[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

PREPARATION OF SOME AMINO KETONES AND AMINO ALCOHOLS CONTAINING THE ac-TETRAHYDRO-β-NAPHTHYLAMINE, TETRAHYDROISOQUINOLINE, OR β-PHENYLETHYLAMINE NUCLEUS

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Among the general conclusions which have been drawn from the published work on adrenaline, ephedrine, and related compounds (1), is the fact that substitution on the side chain nitrogen atom markedly affects the vasopressor activity of the resulting compound. Thus, the substitution of alkyl radicals larger than the methyl group definitely has been shown to reduce or even destroy pressor action. The same may be said for the substitution of aryl radicals. In spite of the large volume of published work in this field, there appeared to be ample reasons for continuing research along these lines. For example, no one has attempted to substitute a radical on the side chain nitrogen which in itself might, when attached to nitrogen, exert a definite pressor activity. Such a substituent might be expected to augment rather than decrease pressor activity. To test this possibility α-bromoacetophenone, α-bromopropiophenone, α-chloro-*p*-hydroxyacetophenone, α-bromo-β-acetonaphthone, phenylethyl bromide, and phenoxyethyl bromide were condensed with ac-tetrahydro-β-naphthylamine, tetrahydroisoquinoline, and phenylethylamine. The amino ketones were then reduced to the corresponding amino alcohols. ac-Tetrahydro-β-naphthylamine and phenylethylamine are known to exert pressor action. The same cannot be said for tetrahydroisoquinoline. It was included, however, for structural reasons, for like the naphthylamine derivative it may be regarded as a derivative of phenylethylamine. The phenoxyethyl derivatives were prepared not so much expecting potent pressor compounds as to test a generalization. It has often been stated that in the series of pressor compounds it is necessary that the nitrogen atom be attached to the second carbon atom in the side chain, relative to the aromatic ring. Fourneau (2) has shown recently that N-phenylethylenediamine was as active as β-phenylethylamine. This appeared to indicate that a third atom in the side chain, between the ring and the nitrogen atom, did not necessarily reduce pressor activity, providing it was some element other than carbon.

Another aspect of this work also appeared to be of interest. Many attempts have been made to prepare compounds possessing both pressor action and local anesthetic action (1). This has been done in most cases by preparing O-benzoates of amino alcohols of the type $ArCHOHCH_2NH_2 \cdot HCl$. In general, benzoylation did produce local anesthetics, but the pressor activity was either greatly diminished or entirely destroyed. It appeared obvious therefore that anesthetic activity must be introduced in some other manner. Kanao (3) has shown that alcohols of the above type acquire local anesthetic activity when alkyl radicals of higher molecular weight are attached to the nitrogen atom. This suggested that the amino alcohols prepared in the course of this work might possess a similar activity.

The pharmacological tests on these compounds have not been completed. However the tests that have been made indicate that the purposes of this work have been realized to some extent. Both 1-phenyl-2-ac-tetrahydro-β-naphthylaminoethanol hydrochloride (II) and 1-phenyl-2-ac-tetrahydro-β-naphthylaminopropanol hydrochloride (V) in 0.5% solution produced anesthesia of longer duration than did 1% cocaine solution on rabbit's cornea. 1-*p*-Hydroxyphenyl-2-ac-tetrahydro-β-naphthylaminoethanol hydrochloride (XII) and 1-phenyl-2-tetrahydroisoquinolinoethanol hydrochloride (XV) were somewhat less efficient than cocaine. 1-Phenyl-2-tetrahydroisoquinolinoethane hydrochloride (XXII) and 1-*p*-hydroxyphenyl-2-tetrahydroisoquinolinoethanol hydrochloride (XXIV) showed no anesthetic activity.

Compounds II, V, XV, and XXII are reported as being slightly irritating, XXIV as irritating, and XII as producing severe irritation. Since only six compounds have been tested it was not possible to draw any general conclusions, but certain facts are indicated. The presence of a phenolic hydroxyl group decreased the activity in one case (XII) and in another case (XXIV) completely destroyed it. The presence of this group also increased the irritating action of the compounds XII and XXIV. It is also significant that compound XXII, which showed no anesthetic activity, differs from XV only in the absence of the side chain hydroxyl group.

Only two of the compounds have been tested for toxicity. Compound II was more toxic to mice than cocaine while V was less toxic than cocaine. Only one compound has been tested for pressor activity. Compound II in doses of 3–5 mg. (injection in cats) produced a rise in pressure of 30 mm. of mercury. Repeated dosages produced the same rise.

These tests were made possible through the courtesy of the Merck Therapeutic Institute.

EXPERIMENTAL

Analysis. The semi-micro Kjeldahl and the semi-micro Dumas methods were used for the determination of nitrogen. The distillate in the Kjeldahl method was absorbed in 4% boric acid solution and titrated to a methyl red end-point (4). The Volhard and gravimetric methods were used for the determination of chlorine.

α-Bromoacetophenone. The product used was prepared according to the method of Rubin and Day (5).

α-Bromopropiophenone. This was prepared by a method similar to that employed by Schmidt (6). [See also Rubin and Day (5).]

α-Chloro-p-*hydroxyacetophenone.* This was prepared according to Tutin, Caton, and Hann (7) using ligroin, however, instead of carbon disulfide as the solvent. The successful preparation of this compound depended upon careful attention to details of the method used. Hence its preparation is described in detail. Thirty grams (0.277 mole) of anisole and 36 g. (0.318 mole) of chloroacetyl chloride were dissolved in 500 cc. of ligroin. To the rapidly stirred solution, 45 g. (0.336 mole) of anhydrous aluminum chloride was added in small portions at 2–3 minute intervals over a period of 35 minutes. The mixture was heated at 35° for one hour and then 45 g. (0.336 mole) more of aluminum chloride was added in approximately 30 minutes. The resulting mixture was heated for two and one-half hours. The mixture gradually became so viscous that it could no longer be stirred. At the end of the heating period the remaining solvent was removed by distillation. The resulting mass was cooled and decomposed by the addition of ice over a period of thirty minutes. The solid was broken up as much as possible during the addition of the ice and then complete decomposition of the complex was accomplished by slowly adding 200 cc. of concentrated hydrochloric acid. The resulting dark violet solution was cooled and extracted with three 250-cc. portions of ether. The ether extracts were combined and treated with a 200-cc. portion of 5% ammonium carbonate solution to eliminate the excess acid. After removal of the aqueous layer, the ether layer was extracted with five 250-cc. portions of 10% sodium carbonate solution. Acidification of the sodium carbonate extracts, after treatment with charcoal, yielded a crude product which was rather darkly colored. This, upon crystallization from 75% alcohol, yielded 21 g. (44%) of a light yellow product, melting at 148° (corr.).

α-Bromo-β-acetonaphthone. This was prepared according to the method of Immediata and Day (8).

β-Phenoxyethyl bromide. This was prepared essentially according to Bentley, Haworth, and Perkins (9). The product used boiled at 144° (40 mm.) and melted at 35° (corr.).

ac-Tetrahydro-β-naphthylamine hydrochloride. This was prepared according to the method of Organic Syntheses (10) with a slight modification. It was found that the crude hydrochloride from this method could be obtained almost colorless by shaking with 150–200 cc. of ether in the cold.

1,2,3,4-Tetrahydroisoquinoline hydrochloride. This was prepared similarly to the method of Bamberger and Dieckmann (11). This consisted in treating a solution of isoquinoline in absolute alcohol with sodium. The product was isolated as the hydrochloride. The yields were 70–72%, m.p. 195–196° (corr.). Due to the nature of the source of the isoquinoline, it seemed altogether probable that the product might be contaminated with its isomer, tetrahydroquinoline hydrochloride. To determine this, the following method of purification was adopted. The hydrochloride from above was dissolved in water, the free base liberated by an excess of sodium hydroxide solution, and then extracted with ether. After drying the ether solution over sodium

hydroxide pellets, it was chilled and a rapid stream of moist carbon dioxide was passed through it. This process precipitated the carbonate of the more basic tetrahydroisoquinoline. This was removed by filtration, washed with ether, dissolved in 10% acetic acid, and the free base was liberated by an excess of sodium hydroxide solution. It was extracted with ether, dried over sodium hydroxide pellets, and then dry hydrogen chloride gas was passed over the surface of the ether solution. The tetrahydroisoquinoline hydrochloride was filtered, washed with ether, and dried. The melting point of this product compared favorably with that of the first product 195–196° (corr.).

β-Phenylethylamine hydrochloride. This was prepared by the sodium-ethyl alcohol reduction of phenylacetonitrile according to the method of Johnson and Guest (12).

Preparation of the amino ketones. These compounds were prepared from the α-halogen substituted ketones and the amines just described. Two equivalents of the amine were allowed to react with one equivalent of the halogenated compound in dry alcohol or ether solution. The reaction-mixtures were allowed to stand for a definite period of time. Ether was added and the amine salts which settled out were removed by filtration and washed with dry ether. A stream of dry hydrogen chloride was then passed over the surface of the cold ether filtrates. An excess of the gas must be avoided and the solutions should be stirred or shaken during the treatment. The precipitated hydrochlorides were washed with ether and recrystallized from alcohol and ether.

The free bases were prepared by treating solutions of the hydrochlorides in dilute alcohol with a 5% solution of sodium bicarbonate. The mixtures were stirred and allowed to stand in the cold overnight. The filtered products were then recrystallized from dilute alcohol.

The oximes were prepared from the amino ketone hydrochlorides in the usual manner and recrystallized from dilute alcohol.

Preparation of the amino-alcohols. They were prepared from the corresponding amino ketone hydrochlorides by catalytic hydrogenation, usually employing a ten per cent palladium on charcoal catalyst. Solutions of the hydrochlorides in 95% alcohol were shaken in an atmosphere of hydrogen, in an apparatus similar to that of Shaefer (13), until the calculated volume of hydrogen had been absorbed. The mixtures were then heated to boiling and the catalyst removed by filtration. In some cases it was necessary to extract the catalyst with hot alcohol to remove the adsorbed product. The alcoholic filtrates were concentrated to 50–100 cc., ether added and the mixtures were allowed to stand in the cold for several hours to complete the precipitation of the amino alcohol hydrochlorides. The latter were usually recrystallized from alcohol and ether. The free bases, in most cases, were prepared by the method used to obtain the free bases of the amino ketones.

Preparation of the esters. Suspensions of the amino alcohol hydrochlorides in excess benzoyl chloride were heated in an oil-bath. The temperature and time of heating were important factors and varied considerably depending on the amino alcohol used. After cooling to room temperature, the residues were shaken with 100 cc. of dry ether and allowed to stand overnight in the cold. The ether layer was decanted and another 100 cc. of dry ether was added to the residue. When this mixture was allowed to stand overnight in the cold the ester hydrochlorides usually crystallized. The crude products were recrystallized from dry alcohol by the addition of small amounts of ether. The free bases were prepared by the method previously described.

Preparation of β-phenoxyethylamine and β-phenylethylamine derivatives. Solutions

containing two equivalents of the amine and one equivalent of β-phenoxyethyl bromide or β-phenylethyl bromide in absolute alcohol were heated at 65-80°. The solutions were cooled to 10° and 50–100 cc. of dry ether added. After standing for several hours in the cold the amine hydrochlorides were removed by filtration and the filtrates were treated with dry hydrogen chloride. The crude hydrochlorides were then recrystallized from alcohol and ether. The free bases were obtained by the method previously described.

The analytical results and melting points for the new compounds are included in Tables I, II and III.

I. *α-ac-Tetrahydro-β-naphthylaminoacetophenone hydrochloride.* ac-Tetrahydro-β-naphthylamine (7.94 g., 0.054 mole) was dissolved in 150 cc. of dry ether. To this solution of the amine, 5.4 g. (0.027 mole) of α-bromoacetophenone was added in small portions, shaking after each addition until all went into solution. The reaction-mixture was allowed to stand at room temperature for three hours. If allowed to stand longer than five hours the solution became red and the product was hard to purify. After separating the ac-tetrahydro-β-naphthylamine hydrobromide, the hydrochloride of the condensation product was isolated from the filtrate and recrystallized from alcohol. If any red coloration was apparent, the hydrochloride was first washed with 50 cc. of acetone and then recrystallized from alcohol; yield 42%.

The free base of this compound, which was obtained only as an impure oil, was identified as its oxime. The latter was obtained as white prisms by recrystallization from 50% alcohol, m.p. 120° (corr.).

Anal. Calc'd for $C_{18}H_{20}N_2O$:N, 10.37. Found: N, 10.17.

II. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* Five grams (0.016 mole) of the amino ketone hydrochloride (I) was dissolved in 175 cc. of warm alcohol and reduced according to the general method; yield 90%. The product was recrystallized from alcohol and ether. The free base was obtained by the general procedure.

III. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 benzoate hydrochloride.* Three grams (0.0099 mole) of compound II and 10 cc. (0.072 mole) of benzoyl chloride were heated in an oil-bath for three hours at 105°; yield 67%. The free base was prepared by the general method.

IV. *α-ac-Tetrahydro-β-naphthylaminopropiophenone hydrochloride.* To a dry ether solution containing 7.94 g. (0.054 mole) of ac-tetrahydro-β-naphthylamine was added 5.8 g. (0.027 mole) of α-bromopropiophenone. The reaction-mixture was allowed to stand for twelve days at room temperature during which time crystals of ac-tetrahydro-β-naphthylamine hydrobromide separated. When the theoretical amount of the amine hydrobromide was recovered, the chilled ether filtrate was treated with dry hydrogen chloride. During the passage of this gas over the surface of the solution, the contents of the flask were shaken constantly to retard the formation of a gummy material. The hydrochloride which separated was treated with 30 cc. of warm acetone to remove the greater part of the red color from the product. After two recrystallizations from alcohol and ether, a white crystalline product was obtained; yield 43%.

The free base, prepared by the general method, was removed by filtration as soon as possible and dried in a vacuum desiccator. The product was a white, hygroscopic material which turned dark very quickly in the air.

The oxime was prepared from the hydrochloride in the usual manner and recrystallized from 50% alcohol; colorless prisms, m.p. 137° (corr.).

Anal. Calc'd for $C_{19}H_{22}N_2O$: N, 9.52. Found: N, 9.39.

V. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminopropanol-1 hydrochloride.* This compound was prepared from the corresponding amino ketone hydrochloride by the procedure used for compound II, except that 20% palladium on charcoal was used as the catalyst. The time of the reduction was seven hours. After filtration, the catalyst was extracted with 50 cc. of boiling alcohol. The extract was added to the main alcoholic filtrate and concentrated to about 75 cc. Careful addition of 35 cc. of ether caused the product to precipitate in crystalline form; yield 96%. The free base was obtained by the general procedure.

VI. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminopropanol-1 benzoate hydrochloride.* The ester hydrochloride was prepared by the method described for compound III, except that the mixture was heated at 105° for six hours. The mixture was cooled to 15° and 100 cc. of dry ether slowly added. After standing overnight in the ice-box, the ether layer was decanted and another portion (100 cc.) of dry ether was added and shaken vigorously. The ether was again decanted and a third portion of ether was added. This was allowed to stand for two weeks in the ice-box before the oily residue finally crystallized. The crude product was recrystallized from absolute alcohol by the addition of dry ether; yield 23%. The free base was obtained in the usual manner.

VII. *α-ac-Tetrahydro-β-naphthylamino-β-acetonaphthone hydrochloride.* This compound was prepared from ac-tetrahydro-β-naphthylamine and α-bromo-β-acetonaphthone by the method described for compound I. The crude hydrochloride was washed with dry ether and recrystallized from 65% alcohol; yield 38%.

The free base was obtained by the general method except that the reaction-mixture was allowed to stand at room temperature for one hour. Longer standing resulted in the formation of a gummy material. The compound was obtained as light yellow needles by recrystallization from warm 95% alcohol.

The oxime, prepared as before, was recrystallized from 60% alcohol, m.p. 145° (corr.).

Anal. Calc'd for $C_{22}H_{22}N_2O$: N, 8.48. Found: N, 8.50.

VIII. *1-β-Naphthyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* Due to the insolubility of the corresponding amino ketone hydrochloride, only small quantities of it were reduced at one time. Two grams (0.008 mole) was dissolved in 250 cc. of boiling 80% alcohol. This solution was poured into a previously warmed reduction flask and the catalyst, 10% palladium on charcoal, added. The reduction was carried out at 60°, otherwise the procedure was the same as that used for compound II. The product was recrystallized from alcohol and ether; yield 86%.

The free base was prepared by adding the minimum amount of 50% sodium hydroxide solution to a solution of the hydrochloride in 50% alcohol and the mixture allowed to stand in the ice-box overnight. The base was recrystallized from absolute alcohol by the very slow addition of water.

IX. *1-β-Naphthyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 benzoate hydrochloride.* The general method was used with the exception that the reaction-mixture, consisting of 0.0056 mole of the amino alcohol hydrochloride and 0.123 mole of benzoyl chloride, was heated at 114° for two hours. After cooling, 100 cc. of dry ether was added and the reaction-mixture allowed to stand cold overnight. The ether layer was decanted and the gummy residue washed with 50 cc. of dry ether, and then dissolved in 25 cc. of boiling alcohol. When cold, 25 cc. of dry ether was added, and after standing overnight in the ice-box, the desired product crystallized. It was recrystallized from alcohol and ether; yield 40%. The free base, obtained in the usual manner, was recrystallized from alcohol.

TABLE I

DERIVATIVES OF AC-TETRAHYDRO-β-NAPHTHYLAMINE

NO.	FORMULA	M.P. °C (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
I	$C_6H_5COCH_2NHC_{10}H_{11}\cdot HCl$	197–199	$C_{18}H_{20}ClNO$	4.64	4.60	11.75	11.69
II	$C_6H_5CHOHCH_2NHC_{10}H_{11}\cdot HCl$	212–213	$C_{18}H_{22}ClNO$	4.61	4.52	11.67	11.75
	$C_6H_5CHOHCH_2NHC_{10}H_{11}$	78.5	$C_{18}H_{21}NO$	5.24	5.16		
III	$C_6H_5CHCH_2NHC_{10}H_{11}\cdot HCl$ (OCOC$_6$H$_5$)	174–175	$C_{25}H_{26}ClNO_2$	3.43	3.36	8.70	8.65
	$C_6H_5CHCH_2NHC_{10}H_{11}$ (OCOC$_6$H$_5$)	68.5	$C_{25}H_{25}NO_2$	3.77	3.67		
IV	$C_6H_5COCH(CH_3)NHC_{10}H_{11}\cdot HCl$	199–200 decomp.	$C_{19}H_{22}ClNO$	4.44	4.37	11.23	11.36
	$C_6H_5COCH(CH_3)HNC_{10}H_{11}$	40–41	$C_{19}H_{21}NO$	5.01	4.86		
V	$C_6H_5CHOHCH(CH_3)NHC_{10}H_{11}\cdot HCl$	206–208	$C_{19}H_{24}ClNO$	4.41	4.27	11.16	11.03
	$C_6H_5CHOHCH(CH_3)NHC_{10}H_{11}$	69.5–70	$C_{19}H_{23}NO$	4.98	4.89		
VI	$C_6H_5CHCH(CH_3)NHC_{10}H_{11}\cdot HCl$ (OCOC$_6$H$_5$)	139.5–141	$C_{26}H_{28}ClNO_2$	3.21	3.25	8.14	8.20
	$C_6H_5CHCH(CH_3)NHC_{10}H_{11}$ (OCOC$_6$H$_5$)	58.5–59.5	$C_{26}H_{27}NO_2$	3.51	3.49		

VII	$C_{10}H_7COCH_2NHC_{10}H_{11} \cdot HCl$	170 decomp.	$C_{22}H_{22}ClNO$	3.98	3.81	10.08	9.98
	$C_{10}H_7COCH_2NHC_{10}H_{11}$	84.5–85.5	$C_{22}H_{21}NO$	4.44	4.32		
VIII	$C_{10}H_7CHOHCH_2NHC_{10}H_{11} \cdot HCl$	211–12	$C_{22}H_{24}ClNO$	3.96	3.91	10.03	9.93
	$C_{10}H_7CHOHCH_2NHC_{10}H_{11}$	93.5	$C_{22}H_{23}NO$	4.42	4.31		
IX	$C_{10}H_7CH(OCOC_6H_5)CH_2NHC_{10}H_{11} \cdot HCl$	201.5–203	$C_{29}H_{28}ClNO_2$	3.06	3.09	7.75	7.59
	$C_{10}H_7CH(OCOC_6H_5)CH_2NHC_{10}H_{11}$	101.5	$C_{29}H_{27}NO_2$	3.32	3.23		
X	$C_6H_5CH_2CH_2NHC_{10}H_{11} \cdot HCl$	245–246.5	$C_{18}H_{22}ClN$	4.87	4.69	12.33	12.26
XI	p-$HOC_6H_4COCH_2NHC_{10}H_{11} \cdot HCl$	221	$C_{18}H_{20}ClNO_2$	4.41	4.27	11.17	11.29
	p-$HOC_6H_4COCH_2NHC_{10}H_{11}$	117–118	$C_{18}H_{19}NO_2$	4.98	4.90		
XII	p-$HOC_6H_4CHOHCH_2NHC_{10}H_{11} \cdot HCl$	198–199.5	$C_{18}H_{22}ClNO_2$	4.38	4.26	11.09	11.01
	p-$HOC_6H_4CHOHCH_2NHC_{10}H_{11}$	173–175	$C_{18}H_{21}NO_2$	4.95	4.79		
XIII	$C_6H_5OCH_2CH_2NHC_{10}H_{11} \cdot HCl$	226–8	$C_{18}H_{22}ClNO$	4.62	4.61	11.68	11.75

X. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethane hydrochloride.* A solution of 4.12 g. (0.028 mole) of ac-tetrahydro-β-naphthylamine and 2.5 g. (0.014 mole) of phenylethyl bromide in 25 cc. of absolute alcohol was refluxed for four hours; yield 65%. Attempts to prepare the free base resulted only in the isolation of an oil, which could not be purified.

XI. *α-ac-Tetrahydro-β-naphthylamino-*p*-hydroxyacetophenone hydrochloride.* To a suspension of 4.8 g. (0.027 mole) of α-chloro-*p*-hydroxyacetophenone in 10 cc. of absolute alcohol, was added 7.94 g. (0.054 mole) of ac-tetrahydro-β-naphthylamine. The mixture was stirred until all went into solution. A small amount of heat was evolved and the solution became red. The reaction-mixture was allowed to stand for six hours at room temperature. Seventy-five cubic centimeters of ether was added with stirring, and after cooling for one hour, the precipitated amine salt was removed by filtration. The slightly red hydrochloride isolated from the filtrate was washed with ether and recrystallized from 125 cc. of alcohol and a small amount of ether; yield 15%. The free base, obtained in the usual manner, was recrystallized from 95% alcohol.

Although several methods were used to obtain the oxime, none of the trials were successful. In each case the free base was isolated. Attempts to obtain the semicarbazone were also unsuccessful.

XII. *1-*p*-Hydroxyphenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* The amino ketone hydrochloride, XI, was reduced in the usual manner, in the presence of a 10% palladium-charcoal catalyst. The product was recrystallized from alcohol; yield almost quantitative. The free base was prepared in the same way as the free base of the corresponding ketone. It crystallized as white cubic crystals.

XIII. *1-Phenoxy-2-ac-tetrahydro-β-naphthylaminoethane hydrochloride.* A solution of 4.9 g. (0.023 mole) of β-phenoxyethyl bromide in 10 cc. of absolute alcohol was added to 0.048 mole of ac-tetrahydro-β-naphthylamine. This reaction-mixture was heated for two and one-half hours at 70°, after which it was cooled to 15° and 100 cc. of ether added. The product was washed with ether and recrystallized from alcohol; yield 54%. The free base could be obtained only as an impure oil.

XIV. *α-Tetrahydroisoquinolinoacetophenone hydrochloride.* Tetrahydroisoquinoline (7.85 g., 0.059 mole) was dissolved in 150 cc. of dry ether. To the cold ether solution 5.8 g. (0.028 mole) of α-bromoacetophenone was slowly added with shaking. A precipitate began to form almost immediately, and the reaction proceeded with the evolution of heat. The reaction-mixture was allowed to stand at room temperature for one hour with occasional shaking, and the tetrahydroisoquinoline hydrobromide was removed by filtration. The ether filtrate was cooled and a slow current of dry hydrogen chloride gas was passed over the surface of the solution. A mixture of oil and solid was precipitated. The ether was decanted and the residual mass was washed with two 35-cc. portions of dry ether. Fifty cubic centimeters of dry ether was added and the mixture allowed to stand overnight in the ice-box to crystallize. The crude product was washed with ether and purified by dissolving in warm alcohol, cooling, and adding a small amount of ether; colorless leaflets, yield 75%.

The free base was obtained by adding 5% sodium bicarbonate solution to a solution of the hydrochloride in 50% alcohol. After standing in the cold for one hour, the product was filtered and recrystallized from alcohol. The pure product turned yellow in the air, m.p. 63.5-64.5° (corr.). This compound has been previously prepared and reported as melting at 100–101° (14).

The oxime was prepared from the hydrochloride in the usual manner. The crude product was recrystallized from 50% alcohol, m.p. 136.5° (corr.).

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.53. Found: N, 10.47.

XV. *1-Phenyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* This compound was prepared by the hydrogenation of the amino ketone hydrochloride, in 95% alcohol, in the presence of a 10% palladium on charcoal catalyst. The reaction was slow, fifty hours being required for the reduction of 0.0417 mole; colorless plates, yield 91%. The free base was obtained by the general procedure.

XVI. *1-Phenyl-2-tetrahydroisoquinolinoethanol-1 benzoate hydrochloride.* Three grams (0.008 mole) of the amino alcohol hydrochloride was suspended in 10 cc. (0.072 mole) of benzoyl chloride and heated under reflux, gradually raising the temperature over a period of three hours to 118°, and then heating three additional hours at this temperature. The product was isolated and purified according to the general method; colorless needles, yield 88%. The free base was prepared in the usual manner.

XVII. *α-Tetrahydroisoquinolinopropiophenone hydrochloride.* To a dry ether solution containing 7.85 g. (0.059 mole) of tetrahydroisoquinoline was added 6.2 g. (0.0287 mole) of α-bromopropiophenone, and the solution was refluxed for fifteen hours. The product was recrystallized by adding dry ether to its solution in cold absolute alcohol and allowing the mixture to stand in the cold for twenty-four hours; yield 89%.

The free base was obtained by the same procedure used for the base of compound XIV. It was recrystallized from alcohol and water and obtained as white prisms which turned yellow in the air.

The oxime, prepared from the hydrochloride, was recrystallized from 65% alcohol, by dissolving the crude product at 40–50° and allowing the solution to stand for three days at 10°; colorless needles, m.p. 63° (corr.).

Anal. Calc'd for $C_{18}H_{20}N_2O$: N, 10.00. Found: N, 10.18.

XVIII. *1-Phenyl-2-tetrahydroisoquinolinopropanol-1 hydrochloride.* The amino ketone hydrochloride (XVII) in 95% alcohol was hydrogenated in the Adams reduction apparatus (15), using 10% palladium on charcoal as the catalyst, under an initial pressure of 38 pounds. The solution was heated to boiling and the catalyst was removed. The catalyst was then extracted twice with 150-cc. portions of boiling alcohol. The combined alcohol filtrates were concentrated, cooled, and the crystallization of the hydrochloride completed by the addition of a little ether. It was recrystallized from alcohol.

The free base was prepared in a manner similar to that used for the preparation of the amino ketone free base. It was recrystallized from alcohol and water. Attempts to benzoylate this alcohol were unsuccessful, although several methods were tried.

XIX. *α-Tetrahydroisoquinolino-β-acetonaphthone hydrochloride.* To a cold, dry ether solution containing 7.85 g. (0.059 mole) of tetrahydroisoquinoline, 7.4 g. (0.0295 mole) of α-bromo-β-acetonaphthone was slowly added. After shaking thoroughly for fifteen minutes, the reaction-mixture was allowed to stand for one-half hour at room temperature, after which the precipitated tetrahydroisoquinoline hydrobromide was removed by filtration and washed with ether. It was noted that if the reaction-mixture was allowed to stand too long before filtering, the yields of condensation product were decreased. The cold ether filtrate was treated with dry hydrogen chloride and the precipitated hydrochloride was recrystallized from alcohol; white hygroscopic plates, yield 50%.

The free base was obtained by adding an excess of 20% sodium hydroxide solution to a solution of the hydrochloride in 50% alcohol. After standing cold, the base was removed by filtration and recrystallized from warm alcohol by the careful addition of water. The white crystalline product turned pink in the air.

TABLE II

DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE

NO.	FORMULA	M.P. °C. (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XIV	$C_6H_5COCH_2NC_9H_{10}\cdot HCl$ $C_6H_5COCH_2NC_9H_{10}$	168–169 63.5–*64.5	$C_{17}H_{18}ClNO$ $C_{17}H_{17}NO$	4.87 5.57	4.77 5.40	12.33	12.19
XV	$C_6H_5CHOHCH_2NC_9H_{10}\cdot HCl$ $C_6H_5CHOHCH_2NC_9H_{10}$	206–207 56.5–57.0	$C_{17}H_{20}ClNO$ $C_{17}H_{19}NO$	4.83 5.53	4.68 5.38	12.24	12.07
XVI	$C_6H_5CHCH_2NC_9H_{10}\cdot HCl$ | $OCOC_6H_5$	169.5–170.5	$C_{24}H_{24}ClNO_2$	3.56	3.58	9.01	8.90
	$C_6H_5CHCH_2NC_9H_{10}$ | $OCOC_6H_5$	98.5	$C_{24}H_{23}NO_2$	3.92	3.81		
XVII	$C_6H_5COCH(CH_3)NC_9H_{10}\cdot HCl$ $C_6H_5COCH(CH_3)NC_9H_{10}$	173–175 38	$C_{18}H_{20}ClNO$ $C_{18}H_{19}NO$	4.64 5.28	4.77 5.40	11.75	11.90
XVIII	$C_6H_5CHOHCH(CH_3)NC_9H_{10}\cdot HCl$ $C_6H_5CHOHCH(CH_3)NC_9H_{10}$	235 96.8–97.5	$C_{18}H_{22}ClNO$ $C_{18}H_{21}NO$	4.61 5.24	4.69 5.30	11.68	11.75
XIX	$C_{10}H_7COCH_2NC_9H_{10}\cdot HCl$ $C_{10}H_7COCH_2NC_9H_{10}$	188–189.5 71.5	$C_{21}H_{20}ClNO$ $C_{21}H_{19}NO$	4.18 4.65	4.24 4.71	10.50	10.41
XX	$C_{10}H_7CHOHCH_2NC_9H_{10}\cdot HCl$ $C_{10}H_7CHOHCH_2NC_9H_{10}$	219–221 91	$C_{21}H_{22}ClNO$ $C_{21}H_{21}NO$	4.12 4.62	4.07 4.59	10.44	10.32

XXI	$C_{10}H_7CHCH_2NC_9H_{10}\cdot HCl$ $\vert$ $OCOC_6H_5$	164.5–165	$C_{28}H_{26}ClNO_2$	3.16	3.14	7.99	8.03
	$C_{10}H_7CHCH_2NC_9H_{10}$ $\vert$ $OCOC_6H_5$	112	$C_{28}H_{25}NO_2$	3.44	3.40		
XXII	$C_6H_5CH_2CH_2NC_9H_{10}\cdot HCl$	216–218	$C_{17}H_{20}ClN$	5.12	5.07	12.96	13.09
	$C_6H_5CH_2CH_2NC_9H_{10}$	43	$C_{17}H_{19}N$	5.90	5.95		
XXIII	p-$HOC_6H_4COCH_2NC_9H_{10}\cdot HCl$	216–217	$C_{17}H_{18}ClNO_2$	4.61	4.50	11.68	11.75
	p-$HOC_6H_4COCH_2NC_9H_{10}$	154	$C_{17}H_{17}NO_2$	5.24	5.30		
XXIV	p-$HOC_6H_4CHOHCH_2NC_9H_{10}\cdot HCl$	217–219	$C_{17}H_{20}ClNO_2$	4.58	4.61	11.60	11.69
	p-$HOC_6H_4CHOHCH_2NC_9H_{10}$	156	$C_{17}H_{19}NO_2$	5.20	5.12		
XXV	$C_6H_5OCH_2CH_2NC_9H_{10}\cdot HCl$	180.5–182	$C_{17}H_{20}ClNO$	4.84	4.90	12.24	12.31
	$C_6H_5OCH_2CH_2NC_9H_{10}$	35	$C_{17}H_{19}NO$	5.53	5.60		

* Previously reported by Wedekind (14) as melting at 100–101°.

The oxime obtained from the hydrochloride, by the usual method, was recrystallized from 65% alcohol, m.p. 128° (corr.).

Anal. Calc'd for $C_{21}H_{20}N_2O$: N, 8.86. Found: N, 8.71.

XX. *1-β-Naphthyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* The amino ketone hydrochloride (XIX) was dissolved in 85% alcohol and hydrogenated at 60° in the presence of a 10% palladium on charcoal catalyst. Under these conditions the reduction required eleven hours; colorless prisms, yield 82%.

The free base was prepared by the method used for the base of the corresponding amino ketone hydrochloride (XIX). The product was recrystallized from alcohol and water.

XXI. *1-β-Naphthyl-2-tetrahydroisoquinolinoethanol-1 benzoate hydrochloride.* A mixture of 3 g. (0.009 mole) of the amino alcohol hydrochloride (XX) and 12 cc. (0.0417 mole) of benzoyl chloride was gradually heated to 115° and kept at this temperature for three hours. The cooled reaction-mixture was washed several times with dry ether and then dissolved in absolute alcohol. Dry ether was added and the mixture allowed to stand cold for several days or until crystallization occurred. The product was finally recrystallized from a small amount of absolute alcohol; colorless plates, yield 34%. The free base, obtained by the general procedure, was recrystallized from absolute alcohol.

XXII. *1-Phenyl-2-tetrahydroisoquinolinoethane hydrochloride.* Five cubic centimeters (0.028 mole) of phenylethyl bromide was added to a solution of 10 g. (0.059 mole) of tetrahydroisoquinoline in 10 cc. of absolute alcohol. The solution was heated for seven hours; colorless plates, yield 40%. The free base was prepared in the usual manner.

XXIII. *α-Tetrahydroisoquinolino*-p-*hydroxyacetophenone hydrochloride.* A suspension of 5.1 g. (0.028 mole) of α-chloro-*p*-hydroxyacetophenone in 12 cc. of absolute alcohol was added slowly to 7.85 g. (0.059 mole) of tetrahydroisoquinoline, keeping the temperature below 20°. Ten cubic centimeters of dry ether was added and the mixture allowed to stand for one hour. One hundred cubic centimeters of ether was then added and the tetrahydroisoquinoline hydrochloride removed by filtration after fifteen minutes. It was not entirely composed of the amine salt but contained a small amount of dark red material insoluble in water. The cold ether filtrate was then treated very slowly with dry hydrogen chloride. An excess of hydrogen chloride must be avoided, otherwise the product becomes very red. The crude product was dissolved in alcohol and reprecipitated by the addition of ether; white plates, yield 40%. The free base, prepared in the usual manner, was dissolved in 80% alcohol, diluted with water slowly, and cooled. The base crystallized as slightly yellow plates. Repeated trials to obtain the oxime of this compound were unsuccessful.

XXIV. *1*-p-*Hydroxyphenyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* This compound was prepared by the general method from XXIII; colorless needles, yield 91%. The free base was obtained in the usual manner.

XXV. *1-Phenoxy-2-tetrahydroisoquinolinoethane hydrochloride.* To a solution of 3.08 g. (0.023 mole) of tetrahydroisoquinoline in 10 cc. of absolute alcohol was added 2.4 g. (0.011 mole) of β-phenoxyethyl bromide. The solution was heated for three hours at 70°; yield 60%. The free base was prepared by the general method.

XXVI. *α-Phenylethylaminoacetophenone hydrochloride.* To a dry ether solution containing 7.6 g. (0.0628 mole) of β-phenylethylamine, 6.3 g. (0.0314 mole) of α-bromoacetophenone was added. The reaction-mixture was allowed to stand at room temperature for forty-five minutes. The precipitated amine hydrobromide was removed by filtration and washed with dry ether. The filtrate was cooled to 15° and treated with dry hydrogen chloride. The crude amino ketone hydrochloride

was washed with ether and recrystallized from 95% alcohol and a small amount of ether; colorless prisms, yield 30%.

All attempts to prepare the free base failed. The oxime was prepared from the hydrochloride in the usual manner and recrystallized from alcohol, m.p. 123° (corr.).

Anal. Calc'd for $C_{16}H_{18}N_2O$: N, 10.36. Found: N, 10.30.

XXVII. *1-Phenyl-2-phenylethylaminoethanol-1 hydrochloride.* The amino ketone hydrochloride (XXVI) was reduced in 95% alcohol at 60° by the regular procedure. The crude product was recrystallized from alcohol; white prisms, yield 90%. The free base was obtained in the usual manner.

XXVIII. *1-Phenyl-2-phenylethylaminoethanol-1 benzoate hydrochloride.* A suspension of 2 g. (0.0072 mole) of the amino alcohol hydrochloride (XXVII) in 14 g. (0.10 mole) of benzoyl chloride was heated for three hours at 90°. After washing the oily reaction-mixture with several portions of ether, it was allowed to stand cold overnight in contact with ether. The product so obtained was recrystallized from hot alcohol and ether; yield 88%.

The free base was obtained by the addition of sodium hydroxide pellets to a solution of the hydrochloride in 85% alcohol. The mixture was warmed to 50° for ten minutes, then cooled for several hours in an ice-bath. The crude product was recrystallized from alcohol and water.

XXIX. *α-Phenylethylaminopropiophenone hydrochloride.* A solution of 6.7 g. (0.0314 mole) of α-bromopropiophenone in 10 cc. of absolute alcohol was added to 0.0628 mole of β-phenylethylamine. The mixture was allowed to stand at room temperature for one hour, after which time 75 cc. of ether was slowly added. After standing one hour cold, the precipitated amine salt was removed by filtration and the amino ketone hydrochloride was precipitated from the filtrate by treatment with dry hydrogen chloride. Recrystallization from alcohol and ether yielded colorless prisms; yield 63%. The free base was obtained only as an impure oil.

The oxime, prepared from the hydrochloride, was recrystallized from alcohol, m.p. 152.5° (corr.).

Anal. Calc'd for $C_{17}H_{20}N_2O$: N, 10.41. Found: N, 10.28.

XXX. *1-Phenyl-2-phenylethylaminopropanol-1 hydrochloride.* This compound was prepared from compound XXIX by the usual procedure. It was recrystallized from a mixture of alcohol and ether; colorless prisms, yield 83%.

The base was prepared by adding sodium hydroxide pellets to the amino alcohol hydrochloride dissolved in 60% alcohol. This solution was heated for five minutes, then cooled, and water was added to turbidity. This was allowed to stand in the ice-box overnight and the crude product was recrystallized from alcohol and water.

XXXI. *1-Phenyl-2-phenylethylaminopropanol-1 benzoate hydrochloride.* Two grams (0.0007 mole) of the amino alcohol hydrochloride (XXX) was suspended in 14 g. (0.010 mole) of benzoyl chloride and the mixture was heated for six hours at 110°. The solution was cooled, 100 cc. of dry ether was added, and the mixture allowed to stand for several hours in the cold. Since no oily residue separated, the ether was evaporated to a small volume to recover the ester hydrochloride. Recrystallization from 15 cc. of absolute alcohol and 75 cc. of dry ether gave a white hygroscopic powder; yield 50%. The free base was prepared by the procedure used for the base of the corresponding alcohol (XXX).

XXXII. *α-Phenylethylamino-β-acetonaphthone hydrochloride.* To a dry ether solution containing 6.9 g. (0.057 mole) of β-phenylethylamine, was added 7.1 g. (0.028 mole) of α-bromo-β-acetonaphthone. The reaction-mixture was allowed to stand for thirty minutes at room temperature; colorless prisms, yield 30%. The free base was obtained only as an impure oil.

TABLE III

DERIVATIVES OF β-PHENYLETHYLAMINE

NO.	FORMULA	M.P. °C. (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XXVI	$C_6H_5COCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	175–177 decomp.	$C_{16}H_{18}ClNO$	5.08	4.92	12.86	12.98
XXVII	$C_6H_5CHOHCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	205–206	$C_{16}H_{20}ClNO$	5.05	4.98	12.41	12.58
	$C_6H_5CHOHCH_2NHCH_2CH_2C_6H_5$	89.5–90.0	$C_{16}H_{19}NO$	6.22	6.15		
XXVIII	$C_6H_5CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	146.5–148	$C_{23}H_{24}ClNO_2$	3.67	3.61	9.30	9.39
	$C_6H_5CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5$	101	$C_{23}H_{23}NO_2$	4.35	4.24		
XXIX	$C_6H_5COCH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	175–177 decomp.	$C_{17}H_{20}ClNO$	4.84	4.77	12.24	12.41
XXX	$C_6H_5CHOHCH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	208–209	$C_{17}H_{22}ClNO$	4.80	4.71	12.16	12.27
	$C_6H_5CHOHCH(CH_3)NHCH_2CH_2C_6H_5$	101.5–102	$C_{17}H_{21}NO$	5.49	5.40		
XXXI	$C_6H_5CH(OCOC_6H_5)CH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	185	$C_{24}H_{26}ClNO_2$	3.54	3.59	8.96	9.07
	$C_6H_5CH(OCOC_6H_5)CH(CH_3)NHCH_2CH_2C_6H_5$	93.5	$C_{24}H_{25}NO_2$	3.90	3.83		

XXXII	$C_{10}H_7COCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	174–177 decomp.	$C_{20}H_{20}ClNO$	4.32	4.15	10.88	10.99
XXXIII	$C_{10}H_7CHOHCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	194–196	$C_{20}H_{22}ClNO$	4.28	4.21	10.82	10.98
	$C_{10}H_7CHOHCH_2NHCH_2CH_2C_6H_5$	59.5–60	$C_{20}H_{21}NO$	4.81	4.70		
XXXIV	$C_{10}H_7CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	180.5–181.5	$C_{27}H_{26}ClNO_2$	3.24	3.19	8.21	8.33
	$C_{10}H_7CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5$	111.5–112	$C_{27}H_{25}NO_2$	3.54	3.50		
XXXV	$C_6H_5OCH_2CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	230–231	$C_{16}H_{20}ClNO$	5.05	5.04	12.77	12.79

The oxime prepared in the usual way was recrystallized from alcohol, m.p. 123° (corr.).

Anal. Calc'd for $C_{20}H_{20}N_2O$: N, 9.21. Found: N, 9.05.

XXXIII. *1-β-Naphthyl-2-phenylethylaminoethanol-1 hydrochloride.* Four grams (0.0491 mole) of the corresponding amino ketone hydrochloride (XXXII) was dissolved in 250 cc. of 95% alcohol and hydrogenated at 60° by the regular procedure. The crude product was recrystallized from dry alcohol and ether; colorless prisms, yield 95%. The free base was prepared by the general procedure and recrystallized from alcohol and water.

XXXIV. *1-β-Naphthyl-2-phenylethylaminoethanol-1 benzoate hydrochloride.* This ester was prepared by suspending 2 g. (0.006 mole) of the amino alcohol hydrochloride (XXXIII) in 14 g. (0.10 mole) of benzoyl chloride. The mixture was heated for two hours at 100°. The general procedure was then used to obtain the product in crystalline form. It was recrystallized from alcohol and ether; colorless needles, yield 60%. The free base was prepared and crystallized by the general procedure.

XXXV. *1-Phenoxy-2-phenylethylaminoethane hydrochloride.* A solution of 3.91 g. (0.0152 mole) of β-phenoxyethyl bromide was added to 3.8 g. (0.0314 mole) of β-phenylethylamine. The reaction-mixture was heated for two hours at 70°; colorless needles, yield 60%. The free base was obtained only as an impure oil.

SUMMARY

1. A series of ten new amino ketones, derivatives of ac-tetrahydro-β-naphthylamine, tetrahydroisoquinoline, and phenylethylamine, have been prepared.

2. The corresponding amino alcohols have been prepared by catalytic reduction, employing palladium on charcoal as the catalyst.

3. The benzoates of eight of the amino alcohols have been prepared.

4. The preliminary pharmacological report that has been included for six of the above compounds showed them to have anesthetic activity as well as vasopressor activity.

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