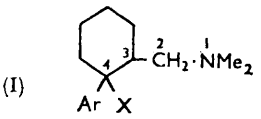
702. *Tertiary Alcohols and Related Compounds Derived from 2-Dimethylaminomethylcyclohexanone.*

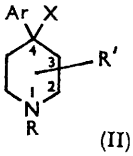
By A. F. Casy, N. J. Harper, and J. R. Dimmock.

The synthesis and esterification of some 1-aryl-2-dimethylaminomethylcyclohexanols are reported. The acid-lability of the 1-2′-thienylcyclohexanol and acetoxy-ester is demonstrated.

This work was undertaken as part of a study of the relation of molecular rigidity to pharmacological activity, the compounds reported (I) representing less rigid analogues of 4-arylpiperidinols and related compounds (II), many of which possess marked pharmacological



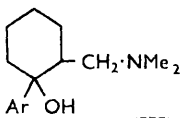
(X = OH, O·COR, etc.;
Ar = aryl;
R and R′ = alkyl.)



(II)

properties.[1] Such piperidine derivatives are relatively rigid molecules due to their cyclic nature and to the bulk of substituent groups. One result of rigidity is that the distance between nitrogen and C-4, a factor of possible importance if the molecule associates with a receptor site, is restricted within narrow limits. While these atoms are separated by three identical σ-bonds in both series, greater variation in the distance between them is permitted in the cyclohexane derivatives (I) as a result of free rotation about bonds in the basic side-chain. Evidence that nitrogen is closer to C-4 in the piperidine series (II) has been obtained from pK_a data (see below).

The amino-alcohols (IIIa—g) were prepared by treating 2-dimethylaminomethylcyclohexanone with the appropriate organolithium or Grignard reagent. Isomers were not



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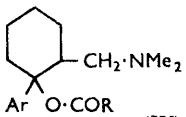

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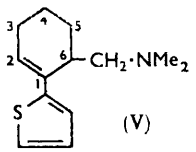


(V)

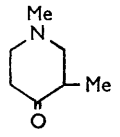
Ar = a: Ph; b: C_6H_4*o*-Me; c: 2-furyl; d: 2-thienyl; e: 2-pyridyl; f: CH_2·C_6H_4*p*-Cl; g: CH_2·C_6H_4*p*-F; h: C:CPh.

encountered and it was assumed that products isolated had the *trans* Ar/CH_2·NMe_2 configuration. Sodium phenylacetylide was employed in the synthesis of the phenylethynyl member (IIIh). The esters (IV) were prepared either by heating the alcohols (III) with acetic anhydride (the substrate itself acting as basic catalyst) or by decomposing the lithium salt of the alcohol with the same reagent. No product could be isolated when the thienyl alcohol (IIId) was heated with acetic anhydride but the same reagent converted the corresponding lithium salt into the acetoxy-ester in good yield. This ester (IVd; R = Me) formed a stable salt when neutralised with ethanolic hydrogen chloride, whereas one mole excess of acid induced elimination, the alkene (V) being isolated. (The corresponding alcohol, IIId, formed the same alkene when merely neutralised with acid.) The n.m.r. spectrum of the elimination product was consistent with the alkene link's being 1—2 rather than 1—6; it showed a well-resolved triplet centred at τ 3·7 that integrated for one proton, assigned to the vinylic hydrogen atom at C-2. Models reveal that a greater degree of

[1] Beckett and Casy, "Progress in Medicinal Chemistry," ed. Ellis and West, Butterworths, London, 1962, Vol. II, p. 68.

planarity between thiophen ring and alkene link is permitted when the double bond is between C-1 and C-2. The direction of elimination, therefore, appears to be governed by energetic factors in that the alkene produced is the one in which greater resonance stabilisation is possible. The ultraviolet absorption characteristics of the alkene (V) ($\lambda_{max.}$ 273 mμ, log ε 4·05) resembled those of 2-vinylthiophen ($\lambda_{max.}$ 276 mμ, log ε 4·03).[2] Esters of 4-2′-furyl- and 4-2′-thienyl-4-piperidinol are similarly unstable in the presence of an excess of ethanolic hydrogen chloride but give corresponding 4-ethoxy-derivatives rather than alkenes as major reaction products.[3] The proposed mechanism for these last reactions,[3] namely acid-catalysed alkyl–oxygen fission, giving carbonium ions which either suffer nucleophilic attack by alcohol or lose a proton, is also considered to apply in the present case. All attempts to esterify the furyl alcohol (IIIc) failed.

The base-weakening effect of carbonyl in the 4-piperidone (VI) is greater than that in the cyclohexanone (VIII) as evident from comparison of their pK_a' values with those of the corresponding t-alcohols (VII and IX) in which electron-withdrawing influences at C-4 are largely eliminated. It follows that the carbonyl group exerts its influence upon the nitrogen lone-pair through field rather than inductive effects, otherwise the magnitudes pK_a'(alcohol) —pK_a'(ketone) should be similar in the two ketones (three σ-bonds intervene



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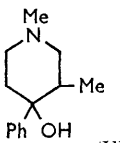

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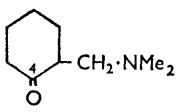

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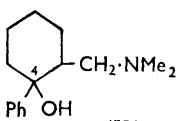

(IX)

pK_a' 7·08 8·71 8·73 8·67

between C-4 and nitrogen in both cases). Further, since the effect of an electron-withdrawing group on the basic ionisation constant decreases with increasing distance from the basic centre, the distance from C-4 to nitrogen must be greater in the more basic of the two γ-keto-amines, *i.e.*, the cyclohexyl derivative (VIII).

Certain of these compounds were screened for hot-plate electro-shock, anti-amphetamine, and anti-reserpine activity, but all were inactive.

Experimental

Some analyses were carried out by Mr. G. S. Crouch, School of Pharmacy, University of London. Equivalent weights of bases and salts were determined by titration with 0·02N-perchloric acid in glacial acetic acid with Oracet Blue B as indicator.

2-*Dimethylaminomethyl*-1-2′-*thienylcyclohexanol* (IIId).—2-Dimethylaminomethylcyclohexanone [4] (14·6 g., 0·1 mole) in ether (15 ml.), was added to cold 2-thienyl-lithium in ether (100 ml.) prepared from lithium (2·6 g., 0·38 g.-atom), bromobenzene (29·5 g., 0·19 mole), and thiophen (15·8 g., 0·24 mole). The mixture, after being heated under reflux for 1 hr., was poured on ice and glacial acetic acid (40 ml.), and the aqueous phase separated, made basic with aqueous ammonia, and extracted with ether. After drying ($MgSO_4$), the extract was evaporated and the residual oil (15·6 g.) distilled to give the alcohol (IIId) (11·7 g.), b. p. 99°/0·2 mm. (Found: C, 65·1; H, 9·0; N, 6·0; equiv. wt. 232. $C_{13}H_{21}NOS$ requires C, 65·3; H, 8·8; N, 5·85%; equiv. wt. 239). It had $\lambda_{max.}$ 234 mμ (log ε 3·99) in ethanol.

Similarly prepared were the *furyl-cyclohexanol* (IIIc), b. p. 73—76°/0·03 mm., n_D^{21} 1·5060 (Found: C, 69·6; H, 9·3; equiv. wt. 223. $C_{13}H_{21}NO_2$ requires C, 70·0; H, 9·5%; equiv. wt. 223); the *pyridyl-cyclohexanol* (IIIe) *hydrochloride*, m. p. 166° (from acetone) (Found: C, 61·8; H, 8·9. $C_{14}H_{23}ClN_2O$ requires C, 62·1; H, 8·6%); the 4-*chlorobenzyl-cyclohexanol* (IIIf) *hydrochloride*, m. p. 230° (from ethanol–ether) (Found: C, 58·7; H, 7·9; N, 4·2; equiv. wt. 330.

[2] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley & Co. Inc., New York, 1951.
[3] Casy, Beckett, and Armstrong, *Tetrahedron*, 1961, **16**, 85.
[4] Frank and Pierle, *J. Amer. Chem. Soc.*, 1951, **73**, 724.

$C_{16}H_{25}Cl_2NO,\frac{1}{2}H_2O$ requires C, 58·7; H, 8·0; N, 4·3%; equiv. wt. 327); and the *p-fluorobenzyl cyclohexanol* (IIIg) *hydrochloride*, m. p. 168—171° (from ethanol–ether) (Found: C, 63·3; H, 8·4; N, 4·65; equiv. wt. 319. $C_{16}H_{25}ClFNO$ requires C, 63·7; H, 8·35; N, 4·6%; equiv. wt. 320).

2-Dimethylamino-1-phenylethynylcyclohexanol (IIIh).—Phenylacetylene (5·26 g., 0·05 mole) in ether (150 ml.) was added over 1 hr. to a stirred mixture of sodium (1·2 g., 0·05 mole), ferrous nitrate (0·16 g.), and liquid ammonia (250 ml.) cooled in an alcohol–carbon dioxide bath. The product was stirred for a further 2 hr. and then treated with 2-dimethylaminomethylcyclohexanone (8·0 g., 0·05 mole) in ether (300 ml.). After 1 hr., when addition was complete, the mixture was stirred for a further 2 hr., and then decomposed with ammonium chloride (3·6 g.), strong aqueous ammonia (24 ml.) and ice (50 g.). Next day the ether was separated and extracted with dilute hydrochloric acid. The aqueous extract was made basic with aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residual oil (6·55 g.) treated with an excess of ethanolic hydrogen chloride. Fractional crystallisation of the product from ethanol–ether gave impure 2-dimethylaminomethylcyclohexanone hydrochloride (1·3 g.), m. p. 145—146° (Mannich and Braun [5] give m. p. 152°) and the *phenylethynylcyclohexanol* (IIIh) *hydrochloride* (1·86 g.) m. p. 127—137°. Several recrystallisations from acetone gave an analytical sample, m. p. 191·5—192° (Found: C, 69·0; H, 8·4; N, 4·9; equiv. wt. 294). $C_{17}H_{24}ClNO$ requires C, 69·5; H, 8·2; N, 4·8%; equiv. wt. 294).

1-Acetoxy-2-dimethylaminomethyl-1-4-fluorobenzylcyclohexane (IVg; R = Me) *Hydrochloride.*—A mixture of the alcohol (IIIg) (1·02 g., 0·004 mole) and acetic anhydride (0·86 g., 0·008 mole) was stirred and heated in an oil bath at 100° for 1·5 hr. On cooling excess of ethanolic HCl was added, the product evaporated and the residue crystallised from ethanol–ether to give the *ester* (IVg; R = Me) *hydrochloride* (0·9 g.), m. p. 208° (Found: C, 62·9; H, 7·6; N, 4·4; equiv. wt. 350. $C_{18}H_{27}ClFNO_2$ requires C, 62·9; H, 7·9; N, 4·1%; equiv. wt. 344).

Similarly prepared were the *hydrochlorides* of the *4-chlorobenzyl ester* (IVf; R = Me), m. p. 198·5° (Found: C, 60·4; H, 7·6; N, 4·1; equiv. wt. 370. $C_{18}H_{27}Cl_2NO_2$ requires C, 60·0; H, 7·6; N, 3·9%; equiv. wt. 360), the phenyl ester (IVa; R = Me), m. p. 198—199° (Slomka and Schueler [6] give m. p. 201—203°), the *o*-tolyl ester (IVb; R = Et), m. p. 198° (Found: C, 67·3; H, 8·9; N, 4·6. $C_{19}H_{30}ClNO_2$ requires C, 67·2; H, 8·9; N, 4·1%) and the *pyridyl ester* (IVe; R = Me) *dihydrochloride*, m. p. 167° (decomp.) (Found: C, 52·45; H, 7·9; equiv. wt. 190. $C_{16}H_{26}Cl_2N_2O_2H_2O$ requires C, 52·3; H, 7·7; equiv. wt. 184).

1-Acetoxy-2-dimethylaminomethyl-1-2′-thienylcyclohexane (IVd; R = Me) *Hydrochloride.*—The thienyl alcohol (IIId) (4 g., 0·017 mole) in ether (8 ml.) was added to a solution of lithium phenyl in ether (25 ml.) prepared from lithium (0·26 g., 0·038 g.-atom) and bromobenzene (2·9 g., 0·018 mole), and the mixture was stirred at room temperature for 0·5 hr., then treated with acetic anhydride (2 g., 0·02 mole) in ether (8 ml.). The product, after being heated under reflux for 8 hr., was poured on to ice and glacial acetic acid and the basic ester (3·5 g.) isolated as usual. The impure ester (1·7 g.) with one molar proportion of HCl in ethanol gave the *thienyl ester* (IVd; R = Me) *hydrochloride* (0·58 g.), m. p. 132° (from ethanol–ether) (Found: C, 56·2; H, 7·5; N, 4·5; equiv. wt. 313. $C_{15}H_{24}ClNSO_2$ requires C, 56·7; H, 7·6; N, 4·4%; equiv. wt. 318). It had an intense adsorption peak at 1730 $cm.^{-1}$. The impure ester (1·8 g.) with two molar proportions of HCl in ethanol gave *6-dimethylaminomethyl-1-2′-thienylcyclohex-1-ene* (V) *hydrochloride* (0·7 g.), m. p. 223·5° (from ethanol) (Found: C, 60·1; H, 7·7. $C_{13}H_{20}ClNS$ requires C, 60·6; H, 7·8%). It had $\lambda_{max.}$ 273 mμ (log ε 4·05) in ethanol. Its n.m.r. spectrum had the characteristics τ 2·5—3·1 (3 aromatic protons) and 3·7 (triplet, 1 vinylic proton). The thienylcyclohexanol (IIId) gave the same alkene (V) hydrochloride, m. p. 222·5°, when neutralised with ethanolic HCl (Found: C, 60·7; H, 7·7. $C_{13}H_{20}ClNS$ requires C, 60·6; H, 7·8%).

The *o-tolyl ester* (IVb; R = Me) *hydrochloride*, m. p. 197—197·5° (from ethanol) (Found: C, 66·3; H, 8·5; N, 4·6. $C_{18}H_{28}ClNO_2$ requires C, 66·4; H, 8·7; N, 4·3%), was similarly prepared.

Dissociation Constants.—Comparative values were obtained by titrating the base or base hydrochloride (40—60 mg.) in 50% ethanol in water (75 ml.) with 0·02N-HCl or -NaOH and applying Henderson's equation to the data so obtained. Measurements of pH were made with a Pye Dynacap pH meter standardised to pH 4 with 0·05M-potassium hydrogen phthalate;

[5] Mannich and Braun, *Ber.*, 1920, **53**, 1874.
[6] Slomka and Schueler, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1951, **40**, 47.

α-1,3-dimethyl-4-phenyl-4-piperidinol, m. p. 101—102°, and freshly distilled 1,3-dimethyl-4-piperidone were employed.[7]

The n.m.r. spectrum was obtained on a 60 Mc. Varian (A-60) instrument (deuteriochloroform solution with tetramethylsilane as internal standard). We thank Smith, Kline and French Laboratories for the pharmacological results and Miss J. Lovenack, School of Pharmacy, University of London, for determining the n.m.r. spectrum.

SCHOOL OF PHARMACY, CHELSEA COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON S.W.3. [*Received, December 4th,* 1963.]

[7] Beckett, Casy, Kirk, and Walker, *J. Pharm. Pharmacol.*, 1957, **9**, 939.