CLV.—*The Cinchona Alkaloids and Substances related to them. Part I. Some Piperidinomethylcarbinol Hydrochlorides.*

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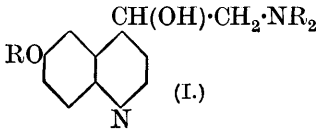
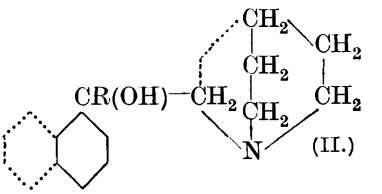
MANY attempts have been made to imitate the fundamental cinchonoid molecule, notably by Rabe and by Kaufmann. The latter author (*Ber.*, 1912, **45**, 3090; 1913, **46**, 57, 2929; D.R.-P. 268,931) attributed the action of quinine to the group $-CH(OH)-\overset{|}{C}H-N<$ and showed that some compounds of the type (I) resembled quinine



(I.)



(II.)

on the basis of the physiological tests then available. The work of Rabe (*Ber.*, 1917, **50**, 144, etc.) was similar, but developed on more complex synthetic lines (compare *Ber.*, 1918, **51**, 1360).

Within recent years, a large number of compounds have been investigated by different workers in an endeavour to obtain a satisfactory antimalarial drug. The majority of these compounds have been essentially different structurally from the cinchona alkaloids. In the present communication, we describe the preparation of a series of compounds of the general formula (II) (in which the dotted lines have no chemical significance) which bear what may be called pictorial resemblance to the cinchona alkaloids (compare the pictorial resemblance between the eucaines and cocaine). These compounds are for the most part readily prepared by treating 1-phenacylpiperidine with a Grignard reagent, although in a few instances, *e.g.*, when R is *n*-hexyl, *n*-heptyl or *cyclo*hexyl, the synthesis has failed completely. For physiological tests, the carbinol hydrochlorides have been prepared, and the following are described in the experimental section: *phenyl-*, *phenylmethyl-*, *phenylethyl-*, *phenyl*-n-*propyl-*, *phenyl*-n-*butyl-*, *diphenyl-*, *phenylbenzyl-*, *phenyl-β-phenylethyl-*, *phenyl-γ-phenylpropyl-*, *phenyl-δ-phenylbutyl-*, and *phenyl-α-naphthyl-ω-piperidinomethylcarbinol hydrochlorides*. None of these compounds possesses antimalarial activity, a fact which suggests that the essential missing factor is the basic quinoline structure. The synthetic method, however, appears to be capable of general application, and is being used in the synthesis

of the less readily accessible quinoline analogues of phenacylpiperidine.

A second synthetic method has been investigated, which is also apparently capable of extension to the synthesis of cinchonoid substances. For example, phenyl β-phenylethyl ketone (III) is readily converted into the bromo-derivative (IV), which reacts with piperidine to give *phenyl α-piperidino-β-phenylethyl ketone* (V). The latter may alternatively be obtained by the action of benzyl chloride on the sodium derivative of phenacylpiperidine.

$$\text{(III.) } Ph{\cdot}CO{\cdot}CH_2{\cdot}CH_2Ph \longrightarrow \text{(IV.) } Ph{\cdot}CO{\cdot}CHBr{\cdot}CH_2Ph$$

$$\downarrow$$

$$Ph{\cdot}CO{\cdot}CH_2{\cdot}NC_5H_{10} \longrightarrow \text{(V.) } Ph{\cdot}CO{\cdot}CH(NC_5H_{10}){\cdot}CH_2Ph$$

This method has been applied to the synthesis of piperidinodeoxybenzoin, $Ph{\cdot}CO{\cdot}CHPh{\cdot}NC_5H_{10}$, a substance previously obtained by Rabe (*Ber.*, 1912, **45**, 2169) by treating sodiodeoxybenzoin with 1-chloropiperidine.

Experimental.

Phenyl α-Piperidino-β-phenylethyl Ketone.—(1) *Preparation of phenyl β-phenylethyl ketone.* The methods described in the literature being found unsatisfactory, the following method was used. β-Phenylethyl bromide was obtained in 91% yield by the interaction of 246 g. of β-phenylethyl alcohol and 115 c.c. of phosphorus tribromide. The bromide (337 g.) was refluxed for 3½ hours with a mixture of 135 g. of potassium cyanide, 135 g. of water, and 340 c.c. of alcohol. β-Phenylpropionitrile was obtained in 91% yield in the second stage, *i.e.*, 81% calculated on the alcohol used. A Grignard reagent prepared from 78 g. of bromobenzene was gradually treated with 26 g. of β-phenylpropionitrile. The vigorous reaction over, the whole was heated for ½ hour on the water-bath, the mixture decomposed in the usual manner, and the ketone purified by distillation under reduced pressure. 18 G. of pure phenyl β-phenylethyl ketone, b. p. 196°/18 mm., were obtained.

(2) *Preparation of phenyl α-bromo-β-phenylethyl ketone.* A solution of the ketone (1 mol.) and bromine (1 mol.) in glacial acetic acid became decolorised at about 50°. It was then poured into water, and the solid product was crystallised from alcohol, the *bromo*-compound (93%) being obtained as needles, m. p. 50—51° (Found : Br, 27·4. $C_{15}H_{13}OBr$ requires Br, 27·7%).

(3) *Action of piperidine on phenyl α-bromo-β-phenylethyl ketone.* Equal weights of the bromo-compound and piperidine were heated together in benzene solution for ½ hour at 100°. The cooled mixture was well shaken with alkali, and the benzene layer was shaken with water and dried over sodium sulphate. Evaporation of the solvent

gave *phenyl α-piperidino-β-phenylethyl ketone*, which crystallised from alcohol in colourless leaflets, m. p. 77—78·5°.

Phenyl α-piperidino-β-phenylethyl ketone was also prepared as follows: Phenacylpiperidine (see below) (1 mol.) was added to powdered sodium (1 atom.) covered with 100 c.c. of toluene. The mixture was boiled until the sodium had disappeared, and then benzyl chloride (1 mol.) was added. The boiling was continued for ½ hour, the mixture cooled and extracted with water, the toluene separated, dried, and removed, and the residue crystallised from methyl alcohol. The product had m. p. 80—81°, and 78—79° in admixture with the product described above (Found: N, 5·3. $C_{20}H_{23}ON$ requires N, 4·8%).

Phenacylpiperidine.—Schmidt and van Ark (*Arch. Pharm.*, 1900, **238**, 330) obtained this compound in an impure condition, but did not characterise it.

(*a*) The method of Rabe, Schneider, and Braasch (*Ber.*, 1908, **41**, 874) was used, benzene being substituted for ether, and gave a 60% yield (b. p. 168°/26 mm.).

(*b*) A considerable saving of piperidine was effected by using the following process: A solution of 80 g. of phenacyl bromide in 400 c.c. of benzene was added within 30 minutes to a well-shaken cold mixture of 50 g. of piperidine, 70 g. of anhydrous potassium carbonate, and 400 c.c. of benzene. Water was added, and the benzene layer was separated and extracted three times with water and then twice with 20% hydrochloric acid. The united acid solutions were made ammoniacal and extracted with ether. The ethereal layer was washed with a little water, dried over sodium sulphate, and evaporated. Distillation of the residue under diminished pressure gave 50 g. of almost colourless phenacylpiperidine of constant b. p.

m-*Nitrophenacyl Bromide.*—The preparation by the method of Evans and Brooks (*J. Amer. Chem. Soc.*, 1908, **30**, 406) was less satisfactory than the following modification of the process described by Hunnius (*Ber.*, 1877, **10**, 2008): phenacyl bromide was slowly added to 10 parts of nitric acid (*d* 1·5) at − 10° to − 5°, the solution poured on ice, and the precipitate collected, digested with ether to remove the *o*-nitro-compound, and crystallised from alcohol; the yield of *m*-nitrophenacyl bromide, m. p. 80—81°, was 70%.

Action of Piperidine on m-*Nitrophenacyl Bromide.*—Although the bromide condensed readily with piperidine under the conditions used for the preparation of phenacylpiperidine (second method), the isolation of the product was not accomplished. Vacuum distillation caused explosive decomposition. Purification by crystallisation gave oily products, and although the picrate was obtained

as a highly crystalline substance, m. p. 175—176°, its subsequent decomposition by alkali gave amorphous products. In a second experiment, a benzene solution of *m*-nitrophenacyl bromide (1 mol.) was added to one of piperidine (2 mols.). After several hours, the precipitated piperidine hydrobromide was removed by filtration, and the filtrate evaporated. When the residue was stirred with dilute acetic acid, an amorphous solid was obtained which could not be made to crystallise and had an indefinite m. p.

Piperidinodeoxybenzoin.—A mixture of equal weights of benzoin and thionyl chloride was warmed until a clear solution was obtained, much warm water was then added, and the mixture stirred until it was cold (compare Schroeter, *Ber.*, 1909, **42**, 2348). The chlorodeoxybenzoin obtained was crystallised from chloroform by addition of light petroleum (b. p. 40—60°) and recrystallised from methyl alcohol; it then had m. p. 66—67° (Schroeter gives m. p. 68·5° after softening at 66°; Curtius and Lang, *J. pr. Chem.*, 1891, **44**, 548, give m. p. 65°).

The chloro-compound was covered with its own weight of piperidine, and the mixture warmed to 100° during 20 minutes. It was repeatedly extracted with water, and the gummy residue was crystallised from alcohol, needles, m. p. 85—86°, being obtained (Rabe and Rieper, *loc. cit.*, give m. p. 82°).

Phosphorus trichloride was almost without action on benzoin, and phosphorus pentachloride gave a mixture which could not be purified.

Phenyl-ω-piperidinomethylcarbinol.—Phenacylpiperidine was reduced as described by Rabe (*Annalen*, 1909, **365**, 377), but the product was worked up as follows: the alkaline alcoholic reduction mixture was treated with water, and most of the alcohol distilled off. The residue was extracted with ether, the extract dried over sodium sulphate and evaporated, and the residue distilled under reduced pressure. The base had the properties recorded by Rabe. The *hydrochloride*, prepared from the base and dry hydrogen chloride in light petroleum, had m. p. 192—194° (Found: Cl, 14·5. $C_{13}H_{19}ON,HCl$ requires Cl, 14·7%).

Phenylmethyl - ω - piperidinomethylcarbinol Hydrochloride.—An ethereal solution of phenacylpiperidine (1 mol.) was gradually added to a Grignard reagent prepared from methyl iodide (2 mols.) and magnesium (4 atom.) (with intermediate decantation from undissolved magnesium). The mixture was gently boiled for ½ hour and then decomposed with aqueous ammonium chloride. The ethereal solution was separated and extracted with dilute hydrochloric acid, and the acid layer, after being extracted with a little ether, was rendered ammoniacal and extracted with light petroleum (b. p.

60—80°). This extract was dried over sodium sulphate and saturated with dry hydrogen chloride; the *carbinol hydrochloride* was then obtained as a white microcrystalline powder, m. p. 140—141° after being dried at 100° (Found: N, 5·8; Cl, 14·0. $C_{14}H_{21}ON,HCl$ requires N, 5·5; Cl, 13·9%).

Phenylethyl-ω-piperidinomethylcarbinol hydrochloride was obtained by the method used for the methyl analogue. It was precipitated by hydrogen chloride from a light petroleum solution of the base, crystallised from alcohol–ether, dried at 100°, and obtained as a microcrystalline powder, m. p. 171—173° after softening at 168° (Found: N, 5·6; Cl, 13·5. $C_{15}H_{23}ON,HCl$ requires N, 5·2; Cl, 13·2%).

Phenyl-n-*propyl-ω-piperidinomethylcarbinol Hydrochloride.*—Interaction of phenacylpiperidine and magnesium propyl bromide (2 mols.) was very vigorous. The *carbinol hydrochloride* was obtained, as described under the preceding compounds, as a microcrystalline powder, m. p. 185—187° after being dried at 100° (Found: Cl, 13·0. $C_{16}H_{25}ON,HCl$ requires Cl, 12·5%).

Phenyl-n-*butyl-ω-piperidinomethylcarbinol Hydrochloride.*—When phenacylpiperidine was added to 2 mols. of ethereal magnesium butyl bromide, a solid formed on the surface, but later redissolved. The *hydrochloride* precipitated from light petroleum was crystallised from alcohol–ether and dried at 100°. It was a microcrystalline powder, m. p. 166—169° (Found: Cl, 12·0. $C_{17}H_{27}ON,HCl$ requires Cl, 11·9%).

Action of Magnesium n-*Hexyl and* n-*Heptyl Iodides on Phenacylpiperidine.*—When an ethereal solution of phenacylpiperidine (1 mol.) was added to a Grignard reagent made from magnesium (4 atom.) (decantation) and *n*-hexyl or *n*-heptyl iodide (2 mols.), although normal interaction appeared to occur, the basic compound was completely converted into phenacylpiperidine hydrochloride (Found: Cl, 14·7. Calc.: Cl, 14·8%), m. p. 213—219° or 216—220°; mixed m. p. 215—220°).

Diphenyl-ω-piperidinomethylcarbinol Hydrochloride.—After addition of the phenacylpiperidine to the magnesium phenyl bromide solution (2 mols.) the mixture was heated for some time, cooled, and decomposed with ammonium chloride solution. The ethereal layer was extracted with dilute hydrochloric acid, and the extract was shaken with ether, boiled to remove ether, and kept; the *carbinol hydrochloride* then separated in long colourless needles, m. p. 214—218° after drying at 100° (Found: N, 4·5; Cl, 11·9. $C_{19}H_{17}ON,HCl$ requires N, 4·5; Cl, 11·2%).

Phenylbenzyl-ω-piperidinomethylcarbinol Hydrochloride.—On addition of phenacylpiperidine to the magnesium benzyl chloride solu-

tion (2 mols.), a white precipitate formed and later dissolved. The mixture was gently boiled for ¼ hour, cooled, and decomposed with ammonium chloride solution. The aqueous layer was extracted with ether and the combined ethereal solutions were shaken with a mixture of equal volumes of water and concentrated hydrochloric acid. The *carbinol hydrochloride*, which separated as a crystalline precipitate, was washed with ether, recrystallised from alcohol and obtained in spear-shaped needles, m. p. 238—244°, sparingly soluble in dilute hydrochloric acid or cold alcohol but very soluble in warm alcohol (Found : Cl, 10·7. $C_{20}H_{25}ON$,HCl requires Cl, 10·7%).

Phenyl-β-phenylethyl-ω-piperidinomethylcarbinol Hydrochloride.—The mixture resulting from the interaction of phenacylpiperidine and 2 mols. of magnesium β-phenylethyl bromide was decomposed with ammonium chloride solution, and the ethereal layer shaken with concentrated hydrochloric acid mixed with an equal volume of water. The *carbinol hydrochloride* which separated was washed with water and ether and dried at 100°. More was obtained by extracting the combined aqueous liquors, rendered ammoniacal, with light petroleum and saturating the dried extract with hydrogen chloride (total yield, 65%); m. p. 211—216° (Found : N, 4·0; Cl, 10·2. $C_{21}H_{27}ON$,HCl requires N, 4·05; Cl, 10·3%).

Phenyl-γ-phenylpropyl-ω-piperidinomethylcarbinol Hydrochloride.—The product resulting from the interaction of phenacylpiperidine with 2 mols. of magnesium γ-phenylpropyl bromide was treated as usual, the *hydrochloride* separating when the ethereal solution was shaken with 20% hydrochloric acid. It was washed with ether and dried at 100°, and then melted at 209—210° (Found : Cl, 9·8. $C_{22}H_{29}ON$,HCl requires Cl, 9·9%).

Phenyl-δ-phenylbutyl-ω-piperidinomethylcarbinol Hydrochloride.—The preparation from phenacylpiperidine and magnesium δ-phenylbutyl bromide (2 mols.) was carried out by the method used for the β-phenylethyl derivative. The *hydrochloride* crystallised from alcohol, containing dilute hydrochloric acid, in colourless needles, m. p. 173—174° after being dried at 100°. It was very soluble in warm alcohol and almost insoluble in cold dilute hydrochloric acid (Found : Cl, 9·5. $C_{23}H_{31}ON$,HCl requires Cl, 9·5%).

Phenyl-α-naphthyl-ω-piperidinomethylcarbinol.—Phenacylpiperidine and magnesium α-naphthyl bromide reacted normally. The mixture was heated for 1 hour in warm water, cooled, and decomposed with ammonium chloride solution. The ethereal layer was shaken with its own bulk of 20% hydrochloric acid and again with a smaller amount of dilute acid. The combined acid extracts were shaken with ether, warmed to expel ether, and rendered ammoniacal. The gum produced became solid after much digestion with hot

water and was then crystallised successively from alcohol and light petroleum (b. p. 80—100°). From both solvents the *carbinol* separated in sparkling nodules, m. p. 114—115° (Found: N, 4·2. $C_{23}H_{25}ON$ requires N, 4·2%).

Action of Magnesium cyclo*Hexyl Bromide on Phenacylpiperidine.*—The preparation was conducted as in the case of the other carbinols. The phenacylpiperidine (1 mol.) appeared to react normally with the Grignard reagent, of which 2, 5, and 10 mols. were used in three experiments. A hydrochloride was obtained (Found: Cl, 13·7, 12·7, and 14·3% respectively); that produced in the last case had m. p. 217—220° after crystallisation from alcohol and was practically pure phenacylpiperidine hydrochloride.

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