Journal of Medicinal and Pharmaceutical Chemistry

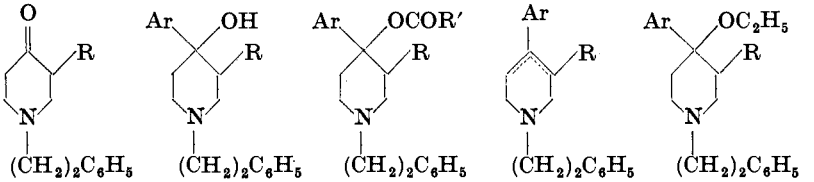
VOL. 2, No. 3 (1960)

Some *N*-Phenethyl-4-Heteroaryl-4-Piperidinols and Related Compounds

A. H. BECKETT, A. F. CASY and P. M. PHILLIPS, *School of Pharmacy, Chelsea College of Science and Technology London, S.W.3*

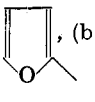
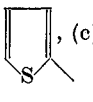
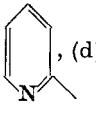
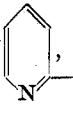
In recent papers, Beckett and co-workers have described structure–activity studies in analgesics related to reversed esters of pethidine.[1,12] This paper reports an extension of these studies with respect to the effect of replacing the 4-phenyl group by other aromatic groups, notably heterocyclic groups.

The synthetic route employed involved treatment of a *N*-2′-phenethyl-4-piperidone (I) with a lithium aryl (one exception) and esterification of the resultant *tert.* alcohol with an acid anhydride–pyridine mixture.



(I) (II) (III) (IV) (V)

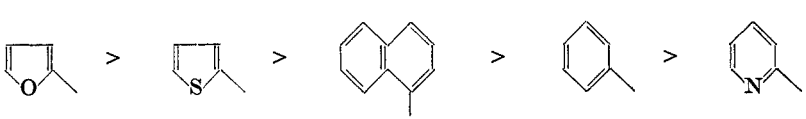
R = H or CH_3

Ar = (a)  , (b)  , (c)  , (d) $C_6H_5CH_2$—, (e)  , (f) 1—$C_{10}H_7$

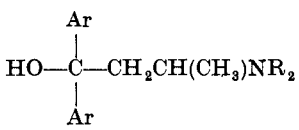
The lithium aryls used to prepare the alcohols (II)a, b and e were prepared by metallation of the appropriate aryl hydrocarbon with lithium phenyl; lithium 1-naphthyl [for (II)f; R = H and CH_3] was obtained directly from 1-bromonaphthalene and

lithium 2-pyridyl [for (II)c] by interchange between lithium *n*-butyl and 2-bromopyridine. A Grignard reagent was employed for the benzyl alcohol (II)d. Esterification by the acid anhydride–pyridine method proceeded normally only in the cases of alcohols (IIc) ($R = CH_3$) and (IId) ($R = H$); the alcohols (IIa) ($R = CH_3$), (IIb) ($R = CH_3$), (IId) ($R = CH_3$), (IIe) ($R = CH_3$) and (IIf) ($R = H$ and CH_3) gave eliminated products (IV) under the same conditions. Esters of 4-piperidinols have been prepared by direct acylation of Grignard reagent–ketone complexes and corresponding lithium phenyls.[2] This process was applied in the above cases in which elimination had been encountered; the crude esters were prepared in this way but difficulties were met when isolation as hydrochloride salts was attempted. Thus, the crude product derived by direct acylation of the lithium furyl-ketone (I; $R = CH_3$) complex with propionic anhydride had an equivalent weight consistent with that of the ester (IIIa; $R = CH_3$, $R' = C_2H_5$) and showed the characteristic carbonyl stretching frequency (1,738 cm^{-1}). Treatment of the base with excess of ethanolic hydrochloric acid gave, however, the ethyl *ether* (Va; $R = CH_3$) hydrochloride rather than the expected ester salt. This formulation is based upon analytical data, the absence of absorption frequencies due to the ester group, and the fact that both acetic and propionic anhydrides gave the same product which was unchanged following attempted alkaline hydrolysis. The products derived in the same way from lithium 2-thienyl and 1-naphthyl proved also to be ethyl ether salts. It is significant that those alcohols giving elimination products on treatment with an acid anhydride–pyridine mixture form esters that are readily transformed into ethers; it is shown below that these results may be interpreted in terms of the electronic character of the 4-aryl substituent.

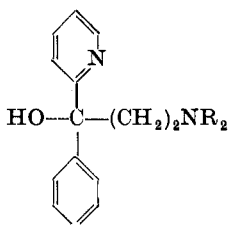
Elimination reactions, both acid and base catalysed, are assisted by electron releasing and opposed by electron attracting groups. The order of electron release of a series of aryl substituents is shown below:[3]



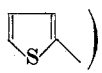
The high degree of electron releasing properties of the 2-furyl, 2-thienyl and 1-naphthyl groups results in olefin formation rather than esterification following acid anhydride–pyridine treatment of the corresponding alcohols. The 2-pyridyl group, in contrast, is electron withdrawing and favours esterification rather than elimination under the above conditions. The result of the electrophilic character of the 2-pyridyl group is further emphasized by the resistance of the alcohol (IIc; $R = CH_3$) to conditions of dehydration successful with the corresponding 4-phenyl alcohol. Similar examples which illustrate differences in ease of dehydration dependent upon differences in the electrophilic character of aryl groups have been reported. Thus, while 1,1-diphenylalcohols (VI; $Ar = C_6H_5$) are dehydrated by a boiling mixture



(VI)

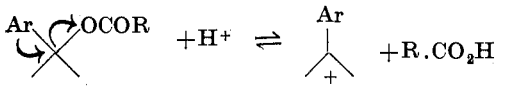


(VII)

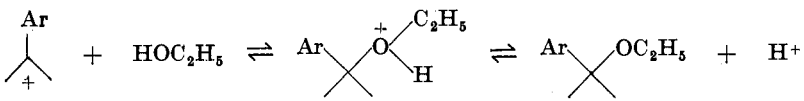
of acetic and hydrochloric acids, the pyridyl alcohol (VII) is unchanged.[4] On the other hand, analogous 1,1-dithienylalcohols (VI; Ar = ) may be converted into olefins by far milder conditions, e.g. by passage of hydrogen chloride through a cold solution of the base in chloroform.[5]

The production of ethers from alcohols in acidic media is probably due to an acid-catalysed process involving carbonium ions.[6] Formation of the latter occurs most readily from *tert.* alcohols and is assisted by electron releasing substituents. These principles explain the conversion of triphenylcarbinol into its methyl ether by boiling methanol,[7] diphenylcarbinol into bisdiphenylmethylether by boiling water[8] and 2-furyldiphenylcarbinol into bis-2-furyldiphenylmethylether by boiling acetic acid.[9] The ethers

encountered in the present work must be formed directly from the esters that result on acylation of the lithium aryl-ketone complexes, since the alcohols [(II)a, b and f] themselves give normal salts on treatment with excess of ethanolic hydrochloric acid. The mechanism of ether formation is therefore proposed as follows:



(VIII)



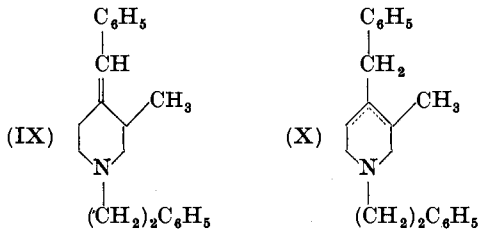
The postulated carbonium ion (VIII) is tertiary and its formation will be assisted by the electron releasing properties of the 2-furyl, 2-thienyl and 1-naphthyl groups. Evidence for acid catalysis (and also for intermediate ester formation) is provided by the isolation of the *ester* (IIIb; R = R′ = CH_3) hydrochloride following careful neutralization of the base with ethanolic hydrochloric acid.

The alcohols (IId; R = H) and (IId; R = CH_3) are esterified and eliminated respectively on treatment with an acid anhydride–pyridine mixture. This difference may be attributed to a fine balance of electronic factors, the additional inductive and hyperconjugative contributions of the 3-methyl group favouring elimination in the latter case. The elimination occurring with the corresponding picolyl alcohol (IIe; R = CH_3) is interpreted similarly.

The olefin derived from the benzyl alcohol (IId; R = CH_3) may be formulated in two ways (IX) and (X), the latter being the more likely on account of the known preference for an endocyclic over an exocyclic bond.[10]

A similar example of formation of a non-conjugated isomer has been given by Eliel, McCoy and Price[11] in the dehydration of 1-benzylcyclopentanol. Evidence for structure (X), derived from ultraviolet absorption measurements (the spectrum is benzenoid

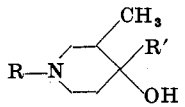
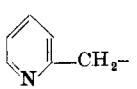
rather than styrenoid) is equivocal since models show the conjugated form (IX) to be non-planar.



The addition of lithium aryls to 3-substituted-4-piperidones can give two diastereoisomeric alcohols which differ in the *cis-trans* relationship of the 3-alkyl and 4-aryl groups. It has been shown,[12] from arguments based upon the stereochemistry of addition to ketones, that the *trans* isomer should be formed in major amounts and that the preponderance of this isomer should increase with increasing size of the aryl addendum in the vicinity of the carbonyl reaction centre. Isomeric ratios obtained experimentally accord with these conclusions.[1,12] Thus, while treatment of *N*-methyl and *N*-phenethyl-3-methyl-4-piperidone with lithium phenyl, *m*- and *p*-tolyl give isomeric mixtures in which one isomer predominates, lithium *o*-tolyl, *o*-methoxyphenyl and 2,6-dimethylphenyl give reaction mixtures which comprise, virtually, one pure isomer. Addition reactions of the present work are comparable to the latter examples since the size of the aryl addendum with respect to the area adjacent to the C–Li bond is large. With the heterocyclic compounds this steric factor is probably considerably increased by solvation of the heteroatoms. It was to be expected, therefore, that the proportions of *cis* isomers in the reaction mixtures would be small. In fact, in all cases studied, the alcohols (II; R = CH_3) were isolated in single isomeric forms which, from the above considerations, are assigned *trans* (CH_3/Ar) configurations. *Trans* isomers of certain 4-phenyl and 4-substituted phenyl-4-piperidinols show a consistent pattern in the 990–1,010 cm^{-1} and 1,350–1,385 cm^{-1} regions of their infrared absorption spectra which is distinct from that found with *cis* isomers.[1,12] It does not necessarily follow that analogous heterocyclic alcohols should fit these patterns since absorption

frequencies may be disturbed, in varying degree, by the electrical characters of the heteroatoms. Thus, whereas the furyl and thienyl alcohols [(II)a and b; R = CH_3] follow the *trans* pattern

Table I. Characteristics of infrared absorption of *N*-substituted 4-aryl-3-methyl-4-piperidinols[a]

 R	R′	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	C_6H_5	*trans*	1,000	1,355	1,383
	o-$CH_3.C_6H_4$		1,001	1,352	1,376
	m-$CH_3.C_6H_4$		1,000	1,355	1,383
	p-$CH_3.C_6H_4$		1,002	1,354	1,382
	C_6H_5	*cis*	no peak	1,372	1,380
	m-$CH_3.C_6H_4$		no peak	1,376	1,383
	p-$CH_3.C_6H_4$		no peak	1,372	1,383
$(CH_2)_2C_6H_5$	C_6H_5	*trans*	1,004	1,351	1,376
	m-$CH_3.C_6H_4$		1,007	1,353	1,376
	p-$CH_3.C_6H_4$		1,003	1,354	1,377
	1-$C_{10}H_7$		998	1,353	1,374
			1,004	1,360	1,385
			1,000	1,360	1,380
			1,006	1,375	1,389
			1,000	1,375	1,388
	$C_6H_5CH_2$-		1,004	1,370	—

[a] Examples of 4-phenyl alcohols have been included to illustrate the two patterns

in all respects, the pyridyl and picolyl alcohols [(II)c and e; R = CH_3] conform only in the 990–1,010 cm^{-1} region (see Table I). It may be of significance, in this respect, that the free O–H

stretching frequencies of the latter alcohols are low (3,395 and 3,365 cm^{-1} respectively) indicative of hydrogen bonding, whereas those of the furyl, thienyl and phenyl alcohols are normal. The methylene group between the aryl and piperidine rings represents, in the picolyl alcohol (IIe; R = CH_3), a further difference from the alcohols for which the above pattern has been established. This structural difference is likewise present in the benzyl alcohol (IId; R = CH_3) which also shows an abnormal *trans* pattern. The naphthyl alcohol (IIf; R = CH_3) most closely resembles the phenyl alcohols and follows the *trans* pattern in both regions.

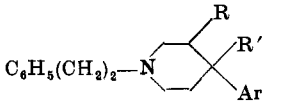
The configurations of the ethers [(V), a, b and d; R = CH_3] are not dependent upon the course of carbonyl addition since it is postulated that they derive from carbonium ions. Barton, Campos-Neves and Cookson[13] have shown the stereochemical fate of *tert.*-carbonium ions in cyclohexane systems to be formation of the more stable epimer in major yield. On these grounds, the configurations of the above ethers will be *trans* (CH_3/Ar) since such isomers, with the bulky aryl groups equatorial, will be thermodynamically more stable than the corresponding *cis* isomers.

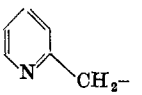
Pharmacological Results and Discussion

The analgesic activities of tertiary alcohols and related compounds reported in this paper were determined in mice by subcutaneous injection, using an adaptation of the hot plate method as described by Janssen and Jageneau.[14] Our thanks are due to Dr. Paul Janssen for carrying out the pharmacological tests. The activities, calculated from ED_{50} values and expressed relative to morphine for convenience, are recorded in Table II, together with those of corresponding 4-phenyl analogues. However, the hot plate method does not distinguish between morphine-type analgesics and other compounds which increase reaction time, and this limitation must be borne in mind in any discussion of structure–action relationships.

One approach to drug design involves isosteric replacement of a group in a compound with desired biological effects. Isosteres may be defined as atoms, ions or molecules in which the peripheral layer of electrons is considered to be identical,[15] e.g. phenyl, pyridyl, furyl and thienyl groups. Isosteric replacement of

Table II. Analgesic activities of *N*-phenethyl-4-aryl-4-piperidinols and related compounds



R	R′	Ar	Analgesic activity (morphine = 100)	Analgesic activity (morphine = 100) of 4-phenyl analogue[a]
CH_3[b]	OH		< 30	70
	OH		38	70
	$OCOCH_3$	,,	63	385
	OH		52	70
	$OCOCH_3$	,,	30	385
	$OCOC_2H_5$	,,	44	430
	OH	$1\text{-}C_{10}H_7$	38	70
H	OH	,,	< 30	35
CH_3[b]	,,	$C_6H_5CH_2$	25	70
H	,,	,,	38	35
	$OCOCH_3$	,,	< 30	633
	$OCOC_2H_5$	,,	< 30	346
	OH		14	35
	$OCOCH_3$	,,	114	633
CH_3	Eliminated product (IV)		< 30	≃22[c]
	,,		< 30	≃22[c]

[a] Reference 1 (*trans* Me/Ar configuration where applicable)
[b] *trans* Me/Ar configuration
[c] Reference 27

phenyl has been reported for numerous analgesics, such as pethidine,[16] the seven-membered ring[17] and reversed ester analogues[18] of pethidine and methadone type compounds;[19] in all cases replacement gives compounds of reduced activity (see later for thiambutene, however). The results of isosteric replacements of 4-phenyl in *N*-phenethyl-4-phenyl-4-piperidinols and related compounds presently reported, accord with this general observation.

The reason for the reduction of activity upon isosteric replacement of phenyl in analgesics may derive from the resultant changes in steric and electronic factors. The analgesic drug–receptor contact has been postulated to depend, in part, upon the van der Waals force bonding between the aromatic ring of the drug and a complementary flat portion of the receptor.[20] A change in steric factors, caused by introduction of a bulky group into the flat phenyl ring, may diminish the area of drug–receptor contact and hence result in a less active compound. That the steric requirements of nitrogen, sulphur and oxygen are at least as great as those of a methyl group has been demonstrated by the carbonyl addition studies currently reported. Steric increases of this order are not necessarily detrimental to analgesic properties since certain 4-*o*-tolyesters are highly active.[1] However, when allowance is made for solvation of the heteroatom, the resultant impairment of fit must be much greater than that indicated by the overall covalent bulk of the heteroatom.

Pressman and others[21, 22] have demonstrated the quantitative effect of the relative spatial dimensions of aryl carbon and nitrogen in antibody–antiserum reactions; the large decrease in antibody combining power observed on passing from the phthalate to the pyridine 2,3-dicarboxylate and pyrazine 2,3-dicarboxylate ions was interpreted as resulting from the bulky character of the hydrated heterocyclic ions in solution.

The changes in analgesic properties resulting from replacement of phenyl bear no consistent relationship to the attendant changes in the electronic character of the aryl group and in the stability of the ester function which result. Substitution of phenyl by thienyl and *o*-tolyl both increase electron availability at the ester site, yet the former leads to an activity loss, not necessarily concomittant with the latter change. The qualitative analgesic effect of

replacement by the electron withdrawing group, pyridyl, with resultant stabilization of the ester, is the same as that of the donating groups, furyl and thienyl, which reduce the ester stability. Reduction of analgesic activity upon isosteric replacement is therefore considered to be due to the attendant increases in steric factors.

The high activity of dimethylthiambutene as compared with its diphenyl analogue is an apparent deviation from the effect of isosteric replacement of phenyl generally observed in analgesics.[19] It is considered, however, that the thiambutenes should be compared, in this respect, to methadone, since similar interactions, namely N→S and N→C = O respectively, have been proposed as factors holding the drug molecules in the required conformation for drug–receptor contact.[23] (These constraining forces are absent in the almost analgesically inactive diphenyl analogue of dimethylthiambutene). The relative analgesic properties of methadone and the thiambutenes are then consistent with the disadvantageous effect of isosteric replacement of phenyl in analgesics.

This discussion is relevant only to groups considered to associate with the flat portion of the analgesic receptor site already described,[20] and does not apply, for example, to the isosteric replacements of phenyl reported by Elpern and others[24] respecting the *N*-phenalkyl group of pethidine analogues. The resultant qualitative variation in effects indicates the less rigid steric requirements of the anionic receptor site and may also be due to attendant changes in ease of dealkylation of the basic centre.[25]

Thus certain isosteric replacements of phenyl help to delineate the steric requirements of the flat portion of the analgesic receptor site in the complementary vicinity of the bond linking the aryl group to the rest of the drug molecule.

Experimental*†

N-2′-Phenethyl-4-(2′-furyl)-3-methyl-4-piperidinol and related compounds. A mixture of freshly distilled furan (1·7 g) and lithium phenyl in ether, prepared from lithium (0·43 g) and bromobenzene

* 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.

(4·75 g) was refluxed for 2 h, cooled (ice-bath) and treated with the piperidone (I; R = CH_3) (5·4 g). The product was stirred for 30 min at room temperature and then added to crushed ice and excess of glacial acetic acid. The solid which separated on storage at 5° was washed with ether, the base liberated with aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the solvent was removed to give the crude furyl alcohol (4·2 g) as an oil. It gave a *hydrochloride*, plates from ether–ethanol; m.p. 187–188° (d). after sintering at 92°.

Anal. Calcd. for $C_{18}H_{24}ClNO_2.C_2H_6O$*: C, 65·3; H, 8·2; equiv. wt., 368. Found: C, 65·15; H, 8·2; equiv. wt., 365. A mixture of the crude alcohol (3·1 g), propionic anhydride (4 ml) and pyridine (4 ml) was refluxed for 3 h and the solvents removed under reduced pressure. The residue, converted into the hydrochloride and recrystallized from ether–ethanol, gave *N-2′-phenethyl-4-(2′-furyl)-3-methyltetrahydropyridine* (IVa; R = CH_3) *hydrochloride*, needles, m.p. 204–204·5° (d.).

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71·2; H, 7·25; N, 4·6; equiv. wt., 304. Found: C, 70·6; H, 7·0; N, 4·7; equiv. wt., 307.

The complex formed from the piperidone (I; R = CH_3) (5·4 g) and lithium furyl, prepared as described above, was cooled (ice-bath) and treated with acetic anhydride (3 ml) in benzene. The product was stirred for 30 min at room temperature, added to crushed ice and excess of acetic acid and worked up as before to give the crude furyl ester (IIIa; R = R′ = CH_3) (5·3 g) (Found: equiv. wt., 336. Calcd. for $C_{21}H_{27}NO_3$ equiv. wt., 341). It had a strong absorption peak at 1,738 cm^{-1}, characteristic of an ester carbonyl group. The base, on treatment with excess of ethanolic hydrochloric acid and crystallization from ether–ethanol gave *N-2′-phenethyl-4-ethoxy-4-(2′-furyl)-3-methyl piperidine hydrochloride*, plates, m.p. 181–182° (d.).

Anal. Calcd. for $C_{20}H_{28}ClNO_2$: C, 68·6; H, 8·0; N, 4·0; equiv. wt., 350. Found: C, 68·7; H, 8·25; N, 4·0; equiv. wt., 349.

N-2′-Phenethyl-4-(2′-thienyl)-3-methyl-4-piperidinol and related compounds. The piperidone (I; R = CH_3) (21·7 g) was treated with lithium thienyl, prepared from thiophen (8·4 g), bromobenzene (19 g) and lithium (1·7 g) by the method described for lithium furyl, and the product worked up as before to give the

* 1 mole ethanol of crystallization.

thienyl alcohol (IIb; R = CH_3) (22·5 g), m.p. 91°, after crystallization from a petroleum ether (b.p. 40–60°) acetone mixture.

Anal. Calcd. for $C_{18}H_{23}NOS$: C, 71·8; H, 7·6; N, 4·65; equiv. wt., 301. Found: C, 71·2; H, 7·6; N, 4·6; equiv. wt., 301. Treatment of the alcohol with propionic anhydride and pyridine as described above gave *N-2′-phenethyl-4-(2′-thienyl)-3-methyltetrahydropyridine* (IVb; R = CH_3) *hydrochloride*, m.p. 208–210° (d.).

Anal. Calcd. for $C_{18}H_{22}ClNS$: C, 67·6; H, 6·9; N, 4·4; equiv. wt., 320. Found: C, 68·0; H, 6·7; N, 4·3; equiv. wt., 322.

Direct treatment of the piperidone (I; R = CH_3)-lithium thienyl complex with acetic anhydride, followed by work up as before gave the crude thienyl ester (IIIb; R = R′ = CH_3). The base, on careful neutralization with ethanolic hydrochloric acid, gave *N-2′-phenethyl-4-acetoxy-3-methyl-4-(2′-thienyl)piperidine hydrochloride*, m.p. 213–214° (d.) after crystallization from ether–ethanol.

Anal. Calcd. for $C_{20}H_{26}ClNO_2S$: C, 63·2; H, 6·85; N, 3·7; equiv. wt., 380. Found: C, 63·6; H, 6·9; N, 3·5; equiv. wt., 384. It had a strong adsorption peak at 1,741 cm^{-1}, characteristic of an ester carbonyl group. Treatment of the crude thienyl ester with excess of ethanolic hydrochloric acid gave *N-2′-phenethyl-4-ethoxy-3-methyl-4-(2′-thienyl)piperidine hydrochloride*, m.p. 200–202° (d.) after crystallization from ether–ethanol.

Anal. Calcd. for $C_{20}H_{28}ClNOS$: C, 65·7; H, 7·7; N, 3·8; equiv. wt., 366. Found: C, 66·9; H, 7·9; N, 4·1; equiv. wt., 368.

The ether (Vb; R = CH_3) gave a *picrate*, needles, m.p. 149–150°.

Anal. Calcd. for $C_{26}H_{30}N_4O_8S$: C, 55·9; H, 5·4; N, 10·0, equiv. wt., 558. Found: C, 54·95; H, 5·5; N, 10·0; equiv. wt., 556.

N-2′-Phenethyl-3-methyl-4-(α-naphthyl)-4-piperidinol and related compounds. The piperidone (I; R = CH_3) (15 g) was treated with lithium α-naphthyl, prepared from lithium (1·4 g) and α-bromonaphthalene (21 g), and the product worked up in the usual manner to give the naphthyl alcohol (IIf; R = CH_3) (21 g). It formed a *hydrochloride*, m.p. 266°, after crystallization from ethanol.

Anal. Calcd. for $C_{24}H_{28}ClNO$: C, 75·4; H, 7·4; Cl, 9·3; equiv. wt., 382. Found: C, 75·4; H, 7·3; Cl, 9·2; equiv. wt., 382. Direct acylation of the piperidone (I; R = CH_3)-lithium α-naphthyl

complex with acetic anhydride (method as before) and treatment of the crude basic product with excess of ethanolic hydrochloric acid gave *N-2′-phenethyl-4-ethoxy-3-methyl-4-(α-naphthyl)piperidine hydrochloride*, plates from ethanol, m.p. 221–223°.

Anal. Calcd. for $C_{26}H_{32}ClNO$: C, 76·1; H, 7·8; Cl, 8·7. Found: C, 75·8; H, 7·5; Cl, 9·1.

N-2′-Phenethyl-4-(α-naphthyl)-4-piperidinol and related compounds. Treatment of the piperidone (I; R = H) (16·5 g) with lithium α-naphthyl, as before, gave the naphthyl alcohol (IIf; R = H) (19·5 g), m.p. 173° after crystallization from benzene.

Anal. Calcd. for $C_{23}H_{25}NO$: C, 83·4; H, 7·6; N, 4·2; equiv. wt., 331. Found: C, 83·8; H, 7·2; N, 4·3; equiv. wt., 332. Treatment of the alcohol with acetic anhydride and pyridine (as before) gave *N-2′-phenethyl-4-(α-naphthyl)-1,2,5,6-tetrahydropyridine*, isolated as the *hydrobromide*, m.p. 264° after crystallization from ethanol.

Anal. Calcd. for $C_{23}H_{24}BrN$: C, 67·1; H, 6·1; Br, 20·3; N, 3·6; equiv. wt., 394. Found: C, 68·2; H, 5·9; Br, 20·1; N, 3·6; equiv. wt., 390. Direct acylation of the piperidone (I; R = H)-lithium α-naphthyl complex with acetic anhydride and treatment of the basic product with excess of ethanolic hydrobromic acid gave *N-2′-phenethyl-4-ethoxy-4-(α-naphthyl)piperidine hydrobromide*, needles from ethanol, m.p. 224°.

Anal. Calcd. for $C_{25}H_{30}BrNO$: C, 68·2; H, 6·8; equiv. wt., 440. Found: C, 67·3; H, 6·8; equiv. wt., 433.

N-2′-Phenethyl-3-methyl-4-(2′-pyridyl)-4-piperidinol and esters. The piperidone (I; R = CH_3) (10·8 g) was added to lithium 2-pyridyl, prepared from lithium *n*-butyl and 2-bromopyridine (7·5 g) by the method of Nunn and Schofield,[26] and the product worked up as usual to give the pyridyl alcohol (IIc; R = CH_3) (9·0 g). It gave a *dihydrochloride*, m.p. 240–241° (d.) from ether–ethanol.

Anal. Calcd. for $C_{19}H_{26}Cl_2N_2O$: C, 61·8; H, 7·0; N, 7·6; equiv. wt., 185. Found: C, 61·1; H, 7·0; N, 7·5; equiv. wt., 190. Esterification by the acid anhydride–pyridine method gave the *acetoxyester* (IIIc; R = R′ = CH_3), isolated as the dihydrochloride, m.p. 203–204° (d.) from ethanol.

Anal. Calcd. for $C_{21}H_{28}Cl_2N_2O_2$: C, 61·3; H, 6·8; N, 6·8; equiv. wt., 206. Found: C, 60·3; H, 6·8; N, 6·7; equiv. wt., 210.

The *propionoxyester* (IIIc; R = CH_3, R′ = C_2H_5) gave a *dihydrochloride*, m.p. 183–184° from ether–ethanol.

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2O_2$: C, 62·1; H, 7·1; N, 6·6; equiv. wt., 213. Found: C, 60·2; H, 7·2; N, 6·7; equiv. wt., 218. The pyridyl alcohol (IIIc; R = CH_3) was recovered after treatment for 1 h with a 3 : 1 mixture of acetic and hydrochloric acids at the reflux temperature.

N-2′-Phenethyl-4-benzyl-4-piperidinol and esters. The piperidone (I; R = H) (17·5 g) was added to benzyl magnesium chloride, prepared from benzyl chloride (22 g) and magnesium (4·3 g), and the product treated in the usual manner to give the benzyl alcohol (IId; R = H) (17·5 g). It formed a *hydrobromide*, needles from ethanol; m.p. 218°.

Anal. Calcd. for $C_{20}H_{26}BrNO$: C, 63·8; H, 6·9; Br, 21·2; N, 3·7; equiv. wt., 376. Found: C, 63·3; H, 6·8; Br, 21·2; N, 3·8; equiv. wt., 378.

Esterification by the acid anhydride–pyridine method gave the *acetoxyester* (IIId; R = H, R′ = CH_3) *hydrobromide*, m.p. 241° from ethanol.

Anal. Calcd. for $C_{22}H_{28}BrNO_2$: C, 63·1; H, 6·7; Br, 19·1; N, 3·4; equiv. wt., 418. Found: C, 63·1; H, 6·7; Br, 19·1; N, 3·4; equiv. wt., 419. The *propionoxyester* (IIId; R = H, R′ = C_2H_5) gave a *hydrobromide*, plates from ethanol, m.p. 214°.

Anal. Calcd. for $C_{23}H_{30}BrNO_2$: C, 61·9; H, 7·0; Br, 18·5; N, 3·3; equiv. wt., 432. Found: C, 61·9; H, 7·0; Br, 18·4; N, 3·6; equiv. wt., 434.

N-2′-Phenethyl-4-benzyl-3-methyl-4-piperidinol and elimination product. The piperidone (I; R = CH_3) (20 g), on treatment with benzyl magnesium bromide in the usual manner, gave the benzyl alcohol (IId; R = CH_3) (23 g). It formed a *hydrobromide*, needles from ethanol, m.p. 235°.

Anal. Calcd. for $C_{21}H_{28}BrNO$: C, 64·6; H, 7·2; Br, 20·5; equiv. wt., 392. Found: C, 64·2; H, 7·4; Br, 20·5; equiv. wt., 392. Treatment of the alcohol with propionic anhydride and pyridine gave the *olefin* (X) isolated as the *hydrobromide*, needles from ethanol, m.p. 212°.

Anal. Calcd. for $C_{21}H_{26}BrN$: C, 67·7; H, 7·0; Br, 21·5; N, 3·8; equiv. wt., 372. Found: C, 67·0; H, 6·9; Br, 21·6; N, 3·8; equiv. wt., 375.

N-2′-Phenethyl-4-(2′-picolyl)-4-piperidinol and acetoxyester. The piperidone (I; R = H) (8 g) was added to lithium 2-picolyl, prepared by metallation of 2-picoline (7·5 g) with lithium phenyl, and the product processed in the usual manner to give the crude picolyl alcohol (IIe; R = H) (10 g). It formed a *dihydrobromide*, rosettes from ethanol, m.p. 220·5°.

Anal. Calcd. for $C_{19}H_{26}Br_2N_2O$: C, 49·8; H, 5·7; Br, 34·8; N, 6·2; equiv. wt., 229. Found: C, 49·8; H, 5·8; Br, 34·5; N, 6·2; equiv. wt., 229.

Direct acylation of the piperidone (I; R = H)-lithium 2-picolyl complex with acetic anhydride gave *N-2′-phenethyl-4-acetoxy-4-(2′-picolyl) piperidine*, isolated as the *dihydrobromide*, m.p. 238° from ethanol.

Anal. Calcd. for $C_{21}H_{28}Br_2N_2O_2$: C, 50·4; H, 5·6; Br, 31·9; N, 5·6; equiv. wt., 250. Found: C, 50·2; H, 5·6; Br, 31·7; N, 5·5; equiv. wt., 253.

N-2′-Phenethyl-3-methyl-4-(2′-picolyl)-4-piperidinol and elimination product. The piperidone (I; R = CH_3) (15 g) treated with lithium 2-picolyl, as before, gave the picolyl alcohol (IIe; R = CH_3) (16 g). It formed a *dihydrobromide*, needles from ethanol, m.p. 250°.

Anal. Calcd. for $C_{20}H_{28}Br_2N_2O$: C, 50·9; H, 6·0; Br, 33·8; N, 6·0; equiv. wt., 236. Found: C, 50·5; H, 6·2; Br, 33·7; N, 6·0; equiv. wt., 237.

Treatment of the alcohol with acetic anhydride and pyridine gave the eliminated product [structure probably analogous to (X)]. It formed a *dihydrobromide*, rosettes from ethanol, m.p. 240°.

Anal. Calcd. for $C_{20}H_{26}Br_2N_2$: C, 51·9; H, 5·9; Br, 35·0; N, 6·6; equiv. wt., 227. Found: C, 51·6; H, 6·2; Br, 34·8; N, 6·7; equiv. wt., 230.

Summary. The synthesis of 4-heteroaryl-4-piperidinols and related compounds derived by addition of lithium aryls to *N*-phenethyl-4-piperidones, is described. Treatment of the alcohols with an acid anhydride–pyridine mixture gives either esters or, more commonly, an elimination product. Direct acylation of lithium aryl-piperidone complexes gives esters which, in certain cases, are readily converted into ether salts by the action of excess of ethanolic hydrochloric acid. These results are interpreted in terms of the electronic character of the 4-aryl substituent.

Configurational assignments are made in cases where isomerism is possible. The analgesic activities in mice of various aminoalcohols and related compounds are given and the results discussed in terms of isosteric replacement of phenyl in analgesics.

Acknowledgements. The authors thank Smith, Kline and French Laboratories for making available an infrared spectrophotometer, and Messrs. T. H. E. Watts and G. H. B. Battershall for carrying out the measurements.

(*Received 2 July, 1959*)

References

[1] Beckett, A. H., Casy, A. F. and Kirk, G. This Journal, **1,** 37 (1959)
[2] Ziering, A., Berger, L., Heineman, S. D. and Lee, J. *J. org. Chem.*, **12,** 894 (1947)
[3] Calloway, N. O. *Chem. Rev.*, **17,** 327 (1935)
[4] Adamson, D. W. and Billinghurst, J. W. *J. chem. Soc.*, (1950) 1039
[5] Beckett, A. H. and Casy, A. F. *J. chem. Soc.*, (1955) 900
[6] Alexander, E. R. *Principles of Ionic Organic Reactions*, p. 214. (1951). London; Chapman and Hall
[7] Strauss, G. and Hüssy, W. *Ber. dtsch. chem. Ges.*, **42,** 2177 (1909)
[8] Stobbe, H. and Zeitschel, O. *Ber. dtsch. chem. Ges.*, **34,** 1967 (1901)
[9] Gilman, H., Franz, R. A., Hewlett, A. P. and Wright, F. *J. Amer. chem. Soc.*, **72,** 3 (1950)
[10] Brown, H. C. *J. org. Chem.*, **22,** 439 (1957)
[11] Eliel, E. L., McCoy, J. W. and Price, C. C. *J. org. Chem.*, **22,** 1533 (1957)
[12] Beckett, A. H., Casy, A. F., Kirk, G. and Walker, J. *J. Pharm., Lond.*, **9,** 939 (1957)
[13] Barton, D. H. R., Campos-Neves, A. da S. and Cookson, R. C. *J. chem. Soc.*, (1956) 3500
[14] Janssen, P. A. J. and Jageneau, A. H. M. *J. Pharm., Lond.*, **9,** 381 (1957)
[15] Erlenmeyer, H. *Bull. Soc. Chim. biol. Paris*, **30,** 792 (1948)
[16] Blicke, F. F. In *Thiophene and its Derivatives*, Hartough, H. D., p. 40. (1952). New York; Interscience
[17] Diamond, J., Brice, W. F. and Tyson, F. T. *J. org. Chem.*, **22,** 399 (1957)
[18] Randall, L. O. and Lehman, G. *J. Pharmacol.*, **93,** 314 (1948)
[19] Braenden, O. J., Eddy, M. D. and Halbach, H. *Bull. Wld. Hlth. Org.*, **13,** 937 (1955) and references there cited
[20] Beckett, A. H. and Casy, A. F. *J. Pharm., Lond.*, **6,** 986 (1954)
[21] Pressman, D. and Pauling, L. *J. Amer. chem. Soc.*, **71,** 2893 (1949)
[22] Pressman, D. and Siegel, M. *J. Amer. chem. Soc.*, **79,** 994 (1957)

[23] Beckett, A. H., Casy, A. F., Harper, N. J. and Phillips, P. M. *J. Pharm., Lond.*, **8**, 860 (1956)
[24] Elpern, B., Gardner, L. N. and Grumbach, L. *J. Amer. chem. Soc.*, **79**, 1951 (1957)
[25] Beckett, A. H. and Casy, A. F. *Bull. Narcot.*, **9**, 37 (1957)
[26] Nunn, A. J. and Schofield, K. *J. chem. Soc.*, (1952) 589
[27] Beckett, A. H. and Kirk, G. Unpublished work.