°.

Anal. Calcd. for $C_{22}H_{26}O_8N_4$: C, 55·65; H, 5·5; N, 11·8; equiv., 474. Found: C, 55·0; H, 5·55; N, 11·8., equiv., 464.

General method for the preparation of tertiary alcohols (II). The piperidone (I) (1 mole) was added drop-wise with stirring to a cooled solution of a lithium aryl in ether prepared from lithium (2·4 atoms) and an aryl bromide (1·2 mole). The mixture was stirred for 2 h at room temperature and then added to crushed ice and excess of glacial acetic acid. The solid which separated was washed with ether, the base liberated with strong aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the solvent was removed and the residue recrystallized from hydrocarbon solvents such as *n*-hexane and petroleum ether mixtures (see Table VII).

Table VII. N-2′-Phenylethyl-4-aryl-4-piperidinols



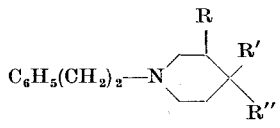
R	R′	m.p.	Analysis calc. C	H	N	equiv.	found C	H	N	equiv.
H	C_6H_5	101–103°	81·0	8·2	5·0	281	80·5	8·3	5·1	283
H	*m*-$CH_3C_6H_4$	112·5–113°	81·3	8·5	4·7	295	81·0	8·4	4·6	299
CH_3	C_6H_5	105–106°	81·3	8·5	4·7	295	80·5	8·5	4·9	293
CH_3	*o*-$CH_3C_6H_4$	84·5°	81·5	8·8	4·5	309	80·3	9·0	4·45	315
CH_3	*m*-$CH_3C_6H_4$	85–86°	81·5	8·8	4·5	309	81·5	8·6	4·6	314
CH_3	*p*-$CH_3C_6H_4$	107°	81·5	8·8	4·5	309	81·0	8·5	4·4	308
CH_3	*o*-$OCH_3C_6H_4$	249–250°*	62·0	6·95	3·45	406	61·8	7·1	3·4	408
CH_3	2,6-$(CH_3)_2C_6H_3$	71–72°	81·7	9·0	4·3	323	81·6	9·0	4·3	327
C_2H_5	*o*-$CH_3C_6H_4$	84·5–85·5	81·7	9·0	4·3	323	82·0	8·8	4·4	324
n-C_3H_7	C_6H_5	97·5–98°	81·7	9·0	4·3	323	80·7	9·1	4·2	327

* Hydrobromide.

N-2′-Phenylethyl-4-phenyl-4-piperidinol. A mixture of 2-phenylethylamine (121 g), an equivalent amount of concentrated hydrochloric acid (93 ml), α-methylstyrene (118 g) and aqueous 37 per cent formaldehyde (200 g) was stirred and heated at 80° for 3 h. The resultant clear solution was refluxed for 5 h and left at room temperature overnight. The product, consisting of two layers, was washed with benzene (3 × 100 ml), made alkaline with aqueous 50 per cent sodium hydroxide solution and extracted with benzene (3 × 100 ml). After drying (K_2CO_3). approximately 200 ml of solvent was evaporated and the residue diluted with *n*-hexane until a faint permanent cloudiness was obtained. The crystals which separated on cooling were collected and recrystallized from light petroleum (b.p. 80–100°) to give *N-2′-phenylethyl-4-phenyl-4-piperidinol* (36·7 g), needles, m.p. 102–103° undepressed on admixture with alcohol prepared by the general method. (Found: equiv., 284. Calcd. for $C_{19}H_{23}ON$ equiv., 281.)

Esterification of tertiary alcohols (general method). A mixture of the tertiary alcohol (2 g), an acid anhydride (3 ml) and pyridine (3 ml) was refluxed for 3 h and the solvents removed under reduced pressure. The residue was converted, in most cases, into a hydrohalide and recrystallized from ether-ethanol (see Table VIII).

Table VIII. N-2′-Phenylethyl-4-acyloxy-4-arylpiperidines



R	R′	R″	form	m.p.	Analysis							
					calc.				found			
					C	H	N	equiv.	C	H	N	equiv.
H	$OCOCH_3$	C_6H_5	HCl	214–215·5°	70·05	7·3	3·9	360	70·1	7·5	3·8	364
H	$OCOC_2H_5$	C_6H_5	HCl	201–202°	70·65	7·55	3·75	374	70·7	7·7	3·7	375
H	$OCOC_3H_7$-n	C_6H_5	HCl	195·5°	71·2	7·8	3·6	388	71·8	7·9	3·6	385
H	$OCOCH_3$	m-$CH_3C_6H_4$	HCl	212°	70·65	7·55	3·75	374	70·7	7·65	3·6	374
CH_3	$OCOCH_3$	C_6H_5	HCl	214–215°	70·65	7·55	3·75	374	70·3	7·7	3·8	376
CH_3	$OCOC_2H_5$	C_6H_5	HCl (A)	179·5–180·5°	71·2	7·8	3·6	388	71·1	8·1	3·6	390
CH_3	$OCOC_2H_5$	C_6H_5	HCl (B)	203·5–204·5°	71·2	7·8	3·6	388	71·4	7·7	3·5	389
CH_3	$OCOCH_3$	o-$CH_3C_6H_4$	Base	102–102·5°	78·6	8·3	4·0	352	79·2	8·3	4·1	354
CH_3	$OCOCH_3$	o-$CH_3C_6H_4$	$HClH_2O$	185–186°	68·0	7·9	3·45	406	68·2	8·0	3·2	398
CH_3	$OCOC_2H_5$	o-$CH_3C_6H_4$	HCl	168°	71·7	8·0	3·5	402	71·5	7·9	3·3	403
CH_3	$OCOCH_3$	m-$CH_3C_6H_4$	HCl	207·5°	71·2	7·8	3·6	388	70·0	7·95	3·6	395
CH_3	$OCOC_2H_5$	m-$CH_3C_6H_4$	HCl	185–185·5°	71·7	8·0	3·5	402	71·1	8·05	3·5	405
CH_3	$OCOCH_3$	p-$CH_3C_6H_4$	HCl	220–221° dec.	71·2	7·8	3·6	388	70·6	7·7	3·7	395
CH_3	$OCOC_2H_5$	p-$CH_3C_6H_4$	HCl	176–177°	71·7	8·0	3·5	402	71·3	8·0	3·4	406
CH_3	$OCOCH_3$	o-$OCH_3C_6H_4$	$HClC_2H_6O$*	133°†	66·7	8·1	3·1	450	66·0	7·8	3·25	445
C_2H_5	$OCOCH_3$	o-$CH_3C_6H_4$	$HClC_2H_6O$*	145°‡	69·7	8·55	3·1	448	70·4	8·5	3·4	448
C_2H_5	$OCOC_2H_5$	o-$CH_3C_6H_4$	$HClC_2H_6O$*	148·5°§	70·2	8·7	3·0	462	71·3	8·7	3·0	464
n-C_3H_7	$OCOCH_3$	C_6H_5	HCl	158·5–159·5°	71·7	8·0	3·5	402	70·8	8·1	3·5	398

* 1 mole ethanol of crystallization. † Sinters at 123°. ‡ Sinters at 98°. § Sinters at 127°.

Infra-red absorption measurements. Determinations were carried out in carbon disulphide solution, concentration range 0·3 to 0·9 per cent w/v. Calibration was accurate to ± 3 cm^{-1} over the region 650 to 2,000 cm^{-1}, and ± 5 cm^{-1} over the region 2,000 to 5,000 cm^{-1}. Infra-red spectra were measured on a Hilger H.800 double-beam automatic recording spectrophotometer fitted with sodium chloride optics, run in cells of path length 0·75 mm and compensated with carbon disulphide.

Summary. The stereochemistry of addition of lithium aryls to certain N-methyl and N-2′-phenylethyl-4-piperidones is reported. Those stereoisomers present as the major proportion of the respective stereoisomeric mixtures (type A isomers) have similar infra-red absorption characteristics which differ from those formed in minor amount (type B isomers). The configurations *trans* and *cis* methyl/aryl are allocated to type A and type B isomers respectively on the basis of considerations of the stereochemistry of addition to ketones, interpretations of infra-red absorption data and hydrolysis studies. The configuration of type A isomers is confirmed by an assessment of steric factors in N-2′-phenylethyl-4-(2,6-dimethylphenyl)-3-methyl-4-piperidinol. The analgesic activities in mice of various imino-alcohols and esters are given and certain structure-activity relationships discussed.

Acknowledgements. The authors thank Smith, Kline and French laboratories for making available an infra-red spectrophotometer, and Mr. T. H. E. Watts for carrying out the measurements. They also thank Mr. J. Walker for carrying out the hydrolysis experiments.

(*Received 11 November, 1958.*)

References

1 Ziering, A., Motchane, A. and Lee, J., *J. org. Chem.*, **22**, 1521 (1957)
2 Ziering, A. and Lee, J., *J. org. Chem.*, **12**, 911 (1947)
3 Beckett, A. H. and Casy, A. F. *J. Pharm., Lond.*, **6**, 986 (1954)
4 Beckett, A. H. and Walker, J. *J. Pharm., Lond.*, **7**, 1039 (1955)
5 Beckett, A. H., Casy, A. F., Kirk, G. and Walker, J. *J. Pharm., Lond.*, **9**, 939 (1957)
6 Bolyard, N. W. and McElvain, S. M. *J. Amer. chem. Soc.*, **51**, 922 (1929)
7 Brooks, P. and Walker, J. *J. chem. Soc.*, 3173 (1957)
8 Howton, D. R. *J. org. Chem.*, **10**, 277 (1945)
9 Nazarov, I. N., Sokolov, D. V. and Rakcheeva, V. N. *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 80 (1954)
10 McElvain, S. M., Dickinson, W. B. and Athey, R. J. *J. Amer. chem. Soc.*, **76**, 5625 (1954)

[11] SCHMIDLE, C. J. and MANSFIELD, R. C. *J. Amer. chem. Soc.*, **77**, 5698 (1955)
[12] ROYALS, E. E. *Advanced Organic Chemistry*, p. 813, 1958. London; Constable
[13] MANNICH, C. and RITSERT, K. *Chem. Ber.*, **57**, 1116 (1924)
[14] MCELVAIN, S. M. and BARNETT, M. D. *J. Amer. chem. Soc.*, **78**, 3140 (1956)
[15] BECKETT, A. H., HARPER, N. J. and WATTS, T. H. E. To be published
[16] JANSSEN, P. A. J. and JAGENEAU, A. H. M. *J. Pharm., Lond.*, **9**, 381 (1957)
[17] BECKETT, A. H. and CASY, A. F. *Bull. Narcot.*, **9**, 37 (1957)
[18] FOSTER, R. H. K. and CARMAN, A. J. *J. Pharmacol.*, **91**, 195 (1947)
[19] ELPERN, B., WETTERAU, W., CARABATEAS, P. and GRUMBACH, L. *J. Amer. chem. Soc.*, **80**, 4916 (1958)
[20] RANDALL, L. O. and LEHMAN, G. *J. Pharmacol.*, **93**, 314 (1948)
[21] THAYER, J. R. and MCELVAIN, S. M. *J. Amer. chem. Soc.*, **49**, 2862 (1927)
[22] ARCHER, S. Private communication of paper presented at the 133rd Meeting of the A.C.S., San Francisco, 1957