[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

9-ALKYLAMINO CARBINOLS DERIVED FROM 9-ACYL-1,2,3,4-TETRAHYDROPHENANTHRENE DERIVATIVES[1]

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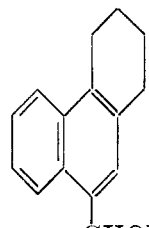
The work here presented was undertaken as a cooperative project with the National Institute of Health as part of a broader general program, the main object of which was a thorough exploration of the synthesis of as wide a variety of N,N-dialkylamino carbinols derived from 1,2,3,4-tetrahydrophenanthrenes of the general type shown in I as possible. It was desired to synthesize the



$CHOHCHR_1NR_2R_3$

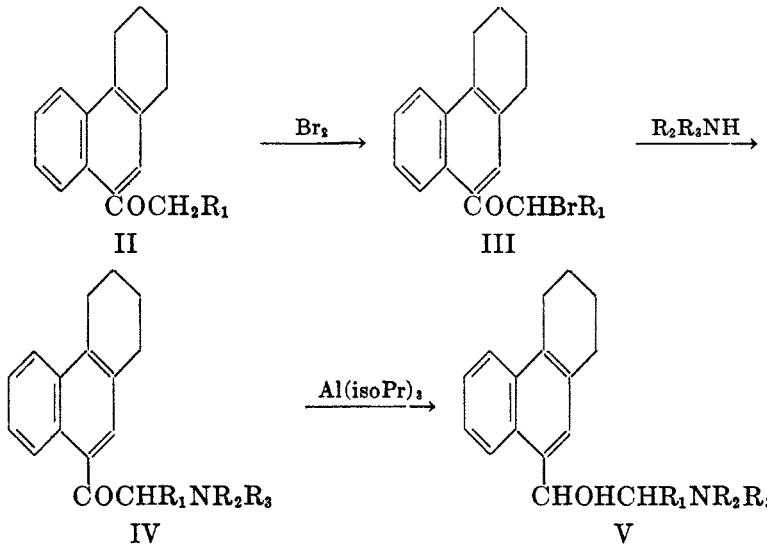
I

entire homologous series with respect to R_2 and R_3, in the case where R_1 = hydrogen and R_2 = R_3, up to the didodecyl compound, and also to introduce branched chain groups for R_2 and R_3 in so far as possible. At the time the work was begun, some of the lower members of the series had already been prepared by the group at the National Institute of Health laboratories, and shown to possess marked antimalarial action (1), so that the substances here reported are those necessary to complete the series. In addition, other representative variations in R_2 and R_3 have been introduced in order to acquire experience in the synthesis of such types, should a further exploration of these other types be demanded as the result of future work. Such variations include the case where R_2 = hydrogen and R_3 = a benzyl group. Similarly, variations in R_1 included the synthesis of representative amino carbinols in the series where R_1 = methyl and ethyl.

The general mode of synthesis used is shown in formulas II–V. In all cases a 9-acyl-1,2,3,4-tetrahydrophenanthrene was brominated in ether solution; the resulting α-bromoalkyl ketone was then condensed with the desired amine and finally the amino ketones were reduced with aluminum isopropoxide to yield the desired amino carbinols. 9-Acetyl- and 9-propionyl-tetrahydrophenanthrene have been previously described by Bachmann and Struve (2) and Bachmann and Cronyn (3). 9-Butyryltetrahydrophenanthrene appears to be new,

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

and its synthesis is described in detail. Likewise, bromoacetyltetrahydrophenanthrene has also been described (2). In general it was found to be neither desirable nor necessary to isolate the unstable amino ketones. Rather, these were reduced either as the free bases or as the hydrochlorides without purification, and the final amino carbinols were isolated as the hydrochlorides.



While at first glance it might appear that all of the reactions would proceed in a similar fashion in all cases, actually in practice it developed that each individual amino carbinol required its own individual experimental conditions and that in no two cases could exactly the same experimental procedure be used with optimum results. As a result of the present study, it has become possible to make some generalizations regarding the synthesis of such compounds. A similar study of amino carbinols in the naphthalene series has recently appeared (5).

In cases where R_1 is hydrogen, condensation of the bromo ketone with secondary amines took place readily at room temperatures provided R_2 and R_3 were straight chain alkyl or benzyl groups. However, in the cases where R_2 and R_3 contained branched chains with the branching in the vicinity of the secondary amino group, as in the case of diisopropyl and diisobutylamine, reaction was much more sluggish and required higher temperatures and longer reaction times. In many cases it was found that the amination reaction proceeded more readily in benzene than in ether. As would be expected, branching of the alkyl chain at a distance from the amino group, as in diisoamyl- and diisohexylamine, had comparatively little effect on the ease of the amination reaction. Not expected was the complete failure of the amination reaction in the cases of di-2-ethylbutyl- and di-2-ethylhexylamine, in which the branching of the carbon chains is at the second carbon atom from the nitrogen atom. It has been found impossible to carry out the amination under any conditions which did not also involve decomposition of the other reactant. However, a study of

TABLE I

PROPERTIES OF AMINO CARBINOLS REPRESENTED BY TYPE FORMULA I

All amino carbinols are described in this table as the hydrochlorides

SN[1]	R_1	R_2	R_3	M.P. °C	ANAL. Calc'd C	ANAL. Calc'd H	ANAL. Found C	ANAL. Found H	CRYSTALLINE FORM
5868	H	iso-C_3H_7	iso-C_3H_7	191–192	73.0	8.9	72.9	9.0	Prisms
5869	H	iso-C_4H_9	iso-C_4H_9	140–141	73.9	9.4	73.9	9.4	Hexagonal plates
3956	H	iso-C_5H_{11}	iso-C_5H_{11}	181–182	74.7	9.7	74.8	9.8	Micro needles
5479	H	iso-C_6H_{13}	iso-C_6H_{13}	118–119	75.4	9.9	75.3	10.2	Long plates
3957	H	n-C_7H_{15}	n-C_7H_{15}	122–123	76.0	10.2	76.2	10.2	Rectangular prisms
5241	H	n-C_9H_{19}	n-C_9H_{19}	125.5–126	77.0	10.6	76.9	10.7	Flat needles
5866	H	n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	116.5–117.5	77.4	10.8	77.1	11.1	Plates
8608	H	n-$C_{11}H_{23}$	n-$C_{11}H_{23}$	111.5–113	77.8	11.0	77.6	11.1	Flat prisms
6901	H	n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	107.5–109	78.2	11.2	78.0	11.5	Rectangular plates
5919	H	n-C_4H_9	$CH_2C_6H_5$	178–179	76.5	8.1	76.6	8.0	Fluffy needles
6903	H	n-C_4H_9	p-$OCH_3CH_2C_6H_4$	165–166	74.1	8.0	74.1	7.7	Micro needles
5921	H	H	iso-C_5H_{11}	193.5–194.5	72.5	8.7	72.3	8.5	Needles
6902	H	H	n-C_9H_{19}	171–172.5	74.3	9.5	74.6	9.4	Long flat needles
5920	H	H	n-$C_{10}H_{21}$	158.5–159.5	74.7	9.6	74.6	9.9	Prisms
7426	CH_3	Tetrahydroisoquinolino		224–225 d.	76.5	7.4	76.2	7.3	Stout prisms
	C_2H_5	C_2H_5	C_2H_5	195.5–196.5	73.0	8.9	72.9	8.8	Prisms

[1] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

an atomic model of the two amines in question showed that the steric arrangement in them is such as to block effectively the secondary amine hydrogen atom as far as the reaction under consideration is concerned. In the cases where R_2 = hydrogen and R_3 = alkyl, reaction of the bromo ketone with the primary amines was so rapid that external cooling was necessary.

In so far as the effect of the nature of R_1 on the amination reaction is concerned, it was found that branching of the chain of the acyl group attached to the ring system exerted a strong inhibitory effect on the amination reaction with the result that the reaction of the 9-α-bromopropionyl and 9-α-bromobutyryl derivatives of tetrahydrophenanthrene with straight chain secondary amines approached the reaction of 9-bromoacetyltetrahydrophenanthrene with diisopropyl- or diisobutyl-amine in sluggishness. In other words, it makes little difference in a qualitative sense on which reactant the chain is branched. In contrast to the circumstances encountered when groups R_2 and R_3 contained a long chain branched at the end, similar branching in R_1 exerted a very pronounced inhibitory effect on the amination reaction. Thus, when the condensation of 9-α-bromoisocaproyltetrahydrophenanthrene with diethylamine was attempted, a period of about six months at room temperature was required for complete reaction. This observation was entirely unexpected, since it seemed reasonable to predict that the isocaproyl derivative would approximate the propionyl or butyryl derivative in its behavior.

$$RCOCH_2Br + C_5H_{11}\underset{\displaystyle K}{\underset{|}{N}}SO_2C_6H_4CH_3 \rightarrow RCOCH_2\underset{\displaystyle C_5H_{11}}{\underset{|}{N}}SO_2C_6H_4CH_3$$

In the reduction of the amino ketones to the carbinols, the major difficulties are caused by the instability of the amino ketones or the tendency of the amino carbinols to undergo hydramine fission. Under the experimental conditions used in the present work, it was difficult to separate one factor from the other when poor yields were encountered. However, previous experience (4) has shown, that where extensive amine cleavage may be expected when the ketones are reduced catalytically, this may be minimized by the use of the Meerwein method of reduction. No particular difficulty was encountered in the reduction of the amino ketones except in the cases where R_2 = hydrogen. Here the yields of carbinols were very poor. Accordingly, an alternate synthesis for this type of substance, involving condensation of isoamyl *p*-toluenesulfonamide with the bromo ketone followed by hydrolysis of the sulfonamide either before or after reduction of the carbonyl group, was explored. However, acid hydrolysis of the sulfonamide of either the amino ketone or amino carbinol resulted in the formation of large amounts of tar from which none of the expected products could be isolated.

The amino carbinols thus prepared are summarized in Table I.

We are indebted to Mr. Saul Gottlieb and to Misses Lois May and Frances Marx for all microanalyses reported in this paper.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure, unless otherwise stated.

9-α-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene. This was prepared by the bromination of 9-acetyl-1,2,3,4-tetrahydrophenanthrene according to the method of Bachmann and Struve (1). The material used in the condensation with amines was recrystallized once from methanol and melted 89.5–90.5°.

9-(2-Diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The method used for the preparation of this compound was used in the synthesis of most of the amino carbinol hydrochlorides, although in some cases, with certain amines, modification of the procedure was necessary.

A solution of 28 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 225 cc. of anhydrous ether was shaken mechanically with 29.4 g. (two equiv.) of diisoamylamine for twelve hours. The solution was filtered, after standing for one hour in the refrigerator, and 21.0 g. of diisoamylamine hydrobromide (95%) was obtained. The ether solution was washed once with 250 cc. of water, once with a 1% sodium hydroxide solution and again with water. The ether solution was then dried over magnesium sulfate and the ether was removed, the last traces being taken off *in vacuo*. The oily orange colored residue was reduced directly according to the Meerwein method, using a mixture of 90 cc. of 1 *M* aluminum isopropoxide solution and 100 cc. of anhydrous isopropyl alcohol. The acetone formed during the reduction was distilled off through a 12-in. Vigreux column, additional isopropyl alcohol being added from time to time to maintain the level of the solution. After three to four hours, the 2,4-dinitrophenylhydrazine test for acetone was negative. The reduction was continued for an additional thirty minutes and the isopropyl alcohol removed under the water-pump vacuum. The dark red residue was cooled somewhat and shaken with 50 cc. of 10% sodium hydroxide solution and 200 cc. of anhydrous ether. After the solid had dissolved completely, the aqueous layer was drawn off and the ether layer washed twice with water and dried over magnesium sulfate. The volume of the solution at this point should be about 350 cc.

The solution was cooled in an ice-salt bath and the amino carbinol precipitated by the very slow addition of a dry ethereal hydrogen chloride solution. The precipitate which formed upon the addition of the first small portions of the hydrogen chloride solution possessed the crystalline character of the amine hydrochloride and the small amount of material thus formed was filtered off and discarded. The amino carbinol hydrochloride was then precipitated by addition of more ethereal hydrogen chloride solution to the filtrate until the solution became turbid. The solution was placed in an ice-salt bath and scratched vigorously to induce crystallization. The light brown crystalline precipitate which formed was filtered off and washed with ether. The weight of crude amino carbinol hydrochloride was 23 g. (60%). Three recrystallizations from acetone-ether or ethyl acetate gave 15 g. of material of analytical purity. Yields of the same order were obtained in the cases of other amino alcohols prepared according to this general method.

9-(2-Diisopropylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. Condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with diisopropylamine did not take place as readily as with diisoamylamine and other longer chained amines. A solution of 24.0 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 90 cc. of benzene was refluxed with three equivalents (24 g.) of diisopropylamine for six hours. The solution was allowed to cool to room temperature and the theoretical amount (14.5 g.) of diisopropylamine hydrobromide was filtered off.

The solution was evaporated under vacuum to remove the last traces of diisopropylamine and benzene and the straw colored residue reduced in the manner described for the above diisoamyl compound, yielding 16.0 g. (58.2%) of crystalline crude amino carbinol hydrochloride. The light tan powder was recrystallized once from acetone-ether, followed by an additional recrystallization from alcohol-ether to give a sample of analytical purity. This

compound was found to be less soluble in most organic solvents than the amino alcohol hydrochlorides of the longer-chained amines.

9-(2-Diisobutylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A solution of 25 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 9.5 g. (2 equiv.) of diisobutylamine in acetone was refluxed for six hours. Most of the acetone was removed *in vacuo* and the diisobutylamine hydrobromide which separated out was filtered off and washed with ether. The remainder of the acetone and ether was then removed under vacuum.

The oily amino ketone was reduced in the manner described for the previous compounds. The amino carbinol hydrochloride precipitated as an oil when dry hydrogen chloride gas was passed slowly over the surface of the ether solution of the amino alcohol cooled in an ice-bath. By dissolving a small portion of the oil in ethyl acetate-alcohol and adding petroleum ether (Skellysolve B) to slight turbidity, crystals were produced when the solution was allowed to stand overnight at room temperature. The crystals were used for seeding the remainder of the oil. Eight grams (21%) of amino carbinol hydrochloride was obtained by this method. Two recrystallizations of the crude product from ethyl acetate gave a sample of analytical purity.

9-(2-Diisohexylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The general method used for the preparation of 9-(2-diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene was followed. The yield of crude amino alcohol hydrochloride starting with 25.0 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was 24.0 g. (65%). Four recrystallizations from acetone-ether with one charcoal treatment gave 8.4 g. of product of analytical purity. This substance is quite hygroscopic and increases in weight slightly upon standing.

9-(2-Diheptylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed.

9-(2-Dinonylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed. Somewhat better yields were obtained in larger runs. Thus when 101 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was condensed with 2 equivalents (179 g.) of dinonylamine and the amino ketone reduced in the usual way, using 380 cc. of 1 *M* aluminum isopropoxide in isopropanol solution, the acetone formed being distilled off through a one-meter Vigreux column, the yield of product, melting at 125–126° after two recrystallizations from ethyl acetate, was 108 g. (61%).

9-(2-Didecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed.

9-(2-Diundecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The same general procedure as above was used, the reaction being slower.

In the condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with diundecylamine, reaction took place to the extent of about 96% after twenty-four hours mechanical shaking and twenty-four hours additional standing in the refrigerator. Purification of the amino carbinol hydrochloride was rather difficult, probably due to the fact that it was contaminated with a small amount of diundecylamine hydrochloride. Three recrystallizations from acetone followed by four recrystallizations from ethyl acetate were necessary to produce an analytical sample.

Diundecylamine was obtained along with undecylamine by the reduction of decylcyanide. Four hundred six grams (500 cc.) of decylcyanide (b.p. 128–131°/10 mm.) was reduced in a pressure bomb with 15 g. of Raney nickel at 125° and an initial pressure of 1300 lbs. After the theoretical amount of hydrogen had been taken up, the reduction was stopped. The product of the reaction was distilled under vacuum. The first crude fraction boiled at 90–100°/0.8 mm. and the second fraction boiled at 190–200°/0.8 mm. Both fractions were redistilled separately. The first fraction gave 226 g. of undecylamine boiling at 94–96°/1 mm., and the second fraction gave 62.5 g. of diundecylamine boiling at 190–194°/0.8 mm. The

second fraction, a white solid, when recrystallized three times from benzene-ethanol under nitrogen gave small colorless needles melting at 51.5–52.5°.

Anal. Calc'd for $C_{22}H_{47}N$: C, 81.1; H, 14.6.
Found: C, 80.8; H, 14.6.

9-(2-Didodecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. When 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and didodecylamine were condensed together under the conditions used with diundecylamine, condensation took place to the extent of 93%. The product of the reaction was worked up according to the method described previously. The crude amino carbinol hydrochloride was purified by four recrystallizations from ethyl acetate.

p-Methoxybenzal-n-butylamine was prepared according to the directions of Einhorn and Pfeiffer (6). A mixture of 25 g. of *n*-butylamine, 75 cc. of water, and 50.5 g. of *p*-anisaldehyde was thoroughly shaken and allowed to stand overnight at room temperature. The mixture was extracted with ether and the ether solution dried over anhydrous potassium carbonate. Evaporation of the ether gave a colorless oil which was distilled *in vacuo*, yielding 65.6 g. (92%) of a colorless oil boiling at 108–109°/1.0 mm. n_D^{25} 1.5384

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.4; H, 9.0.
Found: C, 75.5; H, 8.8.

p-Methoxybenzyl-n-butylamine was prepared by the reduction of *p*-methoxybenzalbutylamine. Four hundred fifty cubic centimeters (440 g.) was reduced in a high pressure bomb using 10 g. of Raney nickel at an initial pressure of 1200 lbs. and at a temperature of 80°. After one and one-half hours, the reaction was stopped after the calculated amount of hydrogen had been taken up. To the filtrate from the catalyst was added 500 cc. of water and 400 cc. of conc'd hydrochloric acid and the mixture was warmed on the steam-bath for two hours. The solid amine hydrochloride was filtered off and treated with alkali to liberate the free base. The free base was purified by distillation under vacuum from sodium and gave 240 g. of a colorless liquid boiling at 120–125°/0.7 mm. n_D^{25} 1.5081.

Anal. Calc'd for $C_{12}H_{19}NO$: C, 74.6; H, 9.9.
Found: C, 74.8; H, 10.1.

9-(2-p-Methoxybenzyl-n-butylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. This compound was prepared according to the general method. Thirty-five grams of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 44.6 g. of *p*-methoxybenzylbutylamine were allowed to stand together in 1000 cc. of ether for three days, after which the amine hydrobromide was filtered off and the product worked up in the usual way. The reduction of the amino ketone was complete after five hours. Upon passing gaseous hydrogen chloride over the ethereal solution of the amino carbinol, an oil separated. Hydrogen chloride gas was passed over the surface until precipitation was complete and then a stream of dry air was blown through the mixture to remove excess hydrogen chloride. The oil-ether mixture was allowed to stand overnight in the refrigerator, after which some crystals had formed. The ether layer was decanted off and the oil taken up in hot acetone and ether added to slight cloudiness. The solution was scratched vigorously in an ice-salt bath, whereupon the whole mass solidified. The yield of light tan product was 27.3 g. (52%). Three recrystallizations of the crude material from acetone-ether gave 15 g. of product melting 165–166°.

9-(2-n-Butylbenzylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The general method used for the preparation of the diisoamyl compound was followed using 50 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 54 g. of benzylbutylamine. There was obtained 40 g. (57%) of crude amino carbinol hydrochloride. One recrystallization from acetone containing 10% alcohol gave 35 g. of pure product.

9-(2-Isoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. To a solution of 25.9 g. of isoamylamine in 500 cc. of anhydrous ether was added 45 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene. The flask was allowed to stand at room temperature, with cooling, for fifteen minutes, with occasional shaking, at the end of which all of the 9-bromoacetyltetrahydrophenanthrene had gone into solution. After six hours

in the refrigerator the solution was red in color. The isoamylamine hydrobromide was filtered off and washed with a small amount of ether, the washings being added to the filtrate, yielding 23.2 g. (93%). The filtrate was treated immediately with a saturated ethereal hydrogen chloride solution and 28.5 g. of crude amino ketone hydrochloride was obtained. If the ether solution was allowed to stand before adding the ethereal hydrogen chloride solution, a yellow precipitate began to form slowly; consequently, the hydrogen chloride was added immediately. The crude amino ketone hydrochloride was stirred well with about one liter of water and filtered. The process was then repeated using 200 cc. of ether. The pure white product thus obtained was reduced in the manner described previously using 150 cc. of 1 *M* aluminum isopropoxide solution and 150 cc. of dry isopropyl alcohol. After two hours a negative acetone test was obtained and the reduction was continued for an additional hour and stopped. The reduced product was worked up as described previously. The amino alcohol hydrochloride was precipitated by the slow addition of dry gaseous hydrogen chloride. Nine and one-tenth grams of a white precipitate formed immediately. Three recrystallizations from ethyl acetate gave an analytical product.

Preparation of the above compound was attempted over the *p*-toluene sulfonamide as follows: To 300 cc. of an ether solution of 33.2 g. of isoamylamine in a 1-liter 3-necked flask fitted with a reflux condenser, mechanical stirrer and dropping-funnel, was added dropwise over the course of two hours, 34.6 g. of *p*-toluene sulfonyl chloride dissolved in 200 cc. of ether. After a short time isoamylamine hydrochloride began to precipitate out. The reaction mixture was stirred at low temperature for five hours and the amine hydrochloride filtered off. The filtrate was washed with dilute hydrochloric acid, then with water, and dried over magnesium sulfate. Upon evaporation of the ether a colorless residue (40 g.) remained; this was distilled under vacuum and gave 36 g. (82%) of a colorless liquid boiling at 178–180°/1 mm. n_D^{25} 1.5171.

Anal. Calc'd for $C_{12}H_{19}NO_2S$: C, 59.7; H, 7.9.
Found: C, 59.8; H, 7.7.

To 36 g. of isoamyl-*p*-toluenesulfonamide dissolved in 300 cc. of anhydrous benzene was added 5.8 g. of potassium. The reaction mixture was heated to reflux and stirred mechanically until complete reaction was effected. The benzene was removed *in vacuo* and the potassium salt dissolved in anhydrous ether. To a stirred ethereal solution of 25 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was added an ether solution of 23.2 g. of potassium isoamyl-*p*-toluene sulfonamide. The reaction mixture was refluxed for four hours, the potassium bromide filtered off, and the ether evaporated, leaving a thick yellow oil. The condensation product was soluble in ether and benzene, but insoluble in ethyl and methyl alcohol. Attempts at recrystallization were unsuccessful.

When the condensation product was refluxed with 25% hydrochloric acid for twenty hours, only tarry products were obtained.

A portion of condensation product was reduced in the usual way with aluminum isopropoxide and isopropyl alcohol according to the Meerwein method. The resulting product upon hydrolysis with dilute acid again gave only tarry products.

9-(2-n-Nonylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The method used for the preceding monoisoamyl compound was followed. Starting with 31.8 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 30.1 g. of *n*-nonylamine, there was obtained 20 g. of crude amino ketone hydrochloride. This was reduced as described previously and gave 9.5 g. (22.5%) of crude amino carbinol hydrochloride. Two recrystallizations from absolute ethanol-ether gave 8.4 g. of pure product.

9-(2-n-Decylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the monoisoamyl compound was followed. From 30 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene there was obtained 14.5 g. of crude amino ketone hydrochloride, which upon reduction gave 8.5 g. of crude amino carbinol hydrochloride. One recrystallization from alcohol-acetone gave 6 g. (14.5%) of pure product.

Attempted condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with di-2-

ethylbutylamine and di-2-ethylhexylamine. When a solution of 10 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and the theoretical amount of di-2-ethylbutylamine or di-2-ethylhexylamine in 100 cc. of ether was shaken mechanically for twenty-four hours, practically no condensation took place. Negative results were also obtained when the solution was refluxed under nitrogen for eight hours or when the reactants were refluxed under nitrogen in benzene for eight hours.

9-(2-Diamylamino-1-acetoxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A mixture of 25 g. of 9-(2-di-*n*-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride, 75 cc. of acetic anhydride, and 150 cc. of dry pyridine was refluxed for two hours. The solution was then allowed to stand at room temperature for forty-eight hours. The solvents were removed under reduced pressure and the residue crystallized from ethyl acetate to give 10 g. of acetoxy compound. After two additional recrystallizations from ethyl acetate, with charcoal decolorization, small colorless needles, melting at 152–154°, were obtained.

Anal. Calc'd for $C_{28}H_{42}ClNO_2$: C, 73.1; H, 9.3.
Found: C, 72.9; H, 9.3.

9-α-Bromopropionyl-1,2,3,4-tetrahydrophenanthrene. A solution of 20 g. of 9-propionyl-1,2,3,4-tetrahydrophenanthrene (m.p. 42–43°), prepared according to the directions of Bachmann and Cronyn (2), in 150 cc. of dry ether in a 500-cc. 3-necked flask fitted with mechanical stirrer, small dropping-funnel, and reflux condenser fitted with a calcium chloride tube, was heated to boiling on a steam-bath. A few drops of bromine were added and after decoloration had taken place, the flask was cooled in an ice-bath to 15° and the remainder of the bromine (13.0 g. in all) was added over the course of twenty minutes. The ether solution was washed with water, then with sodium bisulfite solution, and again with water, and dried over magnesium sulfate. After standing overnight in the ice-box, 10 g. of slightly yellow crystals precipitated from the ethereal solution and were filtered off (m.p. 77–78°). Concentration of the ethereal filtrate and cooling gave four more grams of crystalline bromo ketone. The weight of bromo ketone obtained was thus 14 g. (52.5%). Two recrystallizations from methanol gave translucent rectangular prisms melting at 77–78°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.4; H, 5.4.
Found: C, 64.1; H, 5.5.

9-(2-Tetrahydroisoquinolino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A solution of 40 g. (0.126 mole) of 9-α-bromopropionyl-1,2,3,4-tetrahydrophenanthrene in 200 cc. of dry benzene was allowed to stand with 2 equivalents (33.5 g.) of tetrahydroisoquinoline for 48 hours. Condensation took place to the extent of 85%, as determined by the amount of amine hydrobromide precipitating out. The filtrate was washed twice with water and dried over magnesium sulfate. The ethereal solution was cooled in an ice-bath, ethereal hydrogen chloride was added slowly, and the precipitate which formed was filtered off. This was washed twice with water to dissolve any tetrahydroisoquinoline hydrochloride present, and converted back to the free amino ketone by treatment with 10% sodium hydroxide solution and ether. After redrying with magnesium sulfate and evaporation of the ether, the resulting residue was reduced as described previously, using 240 cc. of aluminum isopropoxide solution. Reduction was complete in ten hours. The reduced product was worked up in the usual manner, and the amino carbinol hydrochloride precipitated by the addition of ethereal hydrogen chloride solution. After three recrystallizations from acetone-methanol-ether, with charcoal decolorization, 20 g. of pure material remained.

9-Butyryl-1,2,3,4-tetrahydrophenanthrene. The procedure of Bachmann and Cronyn (2) for 9-propionyl-1,2,3,4-tetrahydrophenanthrene was followed using 66.9 g. of 1,2,3,4-tetrahydrophenanthrene, 123 g. of anhydrous aluminum chloride, 750 cc. of carbon disulfide, 500 cc. of tetrachloroethane, and 83 g. of butyryl chloride. The tetrahydrophenanthrene was added dropwise to the stirred solution of the other reagents at −15°. Stirring was continued for one hour and the flask was allowed to stand twenty-four hours in the refrigerator. The brown complex was filtered off, washed with a small amount of carbon disulfide, al-

lowed to dry for ten minutes in the air, and hydrolyzed with ice and dilute hydrochloric acid. A light brown oil separated out, which did not solidify upon standing in the refrigerator for some time. The oil was separated off and the aqueous layer extracted twice with 250-cc. portions of ether. The oil was added to the ether extracts and the combined ether solution was dried over magnesium sulfate, the ether distilled off, and the black residue distilled under vacuum, yielding 40.1 g. (43%) of a colorless liquid which boiled at 200–205°/1.1 mm. Upon standing in the refrigerator, the liquid solidified. One recrystallization from ethanol-methanol gave needles melting at 44–45.5°. Two additional recrystallizations from the same solvent mixture gave needles melting at 46–47°.

When the reaction was carried out using nitrobenzene as a solvent, a mixture of two isomers was obtained. Small amounts of both isomers could be obtained by recrystallization. The procedure of Bachmann and Struve (1) for 9-acetyl-1,2,3,4-tetrahydrophenanthrene was followed using 75 g. of 1,2,3,4-tetrahydrophenanthrene, 45.8 g. of butyryl chloride, and 101 g. of anhydrous aluminum chloride. The nitrobenzene layer, after hydrolysis of the product with ice and dilute hydrochloric acid, was separated off and the aqueous layer extracted with benzene. The benzene extracts were added to the nitrobenzene layer and the benzene and nitrobenzene were removed by steam distillation. The residue was vacuum distilled, yielding 73.7 g. of colorless liquid, boiling at 185–195°/0.7 mm., which solidified upon standing overnight in the refrigerator. One recrystallization from methyl alcohol followed by four recrystallizations from petroleum ether (Skellysolve B) gave colorless needles melting at 140–141°. This is probably the 7-isomer.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.7; H, 8.0.
Found: C, 86.0; H, 7.8.

The methyl alcohol mother liquors obtained from the above recrystallization, upon standing for some time in the refrigerator precipitated long slender needles. One additional recrystallization from methyl alcohol gave long, colorless, slender needles melting at 46–47°. This product was identical with the product obtained by the previous method employing carbon disulfide and tetrachloroethane, inasmuch as mixed melting points of several compositions of the two showed no depression.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.7; H, 8.0.
Found: C, 85.5; H, 7.9.

9-α-Bromobutyryl-1,2,3,4-tetrahydrophenanthrene. To a solution of 15 g. of 9-butyryl-1,2,3,4-tetrahydrophenanthrene in 50 cc. of anhydrous ether in a 200-cc. 3-necked flask fitted with dropping-funnel, reflux condenser fitted with a calcium chloride tube, and mechanical stirrer, cooled to 10° in an ice-salt bath, was added the calculated amount (3.1 cc.) of bromine, dropwise. The reaction was instantaneous. The ether solution was washed with water, dried with magnesium sulfate, and the ether removed, leaving a yellow oil. One recrystallization of this oil from methanol gave 14.8 g. (75%) of crystalline material melting at 54.5–55.5°. Three additional recrystallizations from methanol gave long transparent needle-like prisms melting at 55.5–56.5°. The yield of product, based upon the weight of oil obtained after evaporation of the ether, was practically quantitative.

Anal. Calc'd for $C_{18}H_{19}BrO$: C, 65.3; H, 5.8.
Found: C, 65.3; H, 5.7.

9-(2-Diethylamino-1-hydroxybutyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. To a solution of 10 g. of 9-α-bromobutyryl-1,2,3,4-tetrahydrophenanthrene in 50 cc. of dry benzene was added a large excess (50 cc.) of diethylamine and the resulting solution was allowed to stand, with occasional shaking, for twenty-one days. The amine hydrobromide was filtered off and washed with ether. The benzene, ether, and excess amine were distilled off from the filtrate under reduced pressure. To the residue was added 75 cc. of anhydrous ether and the small amount of diethylamine hydrobromide separating out was filtered. The ethereal filtrate was washed twice with water, dried over magnesium sulfate, and the ether distilled off, the last traces being taken off under reduced pressure. The dark oily residue was reduced in the usual manner using 45 cc. of 1 *M* aluminum isopropoxide solution and 45 cc. of dry isopropyl alcohol. A negative acetone test was obtained after

four hours. The reduced product was worked up in the usual manner and upon addition of an ethereal hydrogen chloride solution, an oil separated. Upon addition of 100 cc. of acetone to the flask containing the oil, after the ether layer had been decanted off, an immediate precipitation of a white solid occurred. After the flask had been allowed to cool for several hours in the refrigerator, the precipitate was filtered off; it weighed 4.2 g. (43%). Two recrystallizations from absolute ethanol-ether, with charcoal decolorization, gave 3 g. of colorless prisms melting at 194–196°. Three additional recrystallizations from an absolute ethanol-ethyl acetate-ether mixture gave an analytical product melting at 195.5–196.5°.

9-Isocaproyl-1,2,3,4-tetrahydrophenanthrene. The procedure described for the preparation of 9-butyryl-1,2,3,4-tetrahydrophenanthrene was followed using the appropriate quantities of reagents for 110 g. of 1,2,3,4-tetrahydrophenanthrene. The solvent was carbon disulfide-tetrachloroethane. The light brown oily product of the reaction was distilled under vacuum, yielding 85.9 g. (51%) of a colorless liquid boiling at 195–200°/0.6 mm. The oil solidified upon standing for some time in the refrigerator, after seeding with a crystal obtained by freezing a small part of the oil in a "dry-ice" bath. Two recrystallizations from ethanol-methanol (1:2) gave large colorless needles melting at 33–33.5°.

Anal. Calc'd for $C_{20}H_{24}O$: C, 85.7; H, 8.6.
Found: C, 85.7; H, 8.7.

9-α-Bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene. The procedure described for the preparation of 9-α-bromobutyryl-1,2,3,4-tetrahydrophenanthrene was followed using the appropriate quantities of reagents for 49.1 g. of 9-isocaproyl-1,2,3,4-tetrahydrophenanthrene. After the addition of bromine was complete, the solution was washed with water. At this point a white precipitate began to form. After standing overnight in the refrigerator, the precipitate was filtered off. From the mother liquors additional product was obtained. Recrystallization of the total product thus obtained from methanol-absolute ethanol (2:1) gave 53.8 g. (85%) of material melting at 88–90°. Two additional recrystallizations gave long colorless needles melting at 89.5–90.5°.

Anal. Calc'd for $C_{20}H_{23}BrO$: C, 66.9; H, 6.5.
Found: C, 67.1; H, 6.5.

Reaction of 9-(α-bromoisocaproyl)-1,2,3,4-tetrahydrophenanthrene with secondary amines. A mixture of 15 g. of 9-α-bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene and 61.0 g. (20 equivs.) of diethylamine in 100 cc. of benzene was allowed to stand under nitrogen for six months, at the end of which condensation was complete. The benzene and excess amine were distilled off and the amino ketone residue was reduced according to the usual Meerwein procedure. Only a faint acetone test was obtained. When the reduction product was worked up according to the method described for 9-(2-diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride, an impure amino carbinol hydrochloride was obtained. This could not be obtained in the pure state, probably because of incomplete reduction of the amino ketone, due to the steric effect of the isocaproyl group.

SUMMARY

1. A variety of new amino carbinol hydrochlorides derived from 1,2,3,4-tetrahydrophenanthrene, with the amino carbinol side chain in the 9-position, has been prepared.

2. 9-Butyryl- and 9-isocaproyl-1,2,3,4-tetrahydrophenanthrene have been prepared by the Friedel-Crafts reaction between the corresponding acid chlorides and 1,2,3,4-tetrahydrophenanthrene.

3. 9-α-Bromopropionyl-, 9-α-bromobutyryl-, and 9-α-bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene have been prepared by bromination of the corresponding ketones.

4. Diundecylamine and *p*-methoxybenzylbutylamine have been prepared by catalytic reduction of decylcyanide and *p*-methoxybenzalbutylamine, respectively.

5. *p*-Methoxybenzalbutylamine has been prepared.

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