aliquot of 5 or 10 cc. is withdrawn, by means of a rubber suction bulb connected to a pipet, and hydrolyzed in 10 cc. of distilled water. Titration with standard acid, using phenolphthalein as an indicator, gives the total alkali. Another 5 or 10 cc. aliquot is added to 10 cc. of dry ether containing 1 cc. of benzyl chloride.[8] As the alkyllithium solution is dropped into the benzyl chloride, as rapidly as it drains from the pipet, a yellow color flashes through the liquid. If the RLi solution is concentrated, a white precipitate of lithium chloride forms with the disappearance of the yellow color. The ether solution may become warm enough to boil, but it is not cooled. The mixture is allowed to stand one minute after the addition, then hydrolyzed, and titrated with standard acid. Care must be taken not to overstep the end-point in this titration since the aqueous layer decolorizes before the ether layer. This may be overcome by vigorous shaking near the end point.

The benzyl chloride must be dissolved in ether because coupling with the RLi compound takes place much less readily in most other solvents. In analyses of RLi compounds prepared in petroleum ether, the benzyl chloride should be dissolved in a relatively large volume of ether.

Lithium *n*-butoxide did not cleave benzyl chloride under the conditions of the analysis. When these two reagents were refluxed for one minute and then hydrolyzed, no chloride ion was found in the aqueous layer.

Reaction of Benzyl Chloride with *n*-Butyllithium.—To a large excess of benzyl chloride (0.6 mole) in ether was added 250 cc. (0.158 mole) of *n*-butyllithium. Vigorous refluxing took place, even with a moderate rate of addition. The products isolated were: a small quantity of *n*-octane, 5 g. (21%) of *n*-amylbenzene, and 8.2 g. (31%) of bibenzyl. The bibenzyl was identified both by a mixed m. p. determination, and by the 1,3,5-trinitrobenzene–bibenzyl complex (m. p. 103–104°).[9] Incidentally, no bibenzyl was isolated from reactions of benzyl chloride with either α-naphthyllithium or *p*-dimethylaminophenyllithium.

Capture of Benzyllithium from Reaction of Benzyl Chloride with Ethyllithium.—Ethyllithium was prepared in a customary manner from 43.2 g. (0.4 mole) of ethyl bromide and 5.6 g. (0.8 g. atom) of lithium in 400 cc. of ether. The solution, free of lithium, was cooled to −50°, and 15 g. of benzyl chloride in 50 cc. of cold ether was added rapidly.[10] The usual characteristic yellow color formed, and the colored solution was carbonated with Dry Ice within one minute after the benzyl chloride was added. Subsequent to hydrolysis and removal of the ether, the solution was extracted with petroleum ether, before and after acidification. The petroleum ether and then the propionic acid were removed leaving a small quantity of oil (20 mg.) having a pronounced odor of phenylacetic acid. The oil solidified after standing a week, and the phenylacetic acid was characterized by the preparation of the *p*-bromophenacyl ester (mixed m. p.).

Summary

It has been shown that benzyl chloride is a convenient reagent for the quantitative estimation of organolithium compounds. In the reaction of benzyl chloride with an alkyllithium compound, three coupling products are formed: R.R, R-benzyl and bibenzyl. Benzyllithium is formed transitorily in this reaction as a consequence of a halogen–metal interconversion reaction: $C_2H_5Li + C_6H_5CH_2Cl \rightarrow C_6H_5CH_2Li + C_2H_5Cl$.

(8) The benzyl chloride was purified by drying over phosphorus pentoxide and then distilling at reduced pressure.

(9) Sudborough, *J. Chem. Soc.*, **109**, 1339 (1916).

(10) Under ordinary conditions, the alkyllithium compounds couple so rapidly with benzyl chloride that a negative color test [Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925)] is obtained within one-half minute after mixing the two solutions.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

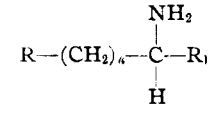
Aminoalkanes as Pressor Substances

BY EWALD ROHRMANN AND H. A. SHONLE

In 1910 Barger and Dale[1] reported a study of the pressor activity of a number of primary aliphatic amines in which the amino group was located on the terminal carbon. They concluded that the pressor activity increases as the length of the carbon chain increases until *n*-hexylamine is reached, this being the most active aliphatic amine which they investigated. *n*-Heptyl and *n*-octylamines were reported to be distinctly less active. They also presented evidence indicating that branching of the carbon chain brought about a decrease in activity.

During the past decade there has been an increased interest shown in some of the secondary aliphatic amines, some of which have been claimed to have high antispasmodic activity. A thorough review of the literature on the pharmacology of the aliphatic amines has been made recently by Dunker and Hartung.[2]

Until the results of the present investigation were known aliphatic amines were considered to be of no practical value as pressor substances. In undertaking this investigation careful consideration was given to the known information concerning the pressor activities of those primary amines containing an aromatic nucleus.[3] In this series of amines, which may be represented as



(where R = phenyl or substituted phenyl and R_1 = hydrogen or alkyl), the position of the amino group with respect to the aromatic nucleus has a very profound effect on the magnitude of the pressor action. For example, compounds such as β-phenethylamine, 1-phenyl-2-aminopropane, etc., show high pressor action, while compounds such as benzylamine and 1-phenyl-3-

(1) Barger and Dale, *J. Physiol.*, **41**, 19 (1910).

(2) Dunker and Hartung, *J. Am. Pharm. Assoc.*, **30**, 619 (1941).

(3) Hartung, *Chem. Rev.*, **9**, 389 (1931).

TABLE I

Amine	B. p. of amine, °C.	$n^{21}D$ of amine	Saturated intermediate ketone b. p., °C.	Formula of amine salt	N analyses, % Calcd.	Found
2-Aminoheptane[a,b]	141.0–142.5	1.4150	150–152	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.52
3-Aminoheptane[a,c]	139–140	....	148–150	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.46
4-Aminoheptane[a,d]	139–140	1.4172	.....	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.40
2-Amino-3-methylhexane[e]	138–140	....	.....	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.75
2-Amino-4-methyl hexane[a]	131–133	1.4210	142–144	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.47
2-Amino-5-methylhexane[a]	131–133	....	142–144	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.34
2-Amino-4,4-dimethylpentane[a]	121–123	....	125–127	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.46
2-Amino-3-methylheptane[e]	159–161	1.4290	.....	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	8.00
2-Amino-4-methylheptane[a]	153–154.5	1.4224	158–161	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	7.75
2-Amino-5-methylheptane[a]	157–157.5	1.4238	164–166	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	7.88
2-Amino-6-methylheptane[a]	154–156	1.4200	166–169	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	7.92
3-Amino-4-methylheptane[f]	155–157	....	.....	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	7.9
3-Amino-6-methylheptane[f]	155–157	....	.....	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	8.08
3-Amino-octane[g]	161–163	1.4243	.....	$(C_8H_{19}N)_2 \cdot H_2SO_4$	7.87	8.05
2-Amino-3,6-dimethylheptane[e]	173–175	1.4299	.....	$(C_9H_{21}N)_2 \cdot H_2SO_4$	7.29	7.29
2-Amino-5-ethylheptane[e]	179–181	1.4393	.....	$(C_9H_{21}N)_2 \cdot H_2SO_4$	7.29	7.41
4-Amino-2,6-dimethylheptane[a]	173–176	....	.....	$C_9H_{21}N \cdot HCl$	7.8	7.6

[a] Prepared from the corresponding saturated ketone. [b] Clarke (ref. 5) reports a b. p. of 142–144° for a product he designated as 2-aminoheptane. None of the melting points of his amine salts check with our melting points. Dunker, *et al.*, ref. 6, report a b. p. of 141.8–142.5°. [c] Ketone was prepared by Dr. R. G. Jones of this Laboratory by the reaction of propionitrile on *n*-butylmagnesium bromide. Dunker, *et al.*, ref. 6, report a b. p. of 140–144° for this amine. [d] Noyes, THIS JOURNAL, **15**, 542 (1893), reports a b. p. of 139–140°. Dunker, *et al.*, ref. 6, report a b. p. of 140–141°. [e] Prepared from the oxime of the corresponding α,β-unsaturated ketone by catalytic hydrogenation. [f] Prepared from the corresponding substituted acetamides by the Hofmann degradation. [g] Amine prepared by Dr. R. G. Jones of this Laboratory by the reaction of propionitrile with *n*-amylmagnesium bromide; conversion to the oxime and subsequent reduction with sodium and ethanol.

aminopropane show very inferior activity.[4] It is of interest to note that of the pressor substances containing an aromatic nucleus, those of the β-phenethylamine type have a pressor action of short duration while those of the 1-phenyl-2-aminopropane type have a pressor action of much longer duration.

In view of the fact that the only aliphatic primary amines which have been studied for pressor action have had the amine group on the terminal carbon, it is evident that the potentialities of the aliphatic amines as pressor substances had not been adequately investigated. The purpose of the present study of aliphatic amines was the correlation of the structure of these amines with their pressor activity. More specifically this problem involved (a) the influence of the location of the amino group in the molecule on the pressor activity and (b) the influence of carbon branching on the pressor action.

Aliphatic amines having seven, eight and nine carbon atoms, with the amino group in varying positions, were prepared by convenient methods. In most of the examples the amines were prepared from the corresponding saturated ketones or from the corresponding α,β-unsaturated ketones. The following methods were used in the preparation of amines from the saturated ketones: (a) reduction of the oxime with sodium and ethanol; (b) reduction of the oxime in ethanol solution with Raney nickel and hydrogen; (c) reduction of the ketone in a solution of ammonia in ethanol with Raney nickel and hydrogen; (d) reaction of the ketone with ammonium formate and subsequent acid hydrolysis. In the preparation of amines from the α,β-unsaturated ketones the oxime was reduced with Raney nickel and hydrogen. The 3-amino-4-methylheptane and 3-amino-6-methylheptane were prepared from the corresponding substituted acetamides by the Hofmann degradation. The amines prepared and their properties are listed in Table I.

The early work concerning the identity of some of the aliphatic amines is in a rather confusing state. This is particularly so in regard to 2-aminoheptane. Clarke[5] described the preparation of what he considered to be 2-aminoheptane by the treatment of a mono-bromo-heptane, which he believed to be 2-bromoheptane, with ethanolic ammonia in a sealed tube at 100°. Dunker, Hartung and Chapman[6] more recently reported on the preparation of several heptylamines including 2-aminoheptane, which they prepared by reducing heptanone-2 oxime with sodium and ethanol.

We have prepared 2-aminoheptane from heptanone-2 by the latter method. Using pure 2-aminoheptane we have prepared a large number of its acid addition salts, including salts of the acids used by Clarke with his amine,[5] namely, the oxalate, hydrochloride, hydrobromide, chloroaurate and chloroplatinate. There is in every case a

(4) Chen, *Archiv. Int. Med.*, **39**, 404 (1927).

(5) Clarke, THIS JOURNAL, **21**, 1027 (1899).

(6) Dunker, Hartung and Chapman, *J. Am. Pharm. Assoc.*, **30**, 623 (1941).

large discrepancy between the melting points of our compounds and those described by Clarke (see Table II). In view of these results and in view of the fact that our 2-aminoheptane was prepared by an unequivocal method, it is obvious that the salts which Clarke reported were not those of 2-aminoheptane but of some other amine. Inasmuch as the 2-bromoheptane used by Clarke was obtained by the bromination of a sample of *n*-heptane obtained from *Pinus sabiniana*,[7,8] it seems most probable that he was working with a mixture of substances. One would expect the bromination of *n*-heptane to yield certain amounts of all the possible monobromides as well as some polybromides. Very careful fractionation through efficient fractionating columns is required to effect a suitable separation of even 1-bromoheptane from 2-bromoheptane. The separation of the 2-, 3- and 4-bromoheptanes would be extremely difficult. Clarke considered the fraction boiling at 165–167° to be 2-bromoheptane.

For analytical purposes we have found that in most cases amine sulfates are more desirable derivatives than are the hydrochlorides. This appears to be particularly true of those amines having the amino group in the C-2 position. The sulfates are easily prepared and easily recrystallized and their only disadvantage is that their melting points are not sufficiently sharp to make them suitable for identification purposes.

While the results of the pharmacological tests are quite interesting, it is rather difficult at this time to draw generalities from them. The pharmacological data are summarized in Table III. It appears fairly certain that in the C_7 and C_8 series of amines the presence of the amino group at the C-2 position is essential for optimum activity. It is also of interest to note that branching is not in most cases detrimental but in some

TABLE II

SALTS OF 2-AMINOHEPTANE

Salt	M. p., °C.	Formula	N analyses, % Calculated	Found
Benzoate	95–97	$C_7H_{17}N \cdot C_7H_6O_2$	5.91	6.0
Carbonate[a]	63–66	$(C_7H_{17}N)_2 \cdot H_2CO_3$	9.66	9.61
Chloroaurate[b]	82–84	$C_7H_{17}N \cdot HAuCl_4$	...	...
Chloroplatinate[c]	225 dec.	$(C_7H_{17}N)_2 \cdot H_2PtCl_6$	4.39	4.54
Gluconate	141–143	$C_7H_{17}N \cdot C_{16}H_{12}O_7$	4.51	4.70
Glycolate	40	$C_7H_{17}N \cdot C_3H_6O_3$	7.33	7.41
n-Hexylsulfonate	105–107	$C_7H_{17}N \cdot C_6H_{14}O_3S$	4.98	4.94
Hydrobromide[e]	65–67	$C_7H_{17}N \cdot HBr$	7.14	7.14
Hydrochloride[d]	81–83	$C_7H_{17}N \cdot HCl$	9.24	9.25
Malate	121–123	$(C_7H_{17}N)_2 \cdot C_4H_6O_5$	7.69	7.34
Maleate	81–83	$(C_7H_{17}N)_2 \cdot C_4H_4O_4$	8.1	8.21
Nicotinate	78–80	$C_7H_{17}N \cdot C_6H_5NO_2$	11.77	12.02
Oxalate[f]	226–228	$(C_7H_{17}N)_2 \cdot C_2H_2O_4$	8.75	8.58
Succinate	106–108	$(C_7H_{17}N)_2 \cdot C_4H_6O_4$	8.04	8.19
Sulfate[g]	230–240	$(C_7H_{17}N)_2 \cdot H_2SO_4$	8.54	8.52

[a] This compound dissociates and sublimes slowly at room temperature. Neutral equivalent; Calcd. for $(C_7H_{17}N)_2 \cdot H_2CO_3$, 145. Found, 143. Melting point was taken in a sealed capillary tube. [b] Clarke (ref. 5) reported a m. p. of 63–64° for the chloroaurate of his amine. A gold analysis on a sample of 2-aminoheptane chloroaurate prepared by the late J. T. Bryant of these Laboratories gave: calcd. for $C_7H_{17}N \cdot HAuCl_4$: Au, 43.3. Found: Au, 43.0. Dunker, *et al.*, ref. 6, reported a m. p. of 77–78.5° for 2-aminoheptane chloroaurate. [c] Clarke (ref. 5) reported that the chloroplatinate of his amine decomposed at 195°. Our sample of 2-aminoheptane chloroplatinate began to darken slightly at 215° and decomposed above 225°. Calcd. for $(C_7H_{17}N)_2 \cdot H_2PtCl_6$: Pt, 30.4. Found: Pt, 30.5. [d] Clarke (ref. 5) reported a m. p. of 133° for the hydrochloride of his amine. [e] Clarke (ref. 5) reported a m. p. of 163° for the hydrobromide of his amine. Miss Mildred Sartor, of these Laboratories, repeated the experiments of Clarke and obtained an aminoheptane substance whose acid addition salts had melting points similar to those reported by Clarke. However, the melting point of 163° reported by Clarke as constant for the aminoheptane hydrobromide could be raised to 183–185° by recrystallization. Since the melting point of 1-aminoheptane hydrobromide is 218–219°; of 3-aminoheptane 193–194°, and of 4-aminoheptane hydrobromide above 250°, Clarke's hydrobromide is probably a mixture of the high melting aminoheptane hydrobromides. [f] Clarke (ref. 5) reported a m. p. of 204–205° dec. for the oxalate of his amine. [g] This substance is now on the market under the name "Tuamine Sulfate" (2-aminoheptane sulfate Lilly). The following references relate to its clinical uses: Proetz, *Ann. Otol., Rhin. and Laryng.*, **51**, 112 (1942); Shea, *ibid.*, **51**, 1143 (1942); Wisehart, *ibid.*, **52**, 581 (1943); Shea, *Arch. Otolaryng.*, **36**, 724 (1942); Tremble, *Canad. Med. J.*, **49**, 496 (1943); Fabricant, "Nasal Medication," the Williams and Wilkins Co., Baltimore, Md., 1942, page 48.

(7) Schorlemmer, *Ann. Chim.*, **188**, 253 (1877).

(8) Venable, *Ber.*, **13**, 1650 (1880).

TABLE III

APPROXIMATE PRESSOR ACTIVITY OF ALIPHATIC AMINES (AS SULFATES) AS DETERMINED IN PITHED CATS

	Amine salt (1 mg.)	Epinephrine equivalent (mg.)[a]
Controls	Ephedrine	0.00676
	1-Phenyl-2-aminopropane	.0045
C_6 Series	1-Aminohexane	.003
	2-Aminohexane	.003
	2-Amino-4-methylpentane	.001
C_7 Series	1-Aminoheptane	.00087
	2-Aminoheptane	.0037
	3-Aminoheptane	.001
	4-Aminoheptane	None
	2-Amino-3-methylhexane	0.00125
	2-Amino-4-methylhexane	.005
	2-Amino-5-methylhexane	.002
	2-Amino-4,4-dimethylpentane	None
C_8 Series	1-Aminooctane	Negligible
	2-Aminooctane	0.0015
	3-Aminooctane	.00075
	2-Amino-3-methylheptane	.001
	2-Amino-4-methylheptane	.0037
	2-Amino-5-methylheptane	.002
	2-Amino-6-methylheptane	.0033
	3-Amino-4-methylheptane	None
	3-Amino-6-methylheptane	None
C_9 Series	2-Amino-5-ethylheptane	0.001
	2-Amino-3,6-dimethylheptane	.0015
	4-Amino-2,6-dimethylheptane (HCl)	None

[a] The amount of epinephrine indicated in this column is approximately equivalent in pressor response to 1 mg. of the amine. These values have been obtained on pithed cats.

cases actually increases the activity. In fact in the 8-carbon series it appears that some branching is a necessity for maximum activity. The complete lack of activity of 2-amino-4,4-dimethylpentane was unexpected, particularly in view of the high activity of 2-amino-4-methylhexane. The presence of a branch on the carbon atom adjacent to the one carrying the amino group appears to be detrimental to the activity.

In general it appears that those aliphatic amines having the amino group on the terminal carbon have a pressor action which is of short duration while the activity of those having the amino group at the C-2 position is of much longer duration. This is analogous to the behavior of pressor amines having an aromatic nucleus such as β-phenethylamine and 1-phenyl-2-aminopropane.

One may conclude that for maximum useful activity the aliphatic amines must have an amino group on the C-2 position and should have either 7 or 8 carbon atoms.

We wish to thank Dr. K. K. Chen and Mr. Edward E. Swanson for the use of their pharmacological data herein reported. Complete pharmacological data will be published later by these workers and their associates. We also wish to thank Dr. R. G. Jones for his valuable assistance in the preparation of some of the intermediates and amines.

The microanalyses were made by the late Mr. T. J. Bryant and Miss Shirley Crandall of this Laboratory.

Experimental

All melting points reported herein are uncorrected.

Methyl Alkyl Ketones.—These were prepared by reaction of an alkyl bromide with sodium acetoacetic ester and subjecting the resulting product to ketonic hydrolysis using the general procedures described in the literature.[9]

α,β-Unsaturated Methyl Alkyl Ketones.—These were prepared by condensing butanone-2 with the appropriate aldehyde using aqueous potassium hydroxide as a catalyst.[10] The crude hydroxyketones thus obtained were purified by distillation in a vacuum. The hydroxy ketones were then distilled with about 1% of their weight of iodine. The water was separated from the distillate and the product dried over magnesium sulfate and fractionated through a 12-plate column packed with glass helices.[11]

Preparation of Oximes.—These were prepared essentially by the method used by Fox, Dunn and Stoddard[12] for the preparation of cyclopentanone oxime. The crude oxime was taken up in ether and dried with anhydrous magnesium sulfate. The oximes were purified by distillation through a 12-inch Vigreux column *in vacuo*.

Preparation of 2-Aminoalkanes Derived from Saturated Methyl Alkyl Ketones.—The methods used for obtaining amines from the corresponding saturated ketones are illustrated by the following preparations of 2-aminoheptane:

Method A.—One half mole of heptanone-2 oxime was dissolved in 1200 cc. of absolute ethanol. The resulting solution was heated to boiling under reflux on a steam-bath and about 5 gram atoms of sodium was added in small pieces as rapidly as possible. When all of the sodium had reacted the mixture was cooled and made acidic with hydrochloric acid. The ethanol was removed *in vacuo* and the concentrated solution remaining was cooled and made strongly alkaline with sodium hydroxide. The liberated amine was taken up in ether and dried over anhydrous magnesium sulfate. The product was then fractionated through a suitable column packed with glass helices, the material distilling at 141–142.5° being collected. The yield was about 60%.

Method B.—A mixture of 57 g. (0.5 mole) of heptanone-2 oxime, 50 cc. of absolute ethanol, and 6 g. of Raney nickel catalyst was subjected to an initial hydrogen pressure of 1000 p. s. i. at 75–80° in a suitable bomb until hydrogen was no longer taken up. The catalyst was removed by filtration and the filtrate acidified with hydrochloric acid and evaporated to dryness. The residue was made alkaline with sodium hydroxide solution and the liberated amine was taken up in ether, dried over anhydrous magnesium sulfate, and fractionated through a suitable column. The yield was 75–80%.

Method C.—A solution of 60 g. of heptanone-2 in 60 cc. of absolute ethanol was cooled to −10° in a salt–ice-bath and saturated at this temperature with anhydrous ammonia. The resulting solution was transferred to a precooled bomb, mixed with 15 g. of Raney nickel catalyst, and subjected to a pressure of 1500 pounds p. s. i. at 75–80° until hydrogen was no longer taken up. The catalyst was removed by filtration and the excess ammonia removed by heating gently under a column. The product was then worked up as described under Method B. The yield was 75–80%.

Method D.—A mixture of 250 g. (4 moles) of ammonium formate and 144 g. (1.25 moles) of heptanone-2 was heated in a 1-liter flask equipped with a thermometer well and a condenser set for distillation. After heating for three hours the temperature reached 185°. The distilled ketone was separated from the water and returned to the reaction mixture and the heating at 185° continued. The reaction mixture was heated at 180–185° for a total of about six hours. The reaction mixture was shaken with 200 cc. of water. The water layer was extracted with 50 cc. of benzene and the resulting benzene extract combined with the main water-insoluble reaction product. The crude reaction product was refluxed for seventy minutes with 150 cc. of concentrated hydrochloric acid. The mixture was then cooled, diluted with water, and made alkaline with sodium hydroxide. The liberated amine was taken up in ether, dried with anhydrous magnesium sulfate, and fractionated through a 12-plate packed column. The yield of product distilling at 141–142.5° was 74 g., or 55%.

The yields appeared to be slightly lower when formamide was used in place of ammonium formate.[13]

Preparation of 2-Aminoalkanes Derived from α,β-Unsaturated Methyl Alkyl Ketones.—The oximes were reduced in ethanol solution with Raney nickel catalyst essentially as in Method B, described previously. The reduction was carried out at 80–85° at 1000–1500 pounds p. s. i. pressure. The amines were worked up as described under Method B above.

Acid Addition Salts of 2-Aminoalkanes.—The sulfates were prepared from the amine (slight excess) and 2 *N* sulfuric acid. Upon evaporation the resulting solution gave white micro-crystalline solids. These were recrystallized from suitable solvents, such as water–acetone or in some cases water–ethanol. The sulfates of 2-aminoalkanes form white, nicely crystalline solids which do not appear to have sharp melting points. At some temperature above 215° they gradually sinter and melt over a considerable temperature range.

Salts of 2-Aminoheptane: 2-Aminoheptane Oxalate.—An excess of 2-aminoheptane (10 g.) was added to a solution of 4 g. of anhydrous oxalic acid in 95% ethanol.

(9) Gilman, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Coll. Vol. I, 2nd ed., pp. 248 and 351.

(10) Powell, THIS JOURNAL, **46**, 2514 (1924); Powell, Murray and Baldwin, *ibid.*, **55**, 1153 (1933); Powell and Baldwin, *ibid.*, **58**, 1871 (1936).

(11) Whitmore and Lux, *ibid.*, **54**, 3448 (1932).

(12) Fox, Dunn and Stoddard, *J. Org. Chem.*, **6**, 411 (1941).

(13) Ingersoll, Brown, Kim, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936).

The ethanol and excess aniline were removed *in vacuo* and the crystalline residue recrystallized from absolute ethanol three times. The salt forms white plates which melt at 226–228° (see Table II). This general procedure was used in the preparation of the other organic acid addition salts of 2-aminoheptane.

2-Aminoheptane Hydrochloride.—Dry hydrogen chloride gas was passed into a solution of pure 2-aminoheptane in anhydrous ether. Since no crystalline material formed the ether was evaporated off, leaving a residue which slowly crystallized. The salt was recrystallized from ether–ethanol. The 2-aminoheptane hydrochloride formed small, compact, white crystals which were somewhat hygroscopic. The product melted at 81–83°. The same product was obtained by mixing an excess of 2-aminoheptane with aqueous hydrochloric acid and evaporating the resulting solution. The crude crystalline residue melted at 78–81°; after recrystallizing from ether–ethanol the melting point was 81–83°.

These samples showed no change in melting point on repeated remelting or on standing for a period of over three years (see Table II).

2-Aminoheptane Hydrobromide.—An excess of 2-aminoheptane was added to a solution of 48% hydrobromic acid and ethanol. The solvents were evaporated *in vacuo* when the hydrobromide crystallized on cooling. The salt crystallized as small white plates from petroleum ether. The product melted at 65–67°.

The 2-aminoheptane hydrobromide showed no change in melting point on repeated remelting. A sample was heated at 100° in the molten state for two hours; on cooling it remelted at 65–67°. A sample which has been kept for a period of more than three years has remained unchanged in melting point (see Table II).

2-Aminoheptane Chloroplatinate.—An aqueous solution of chloroplatinic acid was added to an aqueous solution of 2-aminoheptane hydrochloride. The chloroplatinate separated almost at once as yellow-orange plates. It was recrystallized three times from aqueous ethanol. The product began to darken at 215° and showed extensive decomposition at 225–235° (see Table II).

2-Aminoheptane Chloroaurate.—An aqueous solution of chloroauric acid was added to an aqueous solution of 2-aminoheptane hydrochloride. The mixture was cooled and the product recrystallized three times from water. After drying over phosphorus pentoxide it melted at 82–84°. It formed small yellow-orange plates. The melting point was unchanged on remelting (see Table II).

Summary

Some new aminoalkanes have been prepared for use as pressor substances.

Conditions for optimum pressor activity in aliphatic amines require that the amine group be in the C-2 position and that the compound have 7 or 8 carbon atoms.

The chemistry of 2-aminoheptane and its acid addition salts is discussed.

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The Structure of Isozingiberene

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Direct evidence was obtained[3] recently that the structure of the sesquiterpene cadinene is represented as I, in which the unsaturated linkages are in the 1,2 and the 6,7 positions. In the previous formula[4] for cadinene, due to Ruzicka and Stoll,[5] one double bond was fixed at 3,4 and the other was placed at either the 5,6 (α-cadinene) or the 6,7 (β-cadinene) position. The work which we wish to report indicates that the "β-cadinene" formula (II) of these investigators is actually that of another sesquiterpene, isozingiberene, and that their formula (IV) for cadinene dihydrochloride (III) represents the structure of isozingiberene dihydrochloride.

Isozingiberene (II) is the parent hydrocarbon of the dihydrobromide or dihydrochloride (IV)[6] obtained from the sesquiterpene alcohol zingiberol,[7] or, more commonly, from the monocyclic sesquiterpene zingiberene (V). The usual source for both of these natural products is ginger oil. The crystalline dihydrochloride yields only isozingiberene on treatment with alcoholic potassium hydroxide. A dicyclic hydrocarbon with similar properties is obtained by direct cyclization of zingiberene with acidic reagents.[8] Although this substance is readily converted to isozingiberene dihydrochloride, there is no proof that its double bonds are in exactly the same positions as those found in the hydrocarbon which is regenerated from the same derivative.

The presence of a dicyclic ring system and two unsaturated linkages was confirmed by Semmler and Becker,[8] who obtained a tetrahydro derivative on catalytic hydrogenation. Zingiberene under the same conditions absorbed three molecules of hydrogen. The skeletal structure of the molecule has been established[9] by dehydrogenation to 4-isopropyl-1,6-dimethylnaphthalene (cadalene) (VI), identified by synthesis.[10]

No experimental evidence has been reported for the location of the double bonds in isozingiberene. The formula proposed by Semmler and Becker,[8] interpreted to fit the cadalene skeleton is shown as VII. More recently, Simonsen[11] has suggested

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(3) Campbell and Soffer, THIS JOURNAL, **64**, 417 (1942).

(4) Due to a typographical error this formula appeared[3] with the 6-methyl group in the 7 position.

(5) Ruzicka and Stoll, *Helv. Chim. Acta*, **7**, 84 (1924).

(6) Formula IV is the Ruzicka and Stoll[5] formula for cadinene dihydrochloride.

(7) Brooks, THIS JOURNAL, **38**, 431 (1916).

(8) Semmler and Becker, *Ber.*, **46**, 1814 (1913).

(9) Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, **5**, 345 (1922).

(10) Ruzicka and Seidel, *ibid.*, 369.

(11) "The Terpenes," Cambridge University Press, London, 1932, Vol. II, p. 498; Stewart and Graham, "Recent Advances in Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1936, Vol. II, pp. 113–115; Egloff, "Reactions of Pure Hydrocarbons," Reinhold Publishing Corporation, New York, N. Y., 1937, p. 825.