ence of Lindlar's catalyst. The hydrogenation was allowed to go to completion. The uptake was 24 cc. (2.5 moles) of hydrogen. After completion of the hydrogenation the solution was filtered and evaporated to dryness and the residual oil was dissolved in ethyl acetate. Addition of chloroform precipitated 0.02 g. of amorphous material. The mother liquor was then crystallized from ethyl acetate and petroleum ether (b.p. 65°) to yield 0.047 g. of the hexahydrocarboxylic acid (XII) as colorless prisms of m.p. 168–170°. The substance showed no ferric chloride test. One more crystallization from the same solvent mixture gave the analytical sample, m.p. 192–194°.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.51; H, 7.04.

Lactonization (XVI). A solution of XII in glacial acetic acid containing a drop of concentrated hydrobromic acid (48%) left on evaporation in the desiccator at 20° fine feathery crystals, m.p. 205–207°, at 180° sublimation and transformation to stubby cubes. Although the analysis (found: C, 57.89; H, 6.62) indicated incomplete lactonization or retention of $^1/_2$ mole of water (dried at 100° *in vacuo*), the infrared spectrum (KBr pellet) showed a strong saturated lactone band at 5.62 μ in addition to a band for COOH at 5.80 μ.

Conversion of the hexahydrodicarboxylic acid (XII, *m.p. 194°*) *to the 2,3,6-tricarboxycyclohexanepropionic acid* (XI). A solution of 70 mg. of the hexahydrodicarboxylic acid XII in 5 cc. of absolute ether was reacted at room temperature with 4 cc. of a 0.2*N* ethereal solution of diazomethane. After completion of the reaction and evaporation to dryness the oily dimethyl ester was taken up in 10 cc. of 50% aqueous dioxane. Three equal portions of this solution were mixed with 3 cc. of an aqueous solution of periodic acid containing 6.8 g. of H_5IO_6 in 100 cc. of water. One portion was kept at 80° for 10 hr. Then 0.5 cc. of glacial acetic acid containing 0.5 cc. of 30% H_2O_2 was added and the reaction mixture was kept at 80° for 1 hr. After evaporation to dryness in a vacuum desiccator the residue was taken up in 3 cc. of 50% aqueous dioxane and heated on the steam bath with an equal volume of 5*N* hydrochloric acid. After evaporation to dryness the residual lacquer was extracted with ether. The ether-soluble material was chromatographed in the following three solvent systems: (*A*) phenol-formic acid-water (120 g.:1.6 cc.:40 cc.), R_f value 0.6; (*B*) 2-butanol-formic acid-water (75:15:10), R_f 0.7; (*C*) 99% of a mixture of 2 parts of methanol, 1 part of benzene, 1 part of 1-butanol, and 1 part of water, and 1% of a 15% aqueous ammonia solution, R_f value 0.3. The spraying reagent used was a weakly ammoniacal solution of 0.5 g. of brom phenol blue in 100 cc. of 95% ethanol. The R_f values of authentic XI were identical (see Fig. 1) in every respect.

Conversion of the tetracarboxylic acid X *to one of the hydrolysis products of tetramethyl trans-cis-trans-cyclohexane-1,2,3,4-tetracarboxylate* (XVa). In order to increase the differential reactivity between the conjugated and the unconjugated double bonds in X the tetramethylester (0.586 g.), obtained as a colorless oil by methylation with excess diazomethane in ethereal solution, was hydrogenated in ethyl acetate using 10% palladium-on-carbon as a catalyst. Within 12 min. 39 cc. of hydrogen (1 mole) had been taken up. There was no clear indication of a break in the rate of hydrogen uptake. The hydrogenation was therefore discontinued at this point. The reaction mixture, after evaporation of the solvent, left 0.6 g. of a colorless oil which was heated with 10 cc. of concentrated nitric acid (d = 1.4) at 150° (oil bath) for 2 hr. until the lively evolution of nitrous gases had subsided. After evaporation to dryness the noncrystalline residue was refluxed in 5 cc. of acetyl chloride for 5 hr. and, after evaporation to dryness, separated into a chloroform-soluble part, containing 124 mg. of a light-colored oil, and a chloroform-insoluble part, soluble in ether, consisting of 165 mg. of a brown oil. The infrared spectrum of the chloroform-soluble fraction showed, in chloroform solution, a hydroxyl band at 2.90μ, anhydride bands at 5.36 and 5.58 μ, and a doublet at 5.79–5.82 μ, indicative of free carboxyls. This material, presumably largely the monoanhydride of a tetracarboxylic acid, was reconverted into the free acid by refluxing in water for 2 hr. After evaporation to dryness the brown residue was extracted with ether. This ether extract was used for chromatographic analysis in three different solvent systems (see above and Fig. 2). One of the two spots in the chromatogram of the hydrolyzate of authentic tetramethylester of XVa was identical with that of the major oxidation product from X. Fractionation of the ether-soluble brown residue using chloroform and ethyl acetate gave a small amount of crystalline material showing a characteristic crystalline transformation into colorless long daggers at 160–180°, m.p. 185–186°, depressed to 181° on admixture with a crystalline product (m.p. 195–197°) obtained by hydrolysis of the tetramethyl ester of XVa by refluxing in dioxane 5*N* hydrochloric acid (1:1) for 6 hr.

Acknowledgment. We are greatly indebted to Dr. K. Freter for generous assistance with the preparation and paper chromatographic analysis of compounds, and to Dr. W. A. Alford for titrations and analyses.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Quinuclidines. I. 4-Phenylquinuclidines as Potential Analgesics*

T. D. PERRINE

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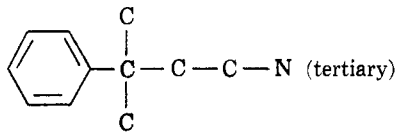
This paper presents the synthesis and structure proof of 4-phenylquinuclidine, the first 4-arylquinuclidine to be reported. The physical and physiological properties are briefly discussed, and several related substances are described.

With few exceptions, substances which are potent analgesics[1] have the common partial structure exemplified in I.

4-Phenylquinuclidine (II) has such a structure. We have been intrigued by the symmetry of II, and felt that examination of it and related compounds might lead to substances of pharmacological interest. Physiological activity in the quinuclidine

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.



I

series is, of course, not without precedent. The cinchona alkaloids are examples. Of more interest is the recent finding by Sternbach and Kaiser[2] that esters of 3-quinuclidinol show striking physiological action compared with the esters of other amino alcohols.

We have synthesized II as well as its 3-keto (III), 3-hydroxy (IV), 3-acetoxy (Va), and 3-propionoxy (Vb) derivatives. These substances are in the process of being tested for analgesic activity in mice.[3]

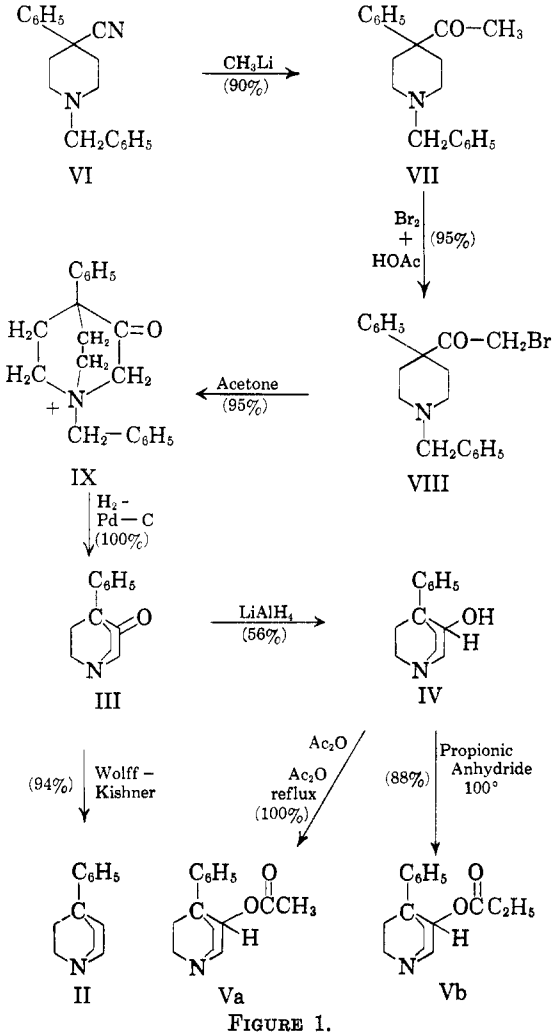


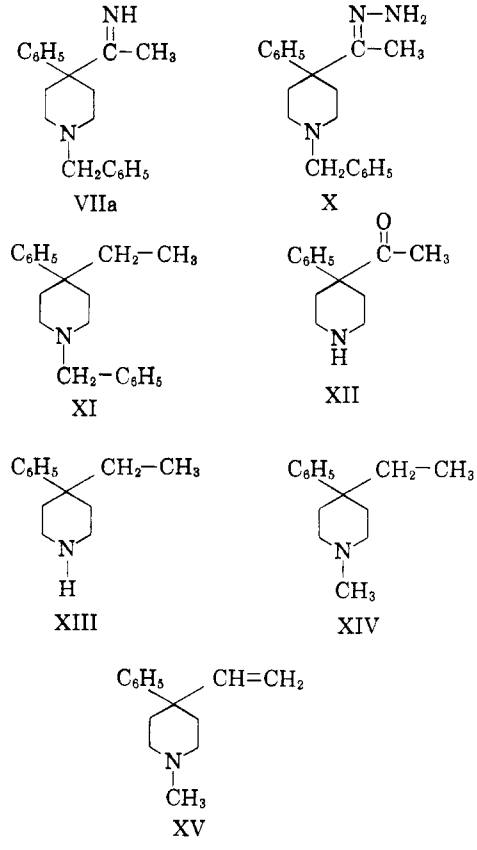
FIGURE 1.

To date we have had only preliminary reports on compounds II and III, both of which show analgesic action. II is apparently quite toxic.

Syntheses were accomplished by the reaction sequence outlined in Fig. 1 (yields being given in parenthesis).

The reaction of 1-benzyl-4-cyano-4-phenylpiperidine (VI)[4] with methyllithium led without complication to the imine of 4-acetyl-1-benzyl-4-phenylpiperidine. Imines of this type seem to be quite stable, and this one was obtained analytically pure by vacuum sublimation followed by recrystallization from ether–petroleum ether. The infrared spectrum shows a strong C=N absorption at 1639 cm.$^{-1}$ Refluxing 5 hr. with 2.5N HCl is sufficient to decompose the imine with formation of the expected ketone (VII).[5]

When compound VII was reduced with hydrogen and a palladium-charcoal catalyst in acidic me-



dium, toluene was evolved, and a quantitative yield of 4-acetyl-4-phenylpiperidine was obtained. Attempted bromination of this material in dioxane led to recovered starting material. However, bromination of VII·HCl in glacial acetic acid led to 1-benzyl-4-bromoacetyl-4-phenylpiperidine (VIII)

(1) H. Isbell [*Bulletin on Narcotics*, **VII**, 5 (1956)] discusses the fact that to date it has not been possible to separate analgesic action from addiction liability, and suggests that this may be the consequence of fashioning analgesics after structure I. He proposes that analgesic action be sought in entirely different structures, utilizing new criteria of analgesic action.

(2) L. A. Sternbach and S. Kaiser, *J. Am. Chem. Soc.*, **74**, 2219 (1952).

(3) These tests are being conducted by Dr. N. B. Eddy and associates at this Institute and will be reported in more detail elsewhere.

(4) We are greatly indebted to Dr. C. M. Suter, of the Sterling-Winthrop Research Institute for a very generous supply of compound VI.

(5) Compound VII shows no analgesic activity.

hydrobromide.[6] When this was converted to the base and dissolved in acetone, 1-benzyl-3-keto-4-phenylquinuclidinium (IX) bromide separated almost immediately.

Hydrogenation of the quaternary bromide in aqueous methanol using 10% Pd-charcoal catalyst required 1 hour or less and led to a quantitative yield of 3-keto-4-phenylquinuclidine (III). Compound III was then reduced by the Huang-Minlon modification[7] of the Wolff-Kishner process to II, and by lithium aluminum hydride to carbinol IV. The latter reaction was not as smooth as one might have expected and the yield of pure IV was only 56%. The secondary product, which had in some degree the properties of a quaternary hydroxide or zwitterion (amorphous gum, very soluble in water, difficulty extractable by chloroform) has not been further examined. Acylation of IV was effected by heating with the appropriate acid anhydrides to give esters Va and Vb.

The structures assigned to the compounds herein reported rest largely on the methods used in their synthesis and their further reactions. Both seem fairly straightforward. The method of forming the bridgehead (VIII → IX) has not previously been reported in the quinuclidine series, although it is fairly similar to the 4 β-bromoethylpiperidine ring closure[8] used for quinuclidine itself. The facile ring closure of 1,4-dimethylpiperazine with ethylene bromide to form the quaternary salt[9] is also of interest in this connection. The infrared absorption[10] of the carbonyl function at 5.77 μ in III as compared with 5.85 μ for 4-acetyl-4-phenylpiperidine (XII), 5.87 μ for VII, 5.86 μ for VII·HCl, and 5.82 μ for VIII·HBr indicates a constraint in bond mobility consistent with the assigned structure.

There is no reason to suppose that a rearrangement would occur in the Wolff-Kishner reduction of III[11]. Clemo and Metcalf[12] have reduced 3-ketoquinuclidine to quinuclidine by this process. There is the possibility of acyl cleavage[13] in these reductions, but our anticipation of trouble in this regard was unwarranted: The reduction proceeded smoothly to compound II. Reasonably unequivocal proof of the latter structure was obtained in the Hoffmann exhaustive methylation, when one of the reaction products[14] (XV), after catalytic hydrogenation, proved to be 4-ethyl-1-methyl-4-phenylpiperidine (XIV) identical in all respects with material prepared by the Wolff-Kishner reduction of XII followed by formaldehyde-formic acid methylation. While it may seem to be questionable logic to advance a Wolff-Kishner product as reference material in this case, we find partial vindication in the case of 1,4-dimethyl-4-phenylpiperidine which we have prepared both by the Wolff-Kishner reduction of the 4-aldehyde and by a totally unrelated method starting with β-methylcinnamic ester.[15]

Our work with the 4-phenylquinuclidines has been a delightful experience. Both salts and bases are very stable substances with high non-decomposition melting points[16] and high vapor pressures, subliming readily either at atmospheric pressure or in vacuum. Several of the substances, notably Va and II perchlorate have characteristic, rather pleasant odors.[17] The crystalline forms encountered are especially beautiful, often consisting of large, chunky, perfectly transparent crystals, when the materials are crystallized from solution or sublimed on the hot stage. As we have noted above, the yields are quite satisfactory in almost every instance, and no difficulty has been encountered in bringing the substances to a state of analytical purity.[18]

EXPERIMENTAL[19]

Melting points and elemental analysis of the compounds prepared are given in Table I.

4-Acetyl-1-benzyl-4-phenylpiperidine (VII) *and its imine* (VIIa). A 0.5 molar quantity (156.4 g.) of 1-benzyl-4-cyano-4-phenylpiperidine[4] hydrochloride was converted to the

(6) Formulation of this substance as an α-bromo ketone is supported by the fact that it produces a rather pronounced and long lasting dermatitis, which is accompanied by a marked sensitization of the skin to sunlight. The onset of the dermatitis is quite insidious, and care should be exercised in handling this material.

(7) Ethylene glycol was used as a solvent.

(8) R. Lukes, *et al.*, *Chem. Listy*, **50**, 1624 (1956); *Chem. Abstr.*, **51**, 2779c.

(9) S. M. McElvain and L. W. Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).

(10) Most spectra determinations are by H. K. Miller of this laboratory, who is making an extended survey of these and related compounds which will probably be reported elsewhere, in detail.

(11) D. Todd, *Org. Reactions*, **4**, 378 (1948).

(12) G. R. Clemo and T. P. Metcalf, *J. Chem. Soc.*, 1989 (1937).

(13) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(14) The other products of the reaction are quinuclidine, identified as its hydrochloride, and a compound which (by analysis) is nearly pure 4-hydroxyethyl-1-methyl-4-phenylpiperidine. The latter exemplifies a rather unusual course for the Hoffmann reaction which is taken by quinuclidine itself.[8] Parenthetically, this alcohol opens up a route to 4-alkyl homologs of pethidine, compounds which are unreported at this time.

(15) Unpublished results obtained in this laboratory.

(16) The physical properties of these compounds lend credence to their formulation as quinuclidines. For example, II melts at 123–125°, III at 157–158°, IV at 199.5°. These high, rather sharp melting points are characteristic of very symmetrical molecules. For example, L. H. Sternback and S. Kaiser [*J. Am. Chem. Soc.*, **74**, 2215 (1952)] report the m.p. 221–223° for 3-quinuclidinol, Clemo and Metcalf[9] give 138° as the m.p. of 3-quinuclidone, while V. Prelog *et al.* [*Ann.*, **32**, 69 (1937)] report 158–159° as the melting point of quinuclidine itself.

(17) When an alcoholic solution of crude III·HBr was concentrated, a rather strong, sweet odor was noted, somewhat reminiscent of vanilla. This has been duplicated to a lesser extent by acidifying dry alcoholic solutions of III with anhydrous acids, and may be due to acetal formation.

(18) An exception to this statement may be found in the case of several of the hydrochlorides, which show considerable tendency to hydrate. Other salts, less soluble in water and other solvents, have given no difficulty in this respect.

TABLE I

DERIVATIVES

Compound	Salt	M.P., °C.	Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Halogen Calcd.	Halogen Found
II[a]	—	123–125	83.37	83.45	9.15	9.14	7.48	7.34		
	$HClO_4$	271–273	54.26	54.41	6.30	6.23			12.32	12.34
	HCl	>350	69.78	69.68	8.11	8.05			15.85	15.86
	Methiodide	280	51.07	51.12	6.12	6.07			38.55	38.95
III	—	157–158	77.58	77.38	7.51	7.42	6.96	7.15		
	HBr	285–287	55.33	55.07	5.72	5.69			28.32	28.13
	HCl	255–270	65.68	65.83	6.79	6.81				
	Methiodide	189–190	48.99	48.75	5.29	5.14			36.98	37.0
	Semicarbazone	267–268	65.09	65.37	7.02	6.95	21.69	21.92		
IV	—	199.5	76.81	76.52	8.43	8.42	6.89	6.89		
	HCl	339–340	65.12	65.04	7.57	7.38			14.79	14.62
Va	—	92–93	73.44	73.31	7.81	7.74	5.71	5.87		
	$HCl \cdot {}^1/_2H_2O$	275–279	61.95	61.90	7.28	7.34	3.1[b]	2.6[b]	12.20	12.32
Vb	—	60	74.10	74.05	8.16	7.96	5.40	5.23		
	HCl	208–210	64.96	64.73	7.50	7.40	4.74	4.83	11.99	11.61
VII	—	102–103	81.87	82.04	7.90	7.82	4.78	4.97		
	HCl $1H_2O$[c]	251–252	69.04	69.13	7.53	7.56	4.03	3.95		
VIIa	—	92–94	82.14	81.89	8.27	8.31	9.58	9.92		
VIII	HBr	Indef.	53.00	52.91	5.11	5.30			35.27	35.45
IX	—	Sublimes								
	Bromide	290–295	64.52	64.48	5.96	6.08			21.47	21.37
	Nitrate	255–256	67.78	67.67	6.26	6.36	7.91	7.91		
X	—	119–121	78.13	78.09	8.20	8.04	13.67	13.63		
XI	HCl	280–287	76.04	75.90	8.30	8.40	4.44	4.66		
XII	HCl	245	65.12	65.14	7.57	7.33	5.84	5.68		
XIII	HCl	210–211	69.16	69.03	8.93	8.80			15.71	15.52
XIV	HCl	228–229	70.12	70.03	9.25	9.21	5.84	5.92	14.79	15.08

[a] Mol. wt. calculated, 187.28; found, 185 (Rast). [b] H_2O, determined *via* $LiAlH_4$. [c] We were unable to obtain VII HCl in its pure anhydrous form. Solvent water is indicated by the hygroscopic nature of the partially dried substance.

base in benzene solution and subsequently dried by azeotropic distillation. To this we added 1 mole of methyllithium in ether. The mixture was let stand 24 hr. and decomposed with ice. The imine (VIIa) of VII precipitated upon the addition of 6*N* HCl to the organic layer and was separated by filtration. A sample of this material was converted to the base and prepared for analysis by sublimation and crystallization from ether-petroleum ether.

The remainder of the VII(a) hydrochloride was hydrolyzed by 5 hr. of refluxing with normal HCl to which enough ethanol had been added to facilitate solution. Upon cooling, VII hydrochloride hydrate separated, and was recovered in 158 g. yield (90%), m.p. *ca.* 250°. We converted this to the base, which was obtained analytically pure upon sublimation (m.p. 101.5–103°). The analytical sample of the hydrochloride was prepared from this base and had the m.p. 251–252°.

4-Acetyl-4-phenylpiperidine (XII). Hydrogenation of 3.5 g. (0.01 mole) of VII HCl hydrate in 40 ml. of methanol, 9 ml. of H_2O and 1 ml. of 2.5*N* HCl, using 2 g. of 10% Pd-C catalyst, yielded 2.4 g. (100%) of XII hydrochloride, which crystallized from ethanol as flat hexagonal plates, m.p. 245°.

Attempted bromination of this substance led only to recovered starting material.

1-Benzyl-4-bromoacetyl-4-phenylpiperidine (VIII).[6] A solution of VII hydrochloride hydrate (26.1 g., 0.075 mole) in 185 ml. of glacial acetic acid was brominated with 100 ml. of an acetic acid solution containing 121 g. of bromine per liter. After standing 3 days, 24.3 g. of chunky crystals had separated, m.p. 190–238° (gas 214°). Fractions *2* and *3* were obtained by the addition of ethyl ether, and weighed 5.4 and 4.5 g., respectively. Fraction *2* melted at 200–225° (gas 214°). Fraction *3* was recrystallized to yield 3.0 g. of material having the same melting point as *2*. Total recovery, 32.6. (95%). This hydrobromide is easily soluble in chloroform, insoluble in water, and was purified for analysis by recrystallization from aqueous ethanol. The melting range is quite indefinite but includes the temperature 200°.

3-Keto-4-phenylquinuclidine (III) *and its quaternary salts* (IX). Conversion of the hydrobromide of VIII to its base was best effected by solution in hot water, rapid chilling, and basification of the solution while it was being vigorously stirred with ether. The base began to cyclize almost immediately upon evaporation of the ether, and in acetone the cyclization appeared to be complete in a few minutes, the product being IX *bromide*. This salt can be recrystallized from ethanol, and sublimes without melting at 290–295°. It is somewhat soluble in water. The yield was 95%.

The *nitrate* of IX was prepared by treating the above bromide in aqueous ethanol with aqueous $AgNO_3$. This salt is soluble to the extent of about 2% in water, from which it crystallizes beautifully in highly refractive chunky crystals which are remarkably transparent and free from imperfections. The m.p. (from ethanol) is 255–256° (gassing).

The *perchlorate* is less soluble in water than the bromide, but was not examined further.

Liberation of III from IX bromide was effected by catalytic hydrogenation of 18.6 g. (50 millimole) batches in 250 ml. of H_2O + 350 ml. of methanol, using 1 g. of 10% Pd-C catalyst. The first hydrogenation required 1 hr., but

(19) All melting point determinations were made on the Köfler hot stage. Those marked "S.T." were taken in evacuated, sealed capillary tubes, whereas the rest were made on microscope slides in the conventional manner. Characteristic changes in crystal structure were often observed to take place below the melting point, and sublimation was a commonplace phenomenon.

we found that subsequent runs (which were made in the same hydrogenation flask without cleaning) required less time for completion—in several instances the reduction was complete in 10 to 15 min.

The resultant III *hydrobromide* was isolated by concentration of the filtered solution *in vacuo*, and the product purified by crystallization from water, m.p. 285–287°. The yield was essentially quantitative.

A rather remarkable phenomenon was observed on concentrating aqueous solutions of this material *in vacuo*. When the concentration was nearly complete, and a heavy crop of crystals had formed, the crystals would assume a brownish coloration and the magma have an odor reminiscent of bromine. The color and odor could be discharged instantly upon the addition of water, and there was apparently no deleterious effect upon the purity of the material.

The base III, m.p. 157–158°, was prepared from the hydrobromide and recrystallized from water.

The *hydrochloride*, prepared from III in ethanolic HCl, and recrystallized from ethanol, melted at 255–270°. The analytical sample, from H_2O-ethanol, was dried 5 hr. at 100° prior to analysis.

The *semicarbazone* was prepared from III hydrobromide and semicarbazide acetate in methanol, followed by conversion to the base and crystallization from ethanol, m.p. 267–268°.

The *methiodide* precipitated almost immediately when a solution of III in acetone was treated with methyl iodide and warmed. After recrystallization from ethanol the melting point was 189–190°.

4-Phenylquinuclidine (II). The Huang-Minlon modification of the Wolff-Kishner reduction was employed, substituting ethylene glycol for the usual diethylene glycol. The reaction of 8 g. of III with 4 g. of 95% hydrazine, 7 g. of 87% KOH pellets and 40 ml. of ethylene glycol led to nitrogen evolution at about 155°. Heating was continued to about 175°, which temperature was maintained until nitrogen evolution ceased (about 2 hr.).

On cooling, II crystallized from the mixture, and was washed with water and recrystallized from aqueous ethanol; m.p. 125°. This was sublimed prior to analysis. The yield was 94%.

The *hydrochloride*, from ethanol-H_2O, did not melt or decompose by 350° (S.T.), but underwent a change in form at 250–255°.

The *perchlorate*, from aqueous ethanol, melted at 271–273°.

The *methoidide*, m.p. 280–281° (from aqueous ethanol), formed with explosive violence when methyl iodide was added to a solution of II in acetone.

3-Hydroxy-4-phenylquinuclidine (IV). To a solution of 26 g. of III in 4 l. of anhydrous ether was added 10 g. of $LiAlH_4$. After standing overnight, the solution gave a positive Michler's ketone color test. Water (60 ml.) was added cautiously and the solid was filtered off and extracted with chloroform. The crude product, which weighed 20.2 g., was recrystallized from ethanol. Fraction 1, 11.2 g., m.p. 198–199°; fraction 2, 3.6 g., m.p. 198–200° (56%). Attempts to recover further quantities of IV led to material which was sparingly soluble in chloroform, and behaved like a quaternary salt. This was not examined further, but it seems possible that reaction with the chloroform may have occurred. Compound IV is nearly insoluble in ether. For analysis, IV was recrystallized from ethanol.

The *hydrochloride*, m.p. 339–340° (without decomposition) was prepared by the action of aqueous HCl on the base in ethanol. This formed a hydrate of undetermined composition, and for analysis was dried 5 hr. at 100°.

3-Acetoxy-4-phenylquinuclidine (Va). The alcohol IV (5.0 g.) was refluxed for 1 hr. with acetic anhydride, poured onto a slurry of ice and 5*N* K_2CO_3 and ether-extracted after 1 hr.; yield, 6.1 g. (100%), m.p. 92–93°. For analysis the product was sublimed.

The *hydrochloride* was prepared by adding 12*N* hydrochloric acid to an ethanol solution of the base; m.p. 275–279° (S.T.). This product formed a very stable hemihydrate which could not be obtained anhydrous by sublimation of the salt in high vacuum. The water content was estimated *via* active hydrogen.

Hydrolysis of this ester with 2.5*N* HCl by refluxing for 1 hr. led to IV hydrochloride, identical in physical properties with authentic IV hydrochloride.

4-Phenyl-3-propionoxyquinuclidine (Vb). This substance was obtained in a procedure parallel to that used for Va, using 4.0 g. of the base and 27 ml. of propionic anhydride (b.p. 76–77°/29 mm.) and heating 1 hr. on the steam bath. The product, 5.3 g., was dissolved in 25 ml. of abs. ethanol, and 1.7 ml. of concd. HCl was added, followed by 150 ml. of dry ether. The Vb *hydrochloride* crystallized at once, and was filtered and washed with ethanol-ether (1:6), ether, and dried *in vacuo* over KOH; yield 5.1 g. (88%); m.p. 208–210°.

The *base*, liberated with NaOH and purified by sublimation, melted at 60°.

4-Acetyl-1-benzyl-4-phenylpiperidine hydrazone (X). Heating a mixture of 3.48 g. (0.01 mole) of VII hydrochloride hydrate, 1 g. of hydrazine, 10 ml. of ethylene glycol and 2 g. of KOH pellets to 205° (internal temperature) for about 15 min. led to no gas evolution. The product was isolated by partitioning between water and chloroform, as a light straw-colored oil which soon crystallized. Recrystallization from ethanol and sublimation yielded pure X, m.p. 119–121°. This showed a strong C=N band in the infrared.

1-Benzyl-4-ethyl-4-phenylpiperidine (XI). When 7.0 g. of VII hydrochloride hydrate was converted to the base, and heated with 4 g. of hydrazine, 8 g. of 87% KOH and 40 ml. of *diethylene glycol* at 200° for 7 hr., N_2 was slowly evolved. The product, XI, was isolated by ether-extraction of the watered reaction mixture, then converted to the *hydrochloride* with 12*N* HCl (5.9 g. yield), which was crystallized from ethanol; yield 4.5 g. This was sublimed, m.p. 280–287° (S.T.).

4-Ethyl-4-phenylpiperidine (XIII). A solution of 4.2 g. of XI hydrochloride in 100 ml. of 70% methanol was hydrogenated in the presence of 1 g. of 10% Pd-C catalyst, a reaction which required 5 hr. The product was crystallized from ethanol-ether as prismatic rods, and further purified by sublimation; m.p. 209°, raised by repeated sublimation to 210–211°. For analysis, the material was recrystallized from alcohol-ether.

4-Ethyl-1-methyl-4-phenylpiperidine (XIV). The methylation of 1.95 g. (10.3 millimoles) of XIII with 2 ml. of 37% formaldehyde and 2 ml. of 90% formic acid by heating 45 min. on the steam bath and then refluxing 5 hr. gave 2.0 g. of a base (mobile oil) which was converted to the *hydrochloride* and recrystallized by dissolution in methanol, adding dioxane and concentrating the mixture to incipient crystallization; m.p. 227.5–229°; yield, 1.9 g.

Hoffmann elimination reaction of II methohydroxide. Vacuum sublimation of II methohydroxide (prepared from the methiodide with Ag_2O) yielded an oil which contained a hydroxyl group (infrared absorption at 2.78 μ) and no vinyl group (absence of absorption at 7 μ, and at 11 μ). When a sample of this material was converted to the hydrochloride and purified by sublimation, the product analyzed for 65.91% carbon and 8.35% hydrogen. The calculated values for $C_{14}H_{22}ClNO$ (mol. wt. 255.79) are: C, 65.73%; H, 8.67%. The product is probably 4-hydroxyethyl-1-methyl-4-phenylpiperidine.[14]

When the methohydroxide was decomposed by heating in a nitrogen atmosphere with 1:1 sodium and potassium hydroxides at 350°, a mobile oil was obtained on ether extraction of the cooled melt. (Stainless steel apparatus was used in this reaction).

On distillation, the product showed all the reactions of a vinyl compound ($KMnO_4$, Br_2, infrared absorption at 10.95,

10.05, and 7.09 μ) and with PtO_2, was completely hydrogenated in 100 sec. to the 4-ethylpiperidine XIV, which was converted to the hydrochloride and found to be identical with authentic material prepared by the Wolff-Kishner reduction of XII followed by formaldehyde–formic acid methylation.

Acknowledgment. Microanalyses were performed by Byron Baer, Paula Parisius, and Evelyn Peake of the Institutes' Microanalytical Laboratory, under the direction of William C. Alford. Some of the infrared determinations[10] were made by William Jones, of the same laboratory.

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Morphinone*

HENRY RAPOPORT, DON R. BAKER, AND HELEN N. REIST

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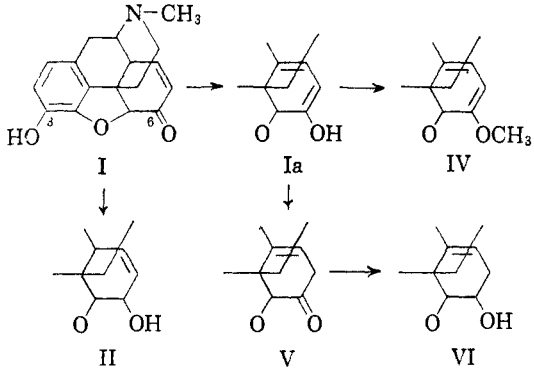
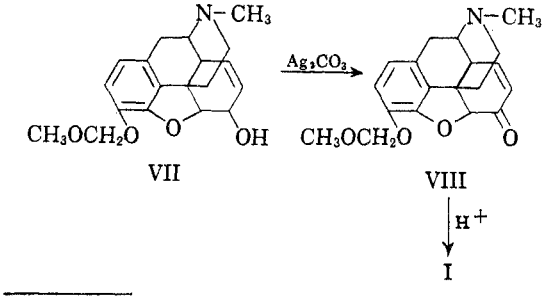
Morphinone, a compound which conceivably might serve as a common precursor for the other morphine alkaloids, has been prepared by silver carbonate oxidation of methoxymethylmorphine to methoxymethylmorphinone, followed by acid hydrolysis. With methyllithium, methoxymethylmorphinone gives the 1,2-adduct which is easily cleaved to 6-methylmorphine. Both monoacetyl derivatives and the diacetyl derivatives of 6-methylmorphine have been prepared. It appears that reactivity at the phenolic hydroxyl group may be influenced by groups at the 6-position.

In recent years there has been considerable interest in morphinone (I) since, as has been pointed out by Schöpf,[1] it (or its enolic form, Ia) conceivably might be the common parent of the other naturally occurring morphine alkaloids. For example, reduction of the carbonyl group would lead to morphine (II), and reduction to the alcohol and methylation of the phenolic hydroxyl would give codeine (III). Conversion to thebaine (IV) might be accomplished by both enol and phenol etherification, while isomerization to the β,γ-unsaturated ketone (IV), either before or after methylation of the phenol, followed by reduction to the alcohol gives neopine (VI).



Further interest in morphinone resides in the fact that it has remained one of the very few ketones still unknown in this series of alkaloids. Codeinone, dihydrocodeinone, and dihydromorphinone are well known compounds.[2] Also neopinone (V, O[3]-methyl ether) recently has been prepared from thebaine.[3] The preparation of morphinone, however, by methods such as employed for the previous ketones, has been precluded by the extreme sensitivity of the molecule. The possibility of overcoming this difficulty was offered by the recent procedure for converting codeine to codeinone[4] in excellent yield by oxidation in benzene with silver carbonate, and it is the application of this method to the preparation of morphinone which is the subject of the present report.

Although the silver carbonate-in-benzene procedure offered the mild, neutral oxidant desired, it was still necessary to protect the phenolic group, and formation of the methoxymethyl ether appeared to be a suitable method, since the protecting group could be removed by mild acid hydrolysis. The oxidation procedure, therefore was applied to the readily prepared methoxymethylmorphine (VII)[5]



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