11. *Aminoalkyl Tertiary Carbinols and Derived Products. Part IV. Spasmolytics. Phenyl- and* cyclo*Hexylphenyl-carbinols.*

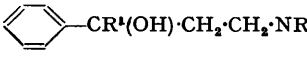
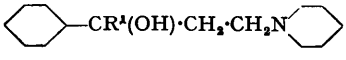
By D. W. Adamson, P. A. Barrett, and S. Wilkinson.

A number of 3-amino-1-phenylalkan-1-ols (I; R^1= alkyl) and 1-*cyclo*hexyl-3-piperidinoalkan-1-ols (II; R^1 = alkyl) were prepared by conventional methods for pharmacological testing.

Amino-1-*cyclo*hexyl-1-phenylalkan-1-ols (III and VII), of interest as spasmolytics, were obtained by controlled partial hydrogenation of the corresponding amino-1 : 1-diphenylalkan-1-ols (IV and VI); complete hydrogenation gave the di*cyclo*hexyl compounds.

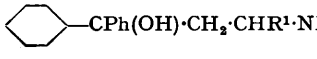
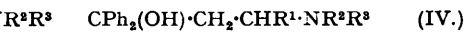
Compounds derived from the amino-carbinols by dehydration and subsequent reduction are described.

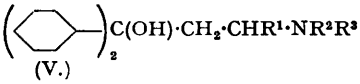
A number of phenylalkanolamines (I; R^1 = alkyl) and *cyclo*hexylphenylalkanolamines (I; $R^1 = CH{<}C_5H_{10}$) were prepared several years ago for pharmacological testing, as part of our programme in this series (Parts I—III; *J.*, 1949, S144; 1950, 885, 1039); the former are the subject of B.P. Appln. 5932/48. A number of these compounds were described recently by Denton, Lawson, Neier, Schedl, and Turner (*J. Amer. Chem. Soc.*, 1949, **71**, 2050, 2053, 2054) and by Ruddy and Buckley (*ibid.*, 1950, **72**, 718). The compounds are of interest as spasmolytics (White and Green, personal communication; Becker, Ananenko, Glenwood, and Miller, *Fed. Proc.*, 1946, **5**, 163; Cunningham *et al.*, *J. Pharm. Exp. Ther.*, 1949, **96**, 151) and it has been reported that 1-*cyclo*hexyl-1-phenyl-3-piperidinopropan-1-ol (I; $R^1 = CH{<}C_5H_{10}$, $NR^2R^3 = N{<}C_5H_{10}$) is a valuable drug in the treatment of Parkinsonism (Doshay and Constable, *J. Amer. Med. Assoc.*, 1949, **140**, 1317; Ellenbogen, *Lancet*, 1950, **1**, 1034; Phillips, Montuschi, and Shakey, *ibid.*, p. 1131).

(I.)  (II.) 

3-Amino-1-phenylalkan-1-ols (I; R^1 = alkyl) were prepared by the same method as that described in the above-mentioned papers, namely, reaction between an alkylmagnesium bromide and the appropriate β-aminopropiophenone. The compounds of this series which have not already been described are included in Table I. The *O*-acetyl and *O*-benzoyl derivatives of the carbinols (I; R^1 = Me, $NR^2R^3 = NMe_2$ and $N{<}C_5H_{10}$) were also prepared. The phenylalkanol amines (I; R^1 = alkyl, $NR^2R^3 = N{<}C_5H_{10}$) were hydrogenated in the presence of platinum to the corresponding 1-*cyclo*hexyl-3-piperidinoalkan-1-ols (II; R^1 = alkyl).

The Grignard reaction was used also in the first instance for the synthesis of 3-amino-1-*cyclo*hexyl-1-phenylpropan-1-ols (III; R^1 = H), but, as found by other workers, the yields were poor

(III.)  (IV.) 


(V.)

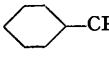
(*ca.* 10%). The product from the reaction between *cyclo*pentylmagnesium bromide and β-piperidinopropiophenone was a mixture of bases, from which only 1-phenyl-3-piperidino-

propan-1-ol (I; R^1 = H, $NR^2R^3 = N{<}C_5H_{10}$), arising by reduction of the amino-ketone, could be isolated. The propensity of *cyclo*pentylmagnesium bromide to reduce instead of add to ketones was discussed by Kharasch and Weinhouse (*J. Org. Chem.*, 1936, **1**, 209), and recently Hey and Musgrave (*J.*, 1949, 3156) noted that reduction of the carbonyl groups occurred in place of normal addition in the reaction between this Grignard reagent and deoxybenzoins.

A more satisfactory route to the *cyclo*hexylphenylcarbinols (III; R^1 = H or alkyl) was found in the catalytic hydrogenation of the readily available 3-amino-1 : 1-diphenylalkan-1-ols (IV; R^1 = H or alkyl) (Part I, *loc. cit.*, and Part V, to follow). In the presence of Adams's platinum catalyst, the diphenylcarbinols absorbed hydrogen as a continuous process, finally to give the di*cyclo*hexylcarbinols (V), there being no abrupt change in the rate of absorption at a point which would correspond to the saturation of only one of the phenyl groups. However, the hydrogenation followed, to a large degree, a stepwise course for it was possible to stop the reduction at a stage which allowed of the isolation in good yield, of the desired *cyclo*hexylphenylcarbinols (III). This is substantially in accord with the conclusions, based on the kinetic and analytical study of the catalytic hydrogenation of compounds containing more than one phenyl nucleus, recorded by Smith, Aldermann, Shacklett, and Welch (*J. Amer. Chem. Soc.*, 1949, **71**, 3772).

The process was examined in detail for the *cyclo*hexylphenylcarbinols which were of particular pharmacological interest. It was expedient to allow absorption of 10—15% in excess of the 3 moles of hydrogen theoretically required, otherwise unchanged diphenylcarbinol, difficult to remove by crystallisation, was present in the product. On the other hand, the fully saturated di*cyclo*hexylcarbinols were readily removed by crystallisation of the basic product, by virtue of their high solubility in organic solvents. The purified products were identical with those prepared from *cyclo*hexylmagnesium bromide and the appropriate β-aminopropiophenone. The ultra-violet absorption spectra, for measurements of which we are indebted to Dr. T. S. G. Jones, as well as mixed melting points with authentic specimens, provided evidence for the structure and purity of the products. As purification proceeded, the fine structure of the absorption band associated with the presence of one phenyl group became more sharply defined and finally was identical with that of the authentic specimens (light absorption in ethanolic solution : maximum, λ 258·5 mμ.; ε 233—250). In other cases, when the basic product did not crystallise and where there was no unequivocal specimen available for comparison, purification was effected by recrystallisation of a salt (hydrochloride or hydrogen oxalate), constancy of m. p. and definition of the ultra-violet spectrum being taken as criteria of purity.

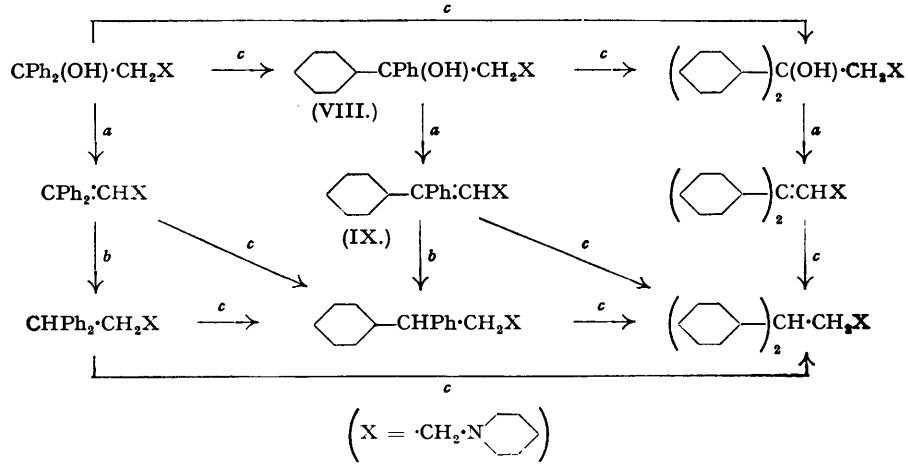
Hydrogenation of diphenylcarbinols substituted in the chain in the 3-position (IV; R^1 = Me or Pr^n; to be described in Part V) proceeded more slowly than that of those lacking the substituent. An example in which the substituent was in the 2-position, *viz.*, 2-methyl-1 : 1-diphenyl-3-piperidinopropan-1-ol, was resistant to hydrogenation under the conditions of our experiments. Hydrogenation was considerably slower when the phenyl groups were substituted as in 3-piperidino-1 : 1-di-*p*-tolylpropan-1-ol, absorption ceasing when only one of the *p*-tolyl groups was saturated.

(VI.) $CPh_2(OH)\cdot[CH_2]_n\cdot NR^1R^2$  $CPh(OH)\cdot[CH_2]_n\cdot NR^1R^2$ (VII.)

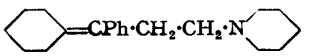
The process was also applied to some ω-amino-1 : 1-diphenylalkan-1-ols (VI; n = 4, 5, 6; to be described in a later paper) from which both the *cyclo*hexylphenyl- and di*cyclo*hexylcarbinols could be prepared. An alternative route was followed in one example : in the catalytic hydrogenation of 5-bromo-1 : 1-diphenylpentan-1-ol, saturation of the first phenyl group was rapidly completed but further reduction was very slow, thereby facilitating the isolation of 5-bromo-1-*cyclo*hexyl-1-phenylpentan-1-ol, from which the 5-piperidino-compound (VII; n = 4, $NR^1R^2 = N{<}C_5H_{10}$) was prepared.

It was of interest to prepare the corresponding alkenyl- and alkyl-amines from the carbinols by dehydration and subsequent reduction, especially since earlier work in these laboratories had shown that some related dithienylalkenylamines were potent analgesics (Part II, *loc. cit.*, Adamson and Green, *Nature*, 1950, **165**, 122) and that phenylpyridylalkenylamines had a powerful antihistamine action (Part III, *loc. cit.*). A series of products of potential pharmacological interest was obviously available from the diphenylcarbinols by adopting combinations of the following processes : (*a*) dehydration, (*b*) hydrogenation of ethylenic linkage in the presence of palladium, (*c*) hydrogenation of ethylenic linkage if present and of one or both phenyl groups in the presence of platinum. This series of reactions was applied to 1 : 1-diphenyl-3-piperidinopropan-1-ol as shown in the appended scheme, and in part to other carbinols as recorded in the experimental section.

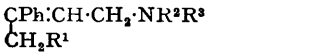
It was possible that dehydration of 1-*cyclo*hexyl-1-phenyl-3-piperidinopropan-1-ol (VIII) had given either 1-*cyclo*hexyl-1-phenyl-3-piperidinoprop-1-ene (IX) or the isomeric 1-*cyclo*hexylidene-1-phenyl-3-piperidinopropane (X), both structures being compatible with the ultra-violet absorption spectrum which exhibited a peak corresponding to the presence of the Ph·C:C group in the molecule. The structure (IX) is assigned to the compound on the basis of its oxidation by potassium permanganate to *cyclo*hexyl phenyl ketone. Two other unsaturated amines isomeric with (IX), *viz.*, 1-*cyclo*hex-1′-enyl- and 1-*cyclo*hex-2′-enyl-1-phenyl-3-piperidinopropane, have been described by Jackman, Nachod, and Archer (*J. Amer. Chem. Soc.*, 1950, **72**, 716) and another, of undetermined structure, by Ruddy and Buckley (*loc. cit.*).



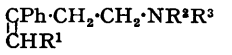
The 3-amino-1-phenylalkan-1-ols (I; R^1 = alkyl) were dehydrated, and some of the alkenylamines so formed catalytically hydrogenated to 1-amino-3-phenylalkanes. The alkenylamine derived from 3-phenyl-1-piperidinononan-3-ol (I; $R^1 = C_6H_{13}$, $NR^2R^3 = N{<}C_5H_{10}$) gave *n*-hexyl phenyl ketone on oxidation and was therefore (XI; $R^1 = C_5H_{11}$, $NR^2R^3 = N{<}C_5H_{10}$). It is assumed that the other alkenylamines also had the allylamine structure (XI), although it is possible that the isomers (XII) were present in minor quantity since the salts of the bases melted over a range and several crystallisations were necessary to attain purity.



(X.)



(XI.)



(XII.)

The compounds now described have been examined for pharmacological properties by Dr. A. C. White and Mr. A. F. Green, of the Biological Division of these Laboratories; they were chiefly of interest on account of their high spasmolytic activity, and a new compound, 1-*cyclo*hexyl-1-phenyl-3-pyrrolidinopropan-1-ol (III; R^1 = H, $NR^2R^3 = N{<}C_4H_8$), and the known piperidino-analogue (VIII) were outstanding in this respect. Some compounds, particularly the quaternary salts derived from the carbinols, had a very strong mydriatic effect, and others were powerful local anæsthetics. Antihistamine activity was not pronounced and no analgesic action was observed. The results of pharmacological examination will be reported elsewhere.

Experimental.

3-Amino-1-phenylalkan-1-ols (Table I, Nos. 1—8).—The *β-tert.*-aminopropiophenone hydrochloride (0·2 mol.) was added in small portions to an ethereal solution of the Grignard reagent made from the appropriate bromoalkane (0·6 mol.). The mixture was then boiled under reflux for 3½ hours in a water-bath kept at 55—65°. The resulting pasty mass was decomposed with crushed ice (100 g.) and 25% aqueous ammonium chloride (150 c.c.), acidified with glacial acetic acid at 0°, and kept in the refrigerator overnight. The bulky precipitate of crude amino-carbinol hydrobromide was filtered off and washed with ether. It was suspended in chloroform and basified by addition of excess of aqueous ammonia, with mechanical stirring. The mixture was filtered, and the chloroform layer separated, washed with water, and dried (Na_2SO_4), and the solvent removed by distillation. The residual crude *amino-carbinols*, when solid, were usually recrystallised from light petroleum (b. p. 40—60°) at low temperatures (acetone–carbon dioxide bath); the yields of purified product were of the order of 60—70%. Those which did not solidify on cooling were purified by distillation under reduced pressure; the yields in these instances were

TABLE I.

3-Amino-1-phenyl- and 3-Amino-1-cyclohexyl-alkan-1-ols, $CR^1R^2(OH)\cdot CH_2\cdot CH_2\cdot NR^3R^4$.

No.	R^1.	R^2.	NR^3R^4.	Formula.	M. p. or b. p.	Solvent for recrystn.*	Analyses. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
1	Ph	CH_3	NMe_2	$C_{12}H_{19}ON$	54°/0·05 mm.	—	75·0	9·8	6·9	—	74·6	9·8	7·3	—
				$C_{12}H_{19}ON,HCl$	165—166°	$EtOH–COMe_2$	—	—	—	15·5	—	—	—	15·5
2	Ph	$C_4H_9^n$	NMe_2	$C_{15}H_{25}ON$	45—46	Petrol	76·7	10·7	6·2	—	76·6	10·6	6·0	—
				$C_{15}H_{25}ON,HCl$	151—152	EtOH–EtOAc	—	—	—	13·2	—	—	—	13·1
3	Ph	$C_3H_7^n$	NEt_2	$C_{16}H_{27}ON$	106—108/0·1 mm.	—	—	—	—	—	—	—	—	—
				$C_{16}H_{27}ON,HCl$	158—160	$CHCl_3–EtOAc$	66·9	9·8	4·8	12·8	67·3	9·5	4·9	12·4
4	Ph	$C_5H_{11}^n$	NEt_2	$C_{18}H_{31}ON$	130—136/0·1 mm.	—	—	—	—	—	—	—	—	—
				$C_{18}H_{31}ON,HCl$	206—208	$CHCl_3–EtOAc$	69·1	9·6	4·5	11·5	68·9	10·2	4·5	11·3
5	Ph	$PhCH_2$	NEt_2	$C_{20}H_{27}ON$	54—55	Petrol	81·0	8·9	4·7	—	80·8	9·1	4·7	—
				$C_{20}H_{27}ON,HCl$	186—187	EtOH	—	—	—	10·6	—	—	—	10·6
6	Ph	$C_3H_7^n$	NBu^n_2	$C_{20}H_{35}ON$	136—138/0·1 mm.	—	—	—	—	—	—	—	—	—
				$C_{20}H_{35}ON,HCl$	115—117	$COMe_2$	69·8	10·4	4·0	10·5	70·3	10·5	4·1	10·4
7	Ph	$C_6H_{13}^n$	$N<C_5H_8$[a]	$C_{20}H_{31}ON$	75—75·5	EtOH	79·3	10·2	5·0	—	79·7	10·3	4·7	—
				$C_{20}H_{31}ON,HCl$	190—191	EtOH	—	—	—	10·7	—	—	—	10·5
8	Ph	$C_8H_{17}^n$	$N<C_4H_8O$	$C_{21}H_{35}O_2N$	52—54	Petrol	75·5	10·6	4·1	—	75·7	10·5	4·2	—
				$C_{21}H_{35}O_2N,HCl$	195—197	$CHCl_3–EtOAc$	—	—	—	9·9	—	—	—	9·6
9	$CH<C_5H_{10}$	C_2H_5	$N<C_5H_{10}$	$C_{16}H_{31}ON,HCl$	176—177	$EtOH–Et_2O$	66·2	11·0	5·0	11·9	66·3	11·1	4·8	12·3
10	$CH<C_5H_{10}$	$C_3H_7^i$	$N<C_5H_{10}$	$C_{17}H_{33}ON,HCl$	150—152	$EtOH–Et_2O$	67·1	11·3	4·6	—	67·2	11·2	4·6	—
11	$CH<C_5H_{10}$	$C_5H_{11}^n$	$N<C_5H_{10}$	$C_{19}H_{37}ON,HCl$	200	$EtOH–Et_2O$	69·0	11·1	4·1	10·9	68·8	11·5	4·2	10·7
12	$CH<C_5H_{10}$	$C_6H_{13}^n$	$N<C_5H_{10}$	$C_{20}H_{39}ON,HCl$	192—194	$EtOH–Et_2O$	69·6	11·5	4·2	—	69·5	11·6	4·1	—

[a] $N<C_5H_8$ = 1 : 2 : 5 : 6-Tetrahydropyridino-.

* Petrol = light petroleum (b. p. 40—60°).

somewhat lower. The *hydrochlorides* of the amino-carbinols were prepared by passing dry hydrogen chloride into a solution of the base in chloroform until acidity to Congo-red was reached. Ether was then added cautiously, with scratching, to the point of crystallisation.

The *β-tert.*-aminopropiophenone hydrochlorides required as starting materials were prepared by the Mannich reaction (Blicke, "Organic Reactions," 1942, vol. 1, p. 303; Part III, *loc. cit.*). *β-(1 : 2 : 5 : 6-Tetrahydropyridino)propiophenone hydrochloride* had m. p. 187—188° after recrystallisation from ethanol (Found: Cl, 14·1. $C_{14}H_{17}ON,HCl$ requires Cl, 14·1%). *β-Di-n-butylaminopropiophenone hydrochloride* had m. p. 61° after recrystallisation from ethyl acetate–ether (Found: N, 4·8; Cl, 12·1. $C_{17}H_{27}ON,HCl$ requires N, 4·7; Cl, 11·9%).

Amino-carbinol Esters.—The amino-carbinol was dissolved in a small volume of anhydrous acetone, cooled to 0°, and a small excess of the acid chloride added dropwise with stirring. The solution was kept for several hours, and the product which separated was filtered off, washed with acetone, and recrystallised from chloroform–acetone. The following were prepared: *3-acetoxy-1-dimethylamino-3-phenylbutane hydrochloride*, m. p. 175° (Found: C, 13·3. $C_{14}H_{21}O_2N,HCl$ requires Cl, 13·1%); *3-benzoyloxy-1-dimethylamino-3-phenylbutane hydrochloride*, m. p. 178—180° (Found: Cl, 10·9. $C_{19}H_{23}O_2N,HCl$ requires Cl, 10·7%); *3-acetoxy-3-phenyl-1-piperidinobutane hydrochloride*, m. p. 168—170° (Found: Cl, 11·8. $C_{17}H_{25}O_2N,HCl$ requires Cl, 11·4%); *3-benzoyloxy-3-phenyl-1-piperidinobutane hydrochloride*, m. p. 175—177° (Found: Cl, 9·9. $C_{22}H_{27}O_2H,HCl$ requires C, 9·5%).

1-cyclo*Hexyl-3-piperidinoalkan-1-ols* (Table I, Nos. 9—12).—The 1-phenyl-3-piperidinoalkan-1-ol (3·0 g.; prepared in a similar manner to that described by Denton *et al.*, *loc. cit.*) was dissolved in glacial acetic acid (30 ml.) to which Adams's platinum catalyst (1·0 g.) was added, and the mixture shaken in an atmosphere of hydrogen. When absorption was complete, the catalyst was filtered off, and the filtrate diluted with water and basified in the cold with potassium hydroxide. The liberated base was extracted with ether, and the ethereal solution washed with water, dried (Na_2SO_4), and evaporated. The oily products were converted into the *hydrochlorides*, which were recrystallised.

*3-Amino-*1-cyclo*hexyl-1-phenylpropan-1-ols by the Grignard Reaction* (Table II, Nos. 2, 3, 5, 8, 11).—The amino-carbinols were prepared from the appropriate β-aminopropiophenone hydrochloride and *cyclo*hexylmagnesium bromide under conditions essentially the same as those described above. The yields of purified product were 10—12%.

The product from the reaction between *cyclo*pentylmagnesium bromide and β-piperidinopropiophenone hydrochloride was an oil which on distillation gave a fraction of b. p. 120—123°/0·1 mm. (42% yield) and a considerable quantity of non-volatile material. The volatile fraction solidified on storage (m. p. 43—45°) and after three crystallisations from ethyl acetate had m. p. 59—61° (Found: C, 76·6; H, 9·3; N, 6·8. Calc. for $C_{14}H_{21}ON$: C, 76·7; H, 9·6; N, 6·4%). The base was converted into the hydrochloride which, after recrystallisation from ethanol–ethyl acetate, had m. p. 136—138° not depressed on admixture with a specimen of 1-phenyl-3-piperidinopropan-1-ol hydrochloride, prepared by catalytic reduction of β-piperidinopropiophenone hydrochloride (Found: N, 5·5; Cl, 13·9. Calc. for $C_{14}H_{21}ON,HCl$: N, 5·5; Cl, 13·9%). Mannich and Lammering (*Ber.*, 1922, **55**, 3510) describe the base as having m. p. 68—69°, hydrochloride, m. p. 138°.

Quaternary Iodides (Table II, Nos. 4, 6, 7, 9, 10, 12).—The methiodides were prepared by mixing the amino-carbinol in a small volume of acetone with an excess (*ca.* 2 mols.) of methyl iodide. After several hours the product was filtered off and recrystallised. The ethiodides were prepared by adding an excess of ethyl iodide to a solution of the amino-carbinol in ethanol and boiling under reflux for 3 hours.

*Amino-*1-cyclo*hexyl-1-phenylalkan-1-ols by Catalytic Reduction.*—1-cyclo*Hexyl-1-phenyl-3-pyrrolidinopropan-1-ol* (Table II, No. 5). 1 : 1-Diphenyl-3-pyrrolidinopropan-1-ol (3 g.) (Part I, *loc. cit.*) was dissolved in glacial acetic acid (15 ml.), Adams's platinum catalyst (2·5 g.) (*Org. Synth.*, 1932, Coll. Vol. I, p. 452) added, and the mixture shaken in an atmosphere of hydrogen until the equivalent of 3·4 mols. had been taken up (2 hours). Water was added, the catalyst removed by filtration, excess of ammonia added, and the liberated base extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated. The residue (2·9 g.) had m. p. 69—75°. Crystallisation from light petroleum (b. p. 40—60°) (4 ml.) gave 1·9 g., m. p. 82—84°; recrystallisation gave 1-*cyclo*hexyl-1-phenyl-3-pyrrolidinopropan-1-ol (1·8 g.; 60%), m. p. 85·5—86·5°, not depressed on admixture with the compound prepared by the Grignard reaction, and giving an identical absorption spectrum (light absorption in 0·17% solution in ethanol: maximum, λ 258·5 mμ., ε 233). The light absorption of a 0·17% ethanolic solution of the corresponding diphenylcarbinol was maximal at λ 258·5 mμ., ε 520.

The experiment was repeated, reductions being stopped when different amounts of hydrogen had been absorbed, and the products recrystallised until pure (m. p. and absorption spectrum). The yields obtained when 3·5 and 4·0 mols. of hydrogen were absorbed were 42 and 23%, respectively; a pure product was not obtained from hydrogenations in which 3·25 mols. or less were absorbed. In an experiment on a larger scale, in which the diphenylcarbinol (30 g.), glacial acetic acid (120 ml.), and platinum catalyst (6 g.) were employed, the hydrogen absorption was stopped at 3·4 mols. after 9 hours; the yield of product (m. p. 84—86°) after three crystallisations was 19·3 g. (64%).

1-cyclo*Hexyl-1-phenyl-3-piperidinopropan-1-ol* (Table II, No. 8). Several small-scale hydrogenations, similar to those described above were carried out to determine the best level at which to stop hydrogen absorption. Yields of 66, 70, 74, and 70% of the product (crystallised to constant m. p. from light petroleum, b. p. 60—80°) were obtained when 3·0, 3·2, 3·3, and 3·4 mols. of hydrogen, respectively, were absorbed. In a larger-scale experiment [the diphenylcarbinol (25 g.), glacial acetic acid (100 ml.), platinum catalyst (2·5 g.)] hydrogenation was stopped when 3·3 mols. had been absorbed (20 hours). The yield of product (m. p. 113—115°; light absorption, maximum λ 258·5 mμ., ε 250; hydrochloride, m. p. 255°), after purification by three crystallisations from light petroleum (b. p. 60—80°), was 20·5 g. (80%). In another experiment in which 3·4 mols. of hydrogen were absorbed the yield was 68%. Similar

TABLE II.

Amino-cyclo*hexylcarbinols*, $C_6H_{11}\cdot CR^1(OH)\cdot[CH_2]_n\cdot CHR^2\cdot NR^3R^4$.

No.	R^1.	*n*.	R^2.	NR^3R^4.	Derivative.	M. p.*	Solvent for recrystn.†	Formula.	Analyses. Found, %. C.	H.	N.	Cl/I.	Required, %. C.	H.	N.	Cl/I.
1	Ph	0	H	$N<C_5H_{10}$	*Hydrochloride*	198°	EtOH–Et_2O	$C_{19}H_{29}ON$,HCl	70·2	9·6	4·1	—	70·5	9·3	4·3	—
2	Ph	1	H	NMe_2	*Base*	44—45	Petrol	$C_{17}H_{27}ON$	78·1	10·0	5·7	—	78·2	10·3	5·4	—
					Hydrochloride	211—212 (*d*) [a]	$COMe_2$	—	—	—	—	—	—	—	—	—
3	Ph	1	H	NEt_2	*Base*	50·5—52	Petrol	$C_{19}H_{31}ON$	78·4	10·7	4·7	—	78·9	10·7	4·8	—
					Hydrochloride	184—185 [b]	EtOH–EtOAc	—	—	—	—	—	—	—	—	—
4					*Methiodide*	160—162	EtOH–EtOAc	$C_{20}H_{34}ONI$	—	—	—	29·1	—	—	—	29·4
5	Ph	1	H	$N<C_4H_8$	*Base*	85·5—86·5	Petrol	$C_{19}H_{29}ON$	79·3	10·2	4·8	—	79·4	10·1	4·9	—
					Hydrochloride	226—227 (d)	EtOH–EtOAc	$C_{19}H_{29}ON$,HCl	—	—	—	11·0	—	—	—	11·0
6	—	—	—	—	*Methiodide*	204—205 (d)	EtOH	$C_{20}H_{32}ONI$	—	—	—	29·6	—	—	—	29·6
7	—	—	—	—	*Ethiodide*	158—159 (d)	EtOH–EtOAc	$C_{21}H_{34}ONI$	—	—	—	27·8	—	—	—	28·7
8	Ph	1	H	$N<C_5H_{10}$	Base	114—115 [c]	Petrol ‡	$C_{20}H_{31}ON$	79·7	10·1	4·8	—	79·7	10·3	4·7	—
					Hydrochloride	255 (d) [d]	EtOH	$C_{20}H_{31}ON$,HCl	—	—	—	10·6	—	—	—	10·5
9	—	—	—	—	Methiodide	203—204 [e]	EtOH	$C_{21}H_{34}ONI$	—	—	—	28·4	—	—	—	28·7
10	—	—	—	—	*Ethiodide*	179—180 (d)	EtOH–EtOAc	$C_{22}H_{36}ONI$	—	—	—	27·7	—	—	—	27·8
11	Ph	1	H	$N<C_4H_8O$	Base	114—116 [f]	Petrol	$C_{19}H_{29}O_2N$	75·1	9·6	4·5	—	75·2	9·6	4·6	—
					Hydrochloride	271—272 (d) [g]	EtOH	$C_{19}H_{29}O_2N$,HCl	—	—	—	10·6	—	—	—	10·5
12	—	—	—	—	*Methiodide*	219—220	EtOH–EtOAc	$C_{20}H_{32}O_2NI$	—	—	—	28·3	—	—	—	28·5
13	Ph	1	Me	NMe_2	*Hydrochloride*	198	EtOH–Et_2O	$C_{18}H_{29}ON$,HCl	69·0	9·7	4·7	11·4	69·3	9·6	4·5	11·4
14	Ph	1	Me	$N<C_5H_{10}$	*Hydrochloride*	244—245	EtOH–Et_2O	$C_{21}H_{33}ON$,HCl	71·8	9·3	3·6	—	71·7	9·7	3·8	—
15	Ph	1	Pr^n	NMe_2	*Hydrochloride*	243—244 (d)	EtOH–EtOAc	$C_{20}H_{33}ON$,HCl	70·5	9·9	4·3	10·5	70·7	10·0	4·1	10·5
16	Ph	1	Pr^n	$N<C_5H_{10}$	*Hydrochloride*	262—263 (d)	EtOH–EtOAc	$C_{23}H_{37}ON$,HCl	72·8	9·9	3·6	9·4	72·7	10·0	3·7	9·4
17	Ph	3	H	$N<C_5H_{10}$	*Hydrogen oxalate*	156—157	$COMe_2$	$C_{22}H_{35}ON,C_2H_2O_4$	69·0	8·6	3·5	—	68·7	8·8	3·3	—
18	Ph	4	H	$N<C_4H_8$	*Base*	98	Petrol	$C_{22}H_{35}ON$	—	—	4·3	—	—	—	4·6	—
					Hydrochloride	128	EtOH–Et_2O	$C_{22}H_{35}ON$,HCl	72·1	9·4	3·8	—	72·2	9·8	3·8	—
19	$CH<C_5H_{10}$	0	H	$N<C_5H_{10}$	*Hydrochloride*	208	EtOH–Et_2O	$C_{19}H_{35}ON$,HCl	69·1	10·6	4·1	—	69·2	10·9	4·3	—
20	$CH<C_5H_{10}$	1	H	$N<C_5H_{10}$	*Hydrochloride*	241—242	EtOH–Et_2O	$C_{20}H_{37}ON$,HCl	69·9	11·1	4·2	—	69·9	11·1	4·1	—
21	$CH<C_5H_{10}$	3	H	NEt_2	*Hydrochloride*	130—131	EtOH–Et_2O	$C_{21}H_{41}ON$,HCl	70·2	11·8	3·8	—	70·1	11·7	3·9	—
22	$CH<C_5H_{10}$	3	H	$N<C_4H_8$	*Hydrogen oxalate*	145	$COMe_2$	$C_{21}H_{37}ON,C_2H_2O_4$	67·3	9·9	3·5	—	67·2	10·0	3·4	—
23	$CH<C_5H_{10}$	4	H	$N<C_4H_8$	*Hydrochloride*	146	EtOH–Et_2O	$C_{22}H_{41}ON$,HCl	71·4	11·5	4·1	—	71·1	11·3	3·8	—
24	$CH<C_5H_{10}$	4	H	$N<C_5H_{10}$	*Hydrochloride*	182	EtOH–Et_2O	$C_{23}H_{43}ON$,HCl	71·6	11·4	3·7	9·1	71·6	11·4	3·6	9·2
25	$CH<C_5H_{10}$	5	H	$N<C_5H_{10}$	*Hydrogen oxalate*	138	EtOH–Et_2O	$C_{24}H_{45}ON,C_2H_2O_4$	68·7	10·4	2·9	—	68·9	10·4	3·1	—

[a–g] Denton *et al.* (*loc. cit.*) give m. p.s: (*a*) 210·5—212·5°, (*b*) 186·9—187·4°, (*c*) 114·3—115·0°, (*d*) 258·5°, (*f*) 116·3—117·0°, (*g*) Sublimes >225°. Ruddy and Buckley (*loc. cit.*) give m. p.s: (*a*) 212—213°, (*c*) 114—115°, (*d*) 245—246°, (*e*) 204·5—206·5°.

* (d) = with decomposition. † Petrol = light petroleum (b. p. 40—46°), except ‡ (b. p. 60—80°).

results were obtained when the hydrogenations were carried out at an initial pressure of 67 atm. The speed of hydrogenation was slower when 10% aqueous acetic acid or ethanol was used as solvent, and was faster when the hydrochloride was used in place of the free base.

Compounds 2, 3, and 18 (Table II) were prepared by similar methods.

1-cyclo*Hexyl*-3-*morpholino*-1-*phenylpropan*-1-*ol* (Table II, No. 11). 3-Morpholino-1 : 1-diphenylpropan-1-ol hydrochloride (1·9 g.) (Part I, *loc. cit.*) in ethanol (60 ml.) and water (10 ml.) was shaken with platinum catalyst (0·1 g.) in an atmosphere of hydrogen. The equivalent of 3 mols. of hydrogen was absorbed during 5 days, a white crystalline solid gradually separating. The mixture was warmed on the steam-bath to dissolve the precipitate, filtered hot, concentrated, and allowed to crystallise. The product (1·65 g., 80%) was pure 1-*cyclo*hexyl-3-morpholino-1-phenylpropan-1-ol hydrochloride, m. p. 271—2° (decomp.), from which the base, m. p. 114—116°, was obtained.

Compounds 1 *and* 13—17 (Table II). The corresponding diphenylcarbinol (5·0 g.) was dissolved in glacial acetic acid (20 ml.), platinum catalyst (1·0—1·5 g.) added, and the mixture shaken in an atmosphere of hydrogen until approximately 3·3 mols. had been absorbed. Water was added, the catalyst filtered off, and the filtrate basified with ammonia. The liberated base was extracted with ether, the ethereal solution dried (Na_2SO_4), and the ether evaporated. The residual oil, which did not crystallise on standing, was converted into its *hydrochloride*, which was recrystallised to purity as determined by constancy of m. p. and by absorption spectrum. (The preparation of the diphenylcarbinols required as starting products will be described in subsequent papers.)

1-(4-*Methyl*cyclo*hexyl*)-3-*piperidino*-1-p-*tolylpropan*-1-*ol*.—3-*Piperidino*-1 : 1-*di*-p-*tolylpropan*-1-*ol* was prepared by reaction of *p*-tolylmagnesium bromide with ethyl β-piperidinopropionate by the general method described in Part I (*loc. cit.*). The base, recrystallised from ethanol, had m. p. 140—141° (Found : C, 81·1; H, 8·7; N, 4·3. $C_{22}H_{29}ON$ requires C, 81·7; H, 9·0; N, 4·3%); *hydrochloride*, recrystallised from ethanol, m. p. 242—243° (decomp.) (Found : Cl, 9·9. $C_{22}H_{29}ON,HCl$ requires Cl, 9·9%).

The di-*p*-tolylcarbinol (4 g.) was dissolved in glacial acetic acid (40 ml.) and shaken in an atmosphere of hydrogen in the presence of platinum catalyst (1·01 g.). Hydrogen absorption ceased when approximately 3 mols. had been taken up. The product, 1-(4-methyl*cyclo*hexyl)-3-piperidino-1-*p*-tolylpropan-1-ol was worked up as the *hydrochloride*, m. p. 242° after recrystallisation from ethanol–ether (Found : C, 71·9; H, 9·4; N, 3·6. $C_{23}H_{35}ON,HCl$ requires C, 72·2; H, 9·8 N, 3·8%).

5-*Bromo*-1-cyclo*hexyl*-1-*phenylpentan*-1-*ol*.—5-Bromo-1 : 1-diphenylpentan-1-ol (15 g.) (to be described in a later paper) was dissolved in ethanol (100 ml.), platinum catalyst (1·5 g.) added, and the mixture shaken in an atmosphere of hydrogen. The speed of hydrogen absorption fell abruptly when 3 mols. of hydrogen had been taken up. The catalyst was filtered off, and the filtrate evaporated under reduced pressure. The residue was warmed on the steam-bath with piperidine (2 mols.). The resulting 5-piperidino-1-*cyclo*hexyl-1-phenylpentan-1-ol was isolated in the usual manner and converted into its hydrogen oxalate (Table II, No. 17).

*Amino-di*cyclo*hexylcarbinols* (Table II, Compounds 19—25).—The corresponding diphenylcarbinols were dissolved in acetic acid and shaken in an atmosphere of hydrogen in the presence of platinum catalyst until the equivalent of 6 mols. of hydrogen had been taken up and absorption had ceased. The products were worked up, as their hydrochlorides or hydrogen oxalates, as described above.

1-*Amino*-3-*phenylalk*-2-*enes* (Table III).—Dehydration of the carbinols to the alkenylamines was carried out by a method which was applied to all cases and is illustrated by the following example. The distilled bases (80—95% yield) were converted into *hydrochlorides* (addition of dry hydrogen chloride to a chloroform solution, followed by ether precipitation) or into *hydrogen oxalates* (addition of oxalic acid to an ethanolic solution, followed by ether precipitation).

3-*Phenyl*-1-*piperidinonon*-2-*ene* (Table III, No. 7).—3-Phenyl-1-piperidinononan-3-ol (12 g.) was dissolved in glacial acetic acid (120 ml.) and concentrated hydrochloric acid (36 ml.), and the solution boiled under reflux for 30 minutes. The solution was concentrated under reduced pressure, and the residue diluted with water and basified with excess of ammonia. The oil which separated was extracted with chloroform, the extract washed with water and dried (Na_2SO_4), and the chloroform evaporated. The residue was distilled under reduced pressure, b. p. 134—136°/0·05 mm.; yield 9·1 g. (80%). Treatment of a chloroform solution of the base with dry hydrogen chloride gave a hydrochloride, m. p. 155—175°; by several recrystallisations from ethanol–ethyl acetate pure 3-*phenyl*-1-*piperidinonon*-2-*ene hydrochloride* (m. p. 212°) was obtained.

Oxidation. Potassium permanganate (4·5 g.) in water (200 ml.) was added dropwise during 1 hour to a solution of the hydrochloride (1·25 g.) in water (20 ml.). The mixture was distilled in steam, and the oil extracted from the distillate by ether. The ethereal extract was dried (Na_2SO_4) and evaporated to give *n*-hexyl phenyl ketone (0·5 g.), b. p. 272°, m. p. 14—15° (lit., b. p. 276°, m. p. 17°) (Found : C, 82·2; H, 9·8. Calc. for $C_{13}H_{18}O$: C, 82·2; H, 9·5%); *p*-nitrophenylhydrazone, m. p. 127—128° (lit., m. p. 127—128°) (Found : C, 70·3; H, 7·5; N, 13·0. Calc. for $C_{19}H_{23}O_2N_3$: C, 70·1; H, 7·1; N, 12·9%).

1-cyclo*Hexyl*-1-*phenyl*-3-*piperidinoprop*-1-*ene* (Table III, No. 11).—Oxidation with aqueous potassium permanganate in a similar manner to that described above gave hexahydrobenzophenone, m. p. 55—56°, after recrystallisation from light petroleum (b. p. 60—80°) (lit., m. p. 59—60°) (Found : C, 83·0; H, 8·6. Calc. for $C_{13}H_{16}O$: C, 83·0; H, 8·5%); semicarbazone, m. p. 174° (lit., m. p. 175°) (Found : N, 17·0. Calc. for $C_{14}H_{19}ON_3$: N, 17·1%).

Phenyl- and cyclo*Hexyl-alkylamines* (Table IV).—The corresponding alkenylamine hydrochloride (5 g.) was dissolved in ethanol (20 ml.) and shaken with 3% palladised charcoal (3·0 g.) in an atmosphere of hydrogen until absorption had ceased. The catalyst was filtered off, the alcohol removed by evaporation, and the residual *hydrochloride* recrystallised to purity. As indicated on p. 54, 1-*cyclo*hexyl-

TABLE III.

1-*Amino*-3-*phenylalk*-2-*enes*, $CPhR^1{:}CH{\cdot}CH_2{\cdot}NR^2R^3$.

No.	R^1.	NR^2R^3.	B. p. of base.	Formula of salt.	M. p. of salt.	Solvent for recrystn. of salt.	Analyses. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
1	Me	NMe_2	122—125°/18 mm.	$C_{12}H_{17}N,HCl$	200—202°	EtOH–$COMe_2$	68·0	8·7	6·5	16·8	68·1	8·5	6·6	16·8
2	Pr^n	NEt_2	87—95/0·1 mm.	$C_{16}H_{25}N,C_2H_2O_4$	113—119	$COMe_2$	67·1	8·5	4·8	—	67·3	8·4	4·4	—
3	$C_5H_{11}{}^n$	NEt_2	110—115/0·1 mm.	$C_{18}H_{29}N,C_2H_2O_4$	57—60	EtOAc	67·9	8·6	4·0	—	68·8	8·9	4·0	—
4	$C_8H_{17}{}^n$	NEt_2	137—140/0·1 mm.	$C_{21}H_{35}N,C_2H_2O_4$	64—65	EtOAc	70·6	9·2	3·6	—	70·6	9·5	3·6	—
5	CH_2Ph	NEt_2	120—123/0·04 mm.	$C_{20}H_{25}N,HCl$	157—159	EtOH–EtOAc	76·1	8·3	4·3	11·5	76·1	8·2	4·4	11·3
6	Pr^n	NBu^n_2	123—125/0·1 mm.	$C_{20}H_{33}N,C_2H_2O_4$	90—95	EtOH–Et_2O	69·8	9·2	3·6	—	70·0	9·3	3·7	—
7	$C_6H_{13}{}^n$	$N<C_5H_{10}$	134—136/0·05 mm.	$C_{20}H_{31}N,HCl$	212	EtOH–EtOAc	74·4	10·0	4·2	11·0	74·7	10·0	4·3	11·0
8	$C_6H_{13}{}^n$	$N<C_5H_8$ [b]	110—118/0·02 mm.	$C_{20}H_{29}N,HCl$	221—221·5	EtOH–EtOAc	75·4	9·4	4·4	11·2	75·1	9·4	4·4	11·1
9	$C_8H_{17}{}^n$	$N<C_4H_8O$	154—156/0·1 mm.	$C_{21}H_{33}ON,C_2H_2O_4$	125—131	EtOH	67·4	8·5	3·5	—	68·0	8·6	3·5	—
10	$CH<C_5H_{10}$	NEt_2	123—125/0·3 mm.[c]	$C_{19}H_{29}N,HCl$	157—160	EtOAc	—	—	4·6	11·6	—	—	4·6	11·5
11	$CH<C_5H_{10}$	$N<C_5H_{10}$	—	$C_{20}H_{29}N,HCl$	206	EtOH–Et_2O	74·8	9·7	4·5	11·3	75·1	9·4	4·4	11·1
12	$CH<C_5H_{10}$ [a]	$N<C_5H_{10}$	—	$C_{20}H_{35}N,HCl$	230	H_2O	73·6	11·2	4·2	11·3	73·7	11·1	4·3	10·9

[a] Phenyl group of general formula replaced by *cyclo*hexyl. [b] $N<C_5H_8$ = 1 : 2 : 5 : 6-Tetrahydropyridino-. [c] Found: C, 84·5; H, 10·3; N, 5·3. $C_{19}H_{29}N$ requires C, 84·1; H, 10·7; N, 5·2%.

TABLE IV.

Phenyl- and cyclo*Hexyl-alkylamines*, $CHR^1R^2{\cdot}[CH_2]_n{\cdot}NR^3R^4$.

No.	*n*.	R^1.	R^2.	NR^3R^4.	Derivative.	M. p. or b. p.	Solvent for recrystn.	Formula.	Analyses. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
1	2	Ph	$C_6H_{13}{}^n$	$N<C_5H_{10}$	*Hydrochloride*	200—201°	EtOH–EtOAc	$C_{18}H_{29}N,HCl$	73·4	10·0	4·7	12·2	73·1	10·2	4·7	12·0
2	2	Ph	$C_6H_{13}{}^n$	$N<C_5H_{10}$	*Base*	120—122/0·02 mm.	—	$C_{20}H_{33}N$	83·2	11·6	4·9	—	83·6	11·5	4·9	—
					Hydrochloride	181	EtOH–EtOAc	$C_{20}H_{33}N,HCl$	—	—	4·4	11·2	—	—	4·3	11·0
3	2	Ph	CH_2Ph	NEt_2	*Base*	112—114/0·02 mm.	—	$C_{20}H_{27}N$	85·2	9·8	5·0	—	85·4	9·6	5·0	—
					Hydrochloride	95—97	EtOAc	$C_{20}H_{27}N,HCl$	75·5	8·8	4·5	11·1	75·5	8·8	4·4	11·2
4	2	Ph	$CH<C_5H_{10}$	NEt_2	*Base*	190—192/18 mm.	—	$C_{19}H_{31}N$	83·4	11·4	5·3	—	83·5	11·4	5·1	—
					Hydrochloride	125—126	EtOAc	$C_{19}H_{31}N,HCl$	—	—	4·4	11·3	—	—	4·5	11·4
5	2	Ph	$CH<C_5H_{10}$	$N<C_5H_{10}$	Hydrochloride	222—223 [a]	EtOH–Et_2O	$C_{20}H_{31}N,HCl$	74·6	9·9	4·6	—	74·6	10·0	4·4	—
6	2	$CH<C_5H_{10}$	$CH<C_5H_{10}$	$N<C_5H_{10}$	*Hydrochloride*	268—269	EtOH–Et_2O	$C_{20}H_{37}N,HCl$	73·2	11·5	4·2	11·0	73·3	11·6	4·3	10·8
7	4	$CH<C_5H_{10}$	$CH<C_5H_{10}$	$N<C_4H_8$	*Hydrochloride*	180	EtOH–Et_2O	$C_{21}H_{39}N,HCl$	73·7	11·3	4·2	—	73·8	11·7	4·1	—
8	4	$CH<C_5H_{10}$	$CH<C_5H_{10}$	$N<C_5H_{10}$	*Hydrochloride*	222—224	EtOH–Et_2O	$C_{22}H_{41}N,HCl$	73·9	11·4	4·1	—	74·3	11·8	3·9	—

[a] Ruddy and Buckley (*loc. cit.*) give m. p. 227—228°.

1-phenyl-3-piperidinopropane (No. 5) was also prepared by two other routes: (*a*) hydrogenation (4 mols.) of 1 : 1-diphenyl-3-piperidinoprop-1-ene (Part I, *loc. cit.*) in the presence of platinum catalyst, and (*b*) hydrogenation (3 mols.) of 1 : 1-diphenyl-3-piperidinopropane (Part I, *loc. cit.*) in the presence of platinum catalyst. 1 : 1-Di*cyclo*hexyl-3-piperidinopropane (No. 6) was also prepared by hydrogenation (4 mols.) of 1-*cyclo*hexyl-1-phenyl-3-piperidinoprop-1-ene and by hydrogenation (3 mols.) of 1-*cyclo*hexyl-1-phenyl-3-piperidinopropane in the presence of platinum catalyst. 1 : 1-Di*cyclo*hexyl-5-piperidino- and -5-pyrrolidino-pentane (Nos. 7 and 8) were prepared by complete hydrogenation (platinum catalyst) of the corresponding 5-amino-1 : 1-diphenylpentanes (to be described in a later paper).

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM. [*Received, September 19th*, 1950.]