[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

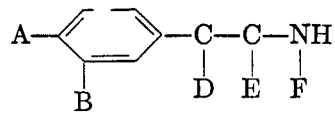
ALIPHATIC ANALOGS OF THE SYMPATHOMIMETIC AMINES[1]

GEORGE M. STEINBERG,[2] HENRY B. HASS, AND EARL T. McBEE

Received January 28, 1948

Many compounds are known that have the property of stimulating the central nervous system. Among the most important are picrotoxin, metrazole, strychnine, coramine, camphor, the xanthines and several of the sympathomimetic amines. Of these compounds, the latter group include those that are most successful in the production of the important physiological effect of temporary insomnia.

The sympathomimetic or pressor amines comprise the group of compounds related to epinephrine. In general, they include those compounds having the basic structure,



where A, B, and D may be —H, —OH, or —OMe and E and F may be —H, or alkyl.

Their major importance is derived from the fact that they produce effects in the organism similar to those resulting from the stimulation of the adrenergic nerves. In addition, several produce profound effects on the central nervous system. Whereas it has been shown that a great deal of correlation exists between chemical structure and many of the physiological activities of this series of compounds, comparatively little correlation could be found with respect to the stimulation of the central nervous system.

In an investigation of the effect of seventy-three sympathomimetic amines as stimulants, Schulte and co-workers (1) found that although thirty-three gave positive results, only benzedrine, epinephrine, and ephedrine could be considered powerful stimulants, their potency decreasing in that order.

Numerous studies of these compounds and their alicylic analogs have resulted in the generalizations that optimum analeptic activity may be associated with the 2-propylamino side chain, and that the benzene ring is not a requirement for activity (2, 3, 4, 5, 6).

At the present time benzedrine is being administered to humans. However, because of its toxicity, its powerful and prolonged action and its considerable effect upon the blood pressure, it is not suitable for use as a general analeptic.

In 1942, there was first reported the discovery of an aliphatic amine having considerable pressor activity (7). This compound, 2-heptylamine may be considered as an aliphatic analog of the sympathomimetic amines; the benzene

[1] From the doctoral dissertation of G. M. Steinberg, 1944.

[2] Present address: Engineering Laboratory, Glenn L. Martin Co., Baltimore, Maryland.

nucleus being substituted by a chain of four carbon atoms, and containing a 2-propylamino "side chain."

It was considered desirable to make a study of the effect of substitution on this molecule on its analeptic and pressor activities.

In 1944, after this work was completed, Rohrmann and Shonle (8) reported on the pressor activity of a number of aliphatic amines. They found that maximum activity could be associated with a seven or eight atom carbon chain with the amino group in the C-2 position.

In the present study, the amino alcohols were prepared by two methods: (a) the reduction of the corresponding nitro alcohol with iron and hydrochloric acid, and (b) the high pressure catalytic hydrogenation over Raney nickel of the oxime and methylimine of the corresponding keto alcohol. Procedure (a) proved to be satisfactory in that it gave the desired product in reasonable yield. Procedure (b) gave a relatively large yield of what seemed, at first, to be the desired product. The compound was a colorless, amine-odored liquid that distilled at a temperature that was close to what was expected. However, the neutral equivalent was abnormally high. Rectification on a spiral column having fifteen theoretical plates gave no improvement. Hence, the impurity must either have nearly the same boiling point as the amino alcohol or else distill with it as a binary azeotrope. The corresponding diol could fit well into either category and its presence could be explained by hydrolysis of the oxime during hydrogenation followed by reduction of the resultant keto alcohol. This hypothesis was given added weight by the fact that if a small quantity of added keto alcohol was hydrogenated with the oxime, the rectified amino alcohol gave an even higher neutral equivalent. Attempts at purification involving the preparation of the hydrochloride, hydrobromide, sulfate, picrate and carbamate failed. The hydrobromide alone precipitated from dry ether, and then only as an oily solid between $-70°$ and $-50°$. An attempt at disproportionation between an acidified aqueous solution and diethyl ether likewise proved unsuccessful. Steam distillation failed due to severe foaming. The problem was solved by the passage of hexane vapors through an acidified aqueous solution of the amine. Notwithstanding the fact that the process was run at 30–40°, by the employment of reduced pressure, a considerable amount of decomposition took place. By this procedure, it was found possible to purify 4-hydroxy-2-heptylamine and its N-monomethylated homolog. However, the presence of a side chain on the No. 3 carbon atom made the compound too unstable to withstand this treatment. Hence, 3-methyl- and 3-ethyl-4-hydroxy-2-heptylamine and their N-monomethylated homologs resisted all of the above enumerated attempts at purification. It was found that the presence of both a methyl and an hydroxyl group on the carbon atom adjacent to the oxime group prevented its hydrogenation under the conditions employed in this work. Thus neither 3-hydroxy-3-methyl-2-heptanone oxime nor 3,4-dihydroxy-3-methyl-2-heptanone oxime could be converted to the corresponding amines.

The saturated alkyl amines were prepared by the reduction of the corresponding saturated and unsaturated ketoximes and ketimines, and by the catalytic hydrogenation of mixtures of the corresponding keto alcohols and methylamine.

The unsaturated alkyl amines were prepared from the amino alcohol by treatment with concentrated hydrochloric acid. This reaction produced as its main products high-boiling neutral substances. The yield of desired compound was very low.

An interesting case of steric hindrance was noted when several attempts to react 2,2-dimethylhexanenitrile with methylmagnesium bromide were unsuccessful.

A preliminary pharmacological study[3] of the pressor activity of N-methyl-4-ethyl-2-heptylamine, 4-ethyl-2-heptylamine, N-methyl-3-ethyl-2-heptylamine, N-methyl-4,4,5,5-tetramethyl-2-heptylamine, and 4,4,5,5-tetramethyl-2-heptylamine, indicated no appreciable activity. No effect on the blood pressure of cats was observed when the test samples were administered intravenously at dose levels of 0.5 and 1.0 mg. per kg. of body weight. Epinephrine in the same doses produced increases in blood pressure of 40–60 mm. which persisted for 10–20 minutes.

EXPERIMENTAL

Preparation of keto alcohols. The method used for the preparation of most of the necessary keto alcohols is a modification of previously used procedures (9, 10). It is illustrated by the preparation of 3-ethyl-4-hydroxy-2-heptanone. In the case of 3,4-dihydroxy-3-methyl-2-heptanone, a modified oxidation procedure was employed (11, 12, 13).

A. 3-Ethyl-4-hydroxy-2-heptanone. Butanal, 150 g., 2.08 moles, was slowly added to a well-stirred mixture of 300 g., 3.48 moles, of 2-pentanone, 80 ml. of ether, and 150 ml. of 15% aqueous sodium hydroxide, cooled to 15°. The mixture was stirred overnight, the organic layer separated and the aqueous layer extracted with ether. The combined ether and organic layers were neutralized with glacial acetic acid, washed with a dilute solution of sodium bicarbonate, dried over magnesium sulfate, and rectified under reduced pressure. The yield was 120 g. of 3-ethyl-4-hydroxy-2-heptanone; conversion 52%; physical constants: b.p. 99–102° (9 mm.), d_4^{25} 0.929, n_D^{25} 1.4413.

Anal.[4] Calc'd for $C_9H_{18}O_2$: C, 68.32; H, 11.45.
Found: C, 67.83, 67.97; H, 11.22, 11.40.

A positive iodoform test, the point of ebullition, and the percentages by weight of carbon and hydrogen combined to eliminate the other two possible products of the reaction: 6-hydroxy-4-nonanone, b.p. estimated by analogy, *ca.* 120° (10 mm.); 2-ethyl-3-hydroxyhexanal, b.p. 85–87° (6 mm.) (9).

B. 3,4-Dihydroxy-3-methyl-2-heptanone. 3-Methyl-3-hepten-2-one, 52 g., 0.41 mole, and 300 ml. of water were placed in a five-liter, three-necked flask fitted with an efficient motor stirrer. Four liters of a 2% aqueous solution of potassium permanganate was added dropwise, keeping the temperature below 15°. The mixture was filtered and the manganese dioxide washed with ether. The aqueous solution was continuously extracted with ether for 12 hours. The combined extracts from 3 runs were dried over magnesium sulfate and distilled under reduced pressure. The product was a syrupy, yellow liquid of which 33 g. boiled between 116 and 120° (8–10 mm.); yield 17%; physical constants: b.p. 167–168° (758 mm.), n_D^{25} 1.4492.

Anal. Calc'd for $C_8H_{16}O_3$: C, 60.0; H, 10.0.
Found: C, 59.1, 59.5; H, 9.95, 9.70.

---

[3] Conducted at the Abbott Laboratories.

[4] The analyst reported that the compound volatilizes easily in the stream of oxygen but that it is hard to burn completely.

TABLE I

PROPERTIES OF AMINES AND PRECURSORS

AMINE	B.P./MM.[a]	M.P. of HCl[f]	d_4^T	n_D^T	% CONVERSION TO AMINE FROM PARENT CP'D	PARENT CP'D (B.P./MM.[a])	ANAL. OF AMINES	
							Cal'd	Found
3-Hydroxy-2-heptylamine	90–92/12 201.5/753	[f]	0.898^{24}	1.4509^{25}	22	2-Nitro-3-heptanol (105/7)	C 64.1 H 12.99	62.9, 63.4 12.91, 12.80
N-Methyl-3-hydroxy-2-heptylamine	67–68/4 85–87.5/8 199.5/747	[f]		1.4449^{24}	62	3-Hydroxy-2-heptylamine[a]	N.E.[b] 145.2	145.6, 146.8
4-Hydroxy-2-heptylamine	70/6 205/749	[f]	0.887^{25}	1.4440^{25}	*ca.* 1	4-Hydroxy-2-heptanone oxime (134/7)	N.E.[b] 131.2	132
N-Methyl-4-hydroxy-2-heptylamine	80/6 206/736	[f]		1.4431^{25}	*ca.* 1	4-Hydroxy-2-heptanone	N.E.[b] 145.2	144
4-Ethyl-2-heptylamine	71.5–71.9/19 174/744	83–84[g]	0.780^{25}	1.4288^{25}	58	4-Ethyl-2-heptanone oxime (98–98.5/4)	N[c] 7.75 Cl 19.64	7.70, 7.75 19.77, 19.71
N-Methyl-4-ethyl-2-heptylamine	67–67.5/9 186/755	100–101[h]	0.785^{25}	1.4321^{25}	14	4-Ethyl-2-heptanone	N[c] 7.22 Cl 18.30	7.15, 7.27 18.33, 18.30
4,4,5,5-Tetramethyl-2-heptylamine	89–92/11 216/755	248–249[h]	0.831^{25}	1.4554^{25}	20	4,4,5,5-Tetramethyl-2-heptanone oxime (108–110/2–3)	N[c] 6.74 Cl 17.06	6.81, 6.75 17.10, 17.00
N,4,4,5,5-Pentamethyl-2-heptylamine	94–96/11 225/755	162–163[h]	0.825^{27}	1.4509^{26}	10	4,4,5,5-Tetramethyl-2-heptanone	N[c] 6.31 Cl 15.98	6.33, 6.25 15.99, 15.89

2-Amino-3-ethyl-3-heptene		130–132[j]			*ca.* 1	3-Ethyl-4-hydroxy-2-heptanone oxime (124–126/2)	C[c] 60.83 H 11.34	60.91, 60.79 11.19, 11.08
3-Ethyl-2-heptylamine	55–56/11 169/755		0.755[25]	1.4160[25]	7.2	3-Ethyl-3-hepten-2-one oxime (96–104/6)	N 9.77	10.00, 10.18
N-Methyl-3-ethyl-2-heptylamine	68–69/18 178/760	189–190[j]	0.783[25]	1.423[25]	5	3-Ethyl-4-hydroxy-2-heptanone (99–102/9)	N[c] 7.23	7.24, 7.32
N,3-Dimethyl-2-heptylamine[d]	63/9 169.5/744	120[k]	0.783[25]	1.4255[25]	9	4-Hydroxy-3-methyl-2-heptanone	N[c] 7.75 Cl 19.64	7.67, 7.69 19.63, 19.71

[a] By direct methylation with methyl iodide.
[b] Neutral equivalent.
[c] Based on hydrochloride.
[d] Hydrochloride sublimed slowly near 90° at an approximate pressure of 10^{-4} mm.
[e] Because of possible errors due to superheating and pressure differential between flask and manometer, values given at pressures below 5 mm. are admittedly inexact. Physical characteristics of new compounds only are listed.
[f] Could not prepare hydrochloride.
[g] Recrystallized from petroleum ether (60–69° fraction.)
[h] Recrystallized from ethyl ether methylene chloride mixture.
[i] Recrystallized from petroleum ether (60–69° fraction) methylene chloride mixture.
[k] Recrystallized from carbon disulfide methylene chloride mixture.
[l] Corrected for emergent stem. All hydrochlorides are white crystalline solids.

Preparation of α,β-unsaturated methyl alkyl ketones. The method is illustrated by the preparation of 3-ethyl-3-hepten-2-one. A single small crystal of iodine was added to 12.5 g., 0.079 mole, of 3-ethyl-4-hydroxy-2-heptanone and the liquid distilled slowly. The distillate separated into two layers. The aqueous layer was extracted with ether, the mixed oil and ether layer dried over magnesium sulfate and distilled. Nine g. of 3-ethyl-3-hepten-2-one was obtained; conversion 81%; physical constants: b.p. 59° (8 mm.), 176° (743 mm.); d_4^{23} 0.855; n_D^{23} 1.4481. M.p. of orange 2,4-dinitrophenylhydrazone 122–123°.

Anal.[5] Calc'd for $C_9H_{16}O$: C, 77.1; H, 11.5.

Found: C, 73.77, 73.81; 74.74, 74.87; 74.47, 74.54; H, 11.02, 11.04; 11.20, 11.24; 10.97, 10.72.

Preparation of saturated ketones. A. 4-Ethyl-2-heptanone. 4-Ethyl-2-heptanone was prepared in 32% yield by the reaction of ethylmagnesium bromide with 3-hepten-2-one following a standard procedure (14).

B. 4,4,5,5-Tetramethyl-2-heptanone. 4,4,5,5-Tetramethyl-2-heptanone was prepared by the reaction of tertiary butylmagnesium chloride (15) with mesityl oxide following a standard procedure (16).

Preparation of oximes. The low temperature and careful adjustment of acidity were deemed necessary in the preparation of the oximes of the easily decomposed keto alcohols; they are not necessary in the other cases. The method is illustrated by the preparation of 3-ethyl-4-hydroxy-2-heptanone oxime.

Potassium carbonate, 66.4 g., 0.48 mole, dissolved in 150 ml. of water, was added to a cool (15°), well-stirred mixture of 125 g., 0.79 mole, of 3-ethyl-4-hydroxy-2-heptanone, and a solution of 68.6 g., 0.99 mole, of hydroxylamine hydrochloride in 150 ml. of water. The stirring was continued for 12 hours, during which the temperature of the reaction mixture was maintained at 20°. The very viscous organic layer was separated from the aqueous layer after dilution with 100 ml. of ether. The aqueous layer was extracted with ether and the combined ether and organic layers were dried over magnesium sulfate and distilled under reduced pressure. The product was 95 g. of 3-ethyl-4-hydroxy-2-heptanone oxime, b.p. 124–126° (2 mm.); conversion 70%.

Preparation of nitro alcohol. 2-Nitro-3-heptanol was prepared by the condensation of pentanal[6] and nitroethane, with 50% conversion, by a standard method (17). The purified 2-nitro-3-heptanol had the following physical constants: b.p. 105° (7 mm.), n_D^{24} 1.4473.

Anal. Calc'd for $C_7H_{15}NO_3$: C, 52.2; H, 9.31.

Found: C, 52.1, 52.0; H, 9.31, 9.35.

Preparation of amines. A. From oximes of keto alcohols. Seventy grams of the oxime, dissolved in 100 ml. of absolute alcohol, was mixed with 7 g. of Raney nickel (18) and hydrogenated for 20 hours at room temperature under an initial pressure of 1500 lbs./sq. in. The reaction product was dried, filtered, stripped of alcohol and low-boiling amines (from decomposition of keto alcohol oxime), and rectified. Two fractions were taken, the first containing the corresponding saturated amine and the second containing the amino alcohol.

The saturated amine fraction was rehydrogenated to ensure against the presence of a small quantity of unsaturated amine (due to decomposition of amino alcohol during rectification). The amino alcohol fraction, believed to contain the corresponding diol as an impurity, was either warmed with an equivalent quantity of concentrated hydrochloric acid to yield the unsaturated amine hydrochloride, or neutralized with dilute hydrochloric acid and distilled with 1500 ml. of hexane under reduced pressure, to yield a diol-free acid solution of the amino alcohol. In either case, the free base was liberated, dried over potassium hydroxide and rectified.

---

[5] The analysis was repeated three times on the same sample. Previous workers have reported similar difficulties with 3-hepten-2-one (9) and 3-methyl-3-hepten-2-one (10).

[6] Conveniently prepared in 41% yield by dichromate oxidation of the alcohol with continuous distillation of the ternary constant boiling mixture. (ROBERTSON, "Laboratory Practice in Organic Chemistry," The McMillan Company, New York, 1937, p. 180.)

B. From methylimines of keto alcohols. A mixture of 50 g. of ketone and 30 g. of methylamine (prepared by bubbling the dry amine into the cold ketone) was mixed with 100 ml. of glacial acetic acid and hydrogenated overnight at room temperature over 7 g. of Raney nickel (18) (or 10 g. of U.O.P. nickel catalyst at 100°) at an initial pressure of 1500 lbs./sq. in. The reaction product was worked up as described under procedure A.

C. From oximes of alkyl ketones. The oximes were reduced to the amines using sodium and alcohol following a standard procedure (19).

D. From methylimines of alkyl ketones. A mixture of 0.17 mole of ketone and 20 ml. of 10 *N* aqueous methylamine solution was shaken for one-half hour. The imine was salted out with 10 g. of sodium hydroxide and dried over potassium hydroxide. It was reduced with sodium and alcohol following a standard procedure (19).

E. From nitro alcohol. A well-stirred mixture of 75 g., 0.27 mole, of ferrous sulfate heptahydrate, 45 g., 0.8 g. atom, of iron powder (100 mesh), 1.85 ml. of water, and 30 ml. of 2.3 *N* hydrochloric acid was heated with a burner until the temperature reached 100°. The burner was removed and 25 g., 0.155 mole, of 2-nitro-3-heptanol was added at such a rate as to maintain the temperature at 100°. An additional 30 g., 0.54 g. atom, of iron powder and 30 ml. of 2.3 *N* hydrochloric acid were added and the temperature returned to 100°. Another 20 g., 0.124 mole, portion of nitro alcohol was added and the solution maintained at 98° for one hour. The cooled reaction mixture was filtered to remove iron powder and 8 g. of sodium hydroxide was added to the filtrate. The precipitated iron oxides were filtered off and 40 g. of sodium hydroxide was added to the filtrate to salt out the amino alcohol. It was found more expedient to extract the amino alcohol with ether in a continuous extractor than to separate the base directly. The ether extract was dried over calcium oxide and rectified. Additional data may be found in Table I.

2,2-Dimethylhexanenitrile. 2,2-Dimethylhexanenitrile was prepared in 38% yield from 2-methylpropanenitrile[7] and 1-bromobutane by the method of Ziegler and Ohlinger (20). The purified nitrile had the following physical constants: b.p. 57–58° (10 mm.), 171° (753 mm.), d_4^{24} 0.799, n_D^{24} 1.4091.

Anal. Calc'd for $C_8H_{15}N$: C, 76.7; H, 12.00.
Found: C, 76.0, 76.1; H, 11.65, 11.70.

ACKNOWLEDGMENT

Grateful thanks are due to the Abbott Laboratories and to the Purdue Research Foundation. Without their financial assistance, this investigation could not have been undertaken.

SUMMARY

1. A series of aliphatic compounds related to 2-heptylamine have been prepared.

2. Preliminary pharmacological studies on several of these compounds indicate no appreciable pressor activity.

LAFAYETTE, IND.

REFERENCES

(1) SCHULTE *et al.*, *J. Pharmacol.*, **71**, 62 (1941).
(2) ELPHRICK AND GUNN, *J. Physiol.*, **81**, 422 (1934).
(3) GUNN, GURD, AND SACKS, J. *Physiol.*, **95**, 485 (1939).
(4) GUNN AND GURD, *J. Physiol.*, **97**, 453 (1940).

[7] Conveniently prepared in 51% yield from lead thiocyanate and zinc isobutyrate [VAN EBBS AND REID, *J. Am. Chem. Soc.*, **38**, 2120 (1916)].

(5) GUNN AND GURD, *J. Physiol.*, **98**, 424 (1940).
(6) TAINTER, *J. Pharmacol.*, **67**, 56 (1939).
(7) PROETZ, *Ann. Otol. Rhinol. Laryngol.*, **51**, 112 (1942).
(8) ROHRMANN AND SHONLE, *J. Am. Chem. Soc.*, **66**, 1516 (1944).
(9) GRIGNARD AND DUBIEN, *Ann. chim.*, [10], **2**, 288 (1924).
(10) POWELL, *J. Am. Chem. Soc.*, **46**, 2514 (1924).
(11) HARRIES, *Ber.*, **34**, 2979 (1901); **35**, 1181 (1902).
(12) HIBBERT AND BURT, *J. Am. Chem. Soc.*, **50**, 1414 (1928).
(13) RAVIER, *Compt. rend.*, **198**, 1786 (1934).
(14) COLONGE, *Bull. soc. chim.*, [5], **3**, 413 (1936).
(15) WHITMORE AND BADERTSCHER, *J. Am. Chem. Soc.*, **55**, 1561 (1933).
(16) WHITMORE *et al. J. Am. Chem. Soc.*, **63**, 643 (1941).
(17) VANDERBILT AND HASS, *Ind. Eng. Chem.*, **32**, 34 (1940).
(18) DRAKE, *Org. Syntheses*, **21**, 15 (1941).
(19) BLATT, *Org. Syntheses*, Coll. Vol. II, 318 (1943).
(20) ZIEGLER AND OHLINGER, *Ann.*, **495**, 107 (1932).