[CONTRIBUTION FROM THE RESEARCH LABORATORY OF E. BILHUBER, INC. AND THE NEWARK COLLEGE OF ENGINEERING][1]

ALIPHATIC AMINES OF PHARMACOLOGIC INTEREST. I. 2-AMINO ALKANOLS AND THEIR DERIVATIVES[2]

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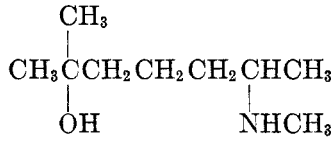
In 1947 Jackson (1) studied the pharmacologic action of the sympathomimetic amine EA-83, 2-methylamino-6-methyl-6-heptanol (Aranthol) (I), and found it to be a strong cardiac and circulatory stimulant of very low toxicity. These



I

fundamental observations on the physiological properties of EA-83 have subsequently been verified and extended by Walton and others (2, 3, 4). Although there have been numerous reports on the pharmacology of aliphatic amines since the original publication of Barger and Dale (5), there is little data in the literature on either the chemistry or the pharmacology of aliphatic amino alcohols closely related to EA-83. In a recent paper, Loubatieres (6) has reported on the pharmacology of a few derivatives of EA-83 and has found that (a) the hydroxyl group may be replaced by chlorine without appreciable loss of activity but with an increase in toxicity and (b) increasing the size of the substituent attached to nitrogen beyond the ethyl group causes a rapid diminution of cardiotonic properties. In view of the limited amount of information available, it seemed desirable to prepare a series of compounds representing a fair cross-section of the possible, simple variations in the structure of EA-83 for pharmacologic investigation.[3]

The work reported here (see Table I) was limited to aliphatic amines possessing chain lengths of six to ten carbon atoms, with an amino group or its lower aliphatic derivative in the 2-position and with methyl groups and hydroxyl or methoxyl groups attached at various points along the chain. Work on other variations is in progress and will be reported at a later date. During the course

[1] Work performed in the laboratories of E. Bilhuber, Inc.

[2] A portion of the material included here was abstracted from a thesis by Charles R. Whitehead, presented to the Graduate Faculty of Newark College of Engineering in partial fulfillment of the requirements of the M. S. degree, June, 1950.

[3] Subsequent to the completion of our work and preparation of our manuscript, Loubatieres, *Arch. Internat. Pharmacodynamie*, **85**, 333 (1951) again reported on the pharmacology of a group of 21 amino alcohols. One of the compounds whose synthesis is described here, 2-methylamino-5-methyl-5-hexanol (EA-139), is included in his study.

TABLE I

AMINES AND AMINO ALCOHOLS

NO.	NAME OF COMPOUND	METHOD	YIELD, %	B.P., °C./MM.	n_D^{25}	ANALYSES		
						N[c]		Base,[a] %
						Found	Calc.	
EA-133	2-Amino-3-hexanol[b]	A	40.5	86–88/14	1.4468	8.05 8.12	8.43	—
130	2-Amino-2-methyl-3-pentanol	A	16	73–76/15	1.4480	11.76 11.84	11.95	98.62
135	2-Amino-4-methyl-3-pentanol[b]	A	42	78–84/18	Solid	8.37	8.43	—
141	2-Amino-3-methyl-3-heptanol	B	16	101–104/15	1.4530	8.99	9.64	97.22 97.30
134	2-Amino-4-heptanol	B	26	87–88/9	1.4459	10.38 10.32	10.68	99.88 99.65
132	2-Amino-3-methyl-4-hexanol	B	38	95–99/16	1.4517	10.46 10.39	10.68	99.64
131	2-Amino-3-methyl-4-heptanol	B	29	107–109/15	1.4515	9.72 9.50	9.65	97.25
136	2-Amino-5-methyl-4-hexanol	B	34	96–99/19	1.4478	10.50 10.55	10.68	99.97
145	2-Amino-2-methyl-5-hexanol	E	46	103–104/15	1.4518	10.41 10.35	10.68	99.29 99.05
139	2-Methylamino-5-methyl-5-hexanol	D	64	105–108/25.5	1.4489	9.47 9.43	9.64	98.55 98.36
143	2-Amino-2-methyl-6-heptanol	E	47	119–122/22	1.4538	9.34 9.31	9.64	99.03 98.89
148	2-Amino-2,4-dimethyl-6-heptanol	E	30	80–84/1.5	1.4527	8.63 8.60	8.80	97.78 97.65
157	2-Amino-2,5-dimethyl-6-heptanol	E	46	85–88/1	1.4580	8.61 8.48	8.80	97.35 96.98
154	2-Methylamino-3,6-dimethyl-6-heptanol	D	16	82/2	1.4555	7.89 7.89	8.08	99.95 99.92
147	2-Methylamino-4,6-dimethyl-6-heptanol	D	47	112/13.5	1.4495	8.04 8.10	8.08	100.56 100.18
151	2-Methylamino-7-heptanol	C	71	104–106/3	1.4570	9.34 9.41	9.64	99.10 99.29
156	2-Methylamino-3-methyl-7-heptanol	C	51	102–104/2.5	1.4609	8.82 8.87	8.80	101.38 101.50
158	2-Methylamino-4,7-dimethyl-7-octanol	C, D	17	100–103/3	1.4538	7.05 6.99	7.48	96.83
159	2-Methylamino-8-octanol	C	83	125–126/8	1.4579	8.43 8.43	8.80	99.28 99.11
140	2-Amino-2,6-dimethyl-8-octanol	E	44	145–148/15	1.4609	8.01 7.95	8.08	100.29 100.18
144	2-Amino-4-methoxy-4-methylpentane	B	37	56–62/29	1.4253	10.30 10.14	10.68	99.86 99.63
160	2-Methylamino-5-methoxy-5-methylhexane	C	41	57–58/4	1.4321	8.74 8.77	8.80	101.09 100.98
150	2-Amino-2-methyl-6-methoxyheptane	E	50	113–114.5/66	1.4290	8.83 8.74	8.80	100.01 99.63

TABLE I—*Continued*

NO.	NAME OF COMPOUND	METHOD	YIELD, %	B.P., °C./MM.	n_D^{25}	ANALYSES		
						N[c]		Base,[a] %
						Found	Calc.	
149	2-Methylamino-6-methoxy-6-methylheptane	C	63	96–97/17.5	1.4356	7.96 7.83	8.08	100.89 100.50
155	2-Dimethylamino-6-methoxy-6-methylheptane	C	42	90–91/10	1.4345	7.34 7.40	7.48	99.29 99.11
152	2-Isopropylamino-6-methoxy-6-methylheptane	C	38	73–75/27	1.4301	6.88 6.92	6.96	99.62 100.13
137	2-Methylamino-5-hexene	C	37	129–130/750	1.4229	11.97 12.02	12.38	98.99 98.98
138	2-Methylamino-5-methyl-5-hexene	C	31	149–150/750	1.4350	10.77 10.79	11.01	99.90 99.79
153	2-Methylamino-3,6-dimethyl-5-heptene	C	45	70.5–74.5/10	1.4480	8.75 8.66	9.02	99.24 99.65
146	2-Methylamino-4,6-dimethyl-5-heptene	C	37	85/35	1.4405	8.88 8.98	9.02	99.85 99.41

[a] Determined by back titration of a weighed sample of amine in 50 ml. of 0.1 *N* H_2SO_4 with 0.1 *N* NaOH using Methyl Red as the indicator. Calculation by the following expression:

$$\frac{\text{Ml. 0.1 } N\ H_2SO_4 - \text{ml. 0.1 } N\ \text{NaOH} \times \dfrac{\text{Gram-Equiv. Wt. of Amine}}{10{,}000}}{\text{Wt. of Sample}} \times 100 = \%\ \text{base.}$$

[b] Analyzed as sulfate. [c] Kjeldahl determination.

of the syntheses employed several unsaturated aliphatic amines were isolated as intermediates. Since these are of interest as potential spasmolytic agents similar to 2-methylamino-6-methyl-5-heptene (Octin), they are also included in Table I.

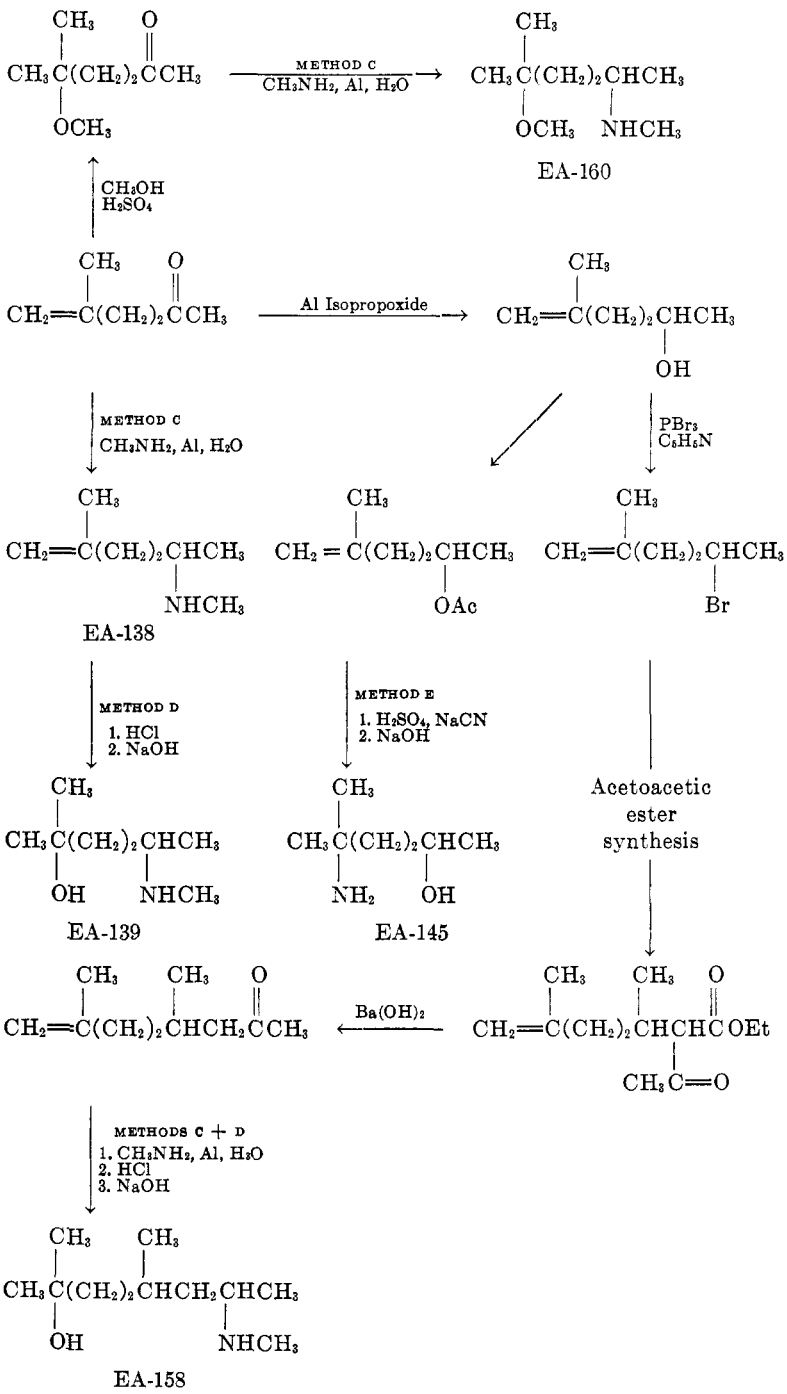
In general, five different methods of synthesis were utilized in the preparation of these derivatives:

Method A: Compounds EA-133, 130, and 135 were prepared by reduction of the corresponding known nitro alcohols using zinc and acetic acid according to the procedure of Zenitz and coworkers (7). One of these, EA-135, is a new compound, while EA-133 and 130 have previously been described by Hass and Vanderbilt (8) and Degering and Hoaglin (9) respectively.

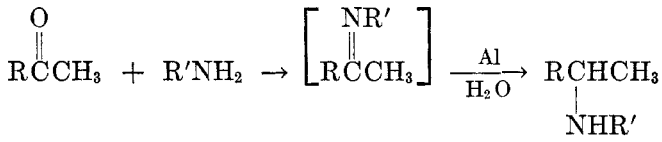
Method B: Sodium and methanol reduction was employed to reduce the oximes of keto alcohols to the corresponding, previously undescribed amines EA-141, 132, 131, and 136 as outlined in the experimental section. Steinberg, Hass, and McBee (10) have previously reported EA-134.

The remainder of the compounds reported in Table I were prepared from hydroxy ketones or unsaturated ketones which are either commercially available or are accessible *via* the acetoacetic ester synthesis. Typical examples of the syntheses employed are illustrated in Flow Sheet I.

FLOW SHEET I

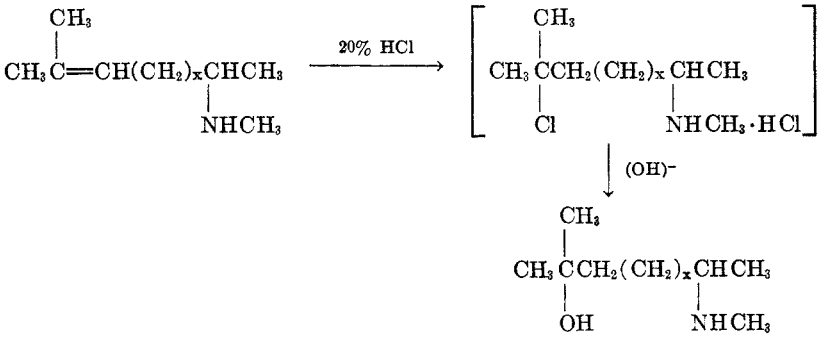

METHOD C
CH3NH2, Al, H2O
EA-160
CH3OH
H2SO4
Al Isopropoxide
METHOD C
CH3NH2, Al, H2O
PBr3
C5H5N
EA-138
METHOD D
1. HCl
2. NaOH
METHOD E
1. H2SO4, NaCN
2. NaOH
Acetoacetic ester synthesis
EA-139
EA-145
Ba(OH)2
METHODS C + D
1. CH3NH2, Al, H2O
2. HCl
3. NaOH
EA-158

Method C: Reductive amination with methylamine or isopropylamine in the presence of activated aluminum by the procedure of Klavehn (11) was found to

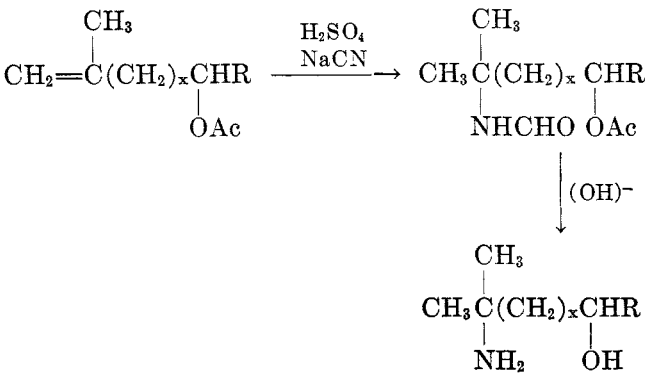


be a very satisfactory method for converting methoxy or hydroxy ketones or unsaturated ketones other than those having α,β-unsaturation into the corresponding methylamino or isopropylamino derivatives. In this manner EA-151, 156, 159, 160, 149, 152, 137, 138, 153, and 146 were obtained.

Method D: Unsaturated amines containing the grouping  were converted to the corresponding tertiary hydroxy compounds in good yield by adding hydrogen chloride across the unsaturation and hydrolyzing the resulting tertiary chloride with strong base as described by Givens and Herbst (12). By this procedure EA-139, 154, 147, and 158 were prepared.



Method E: Ritter and Kalish (13) have recently shown that tertiary alcohols or olefins react with hydrogen cyanide in the presence of sulfuric acid to yield N-*tert*-alkyl formamides which are readily hydrolyzed to the corresponding *tert*-carbinamines. By using unsaturated alcohols in which the hydroxyl group



is blocked by acetylation or etherification, this reaction was successfully employed in the synthesis of EA-145, 143, 148, 157, 140, and 150.

The results of the pharmacological studies with the 2-amino alkanols will be published elsewhere by Dr. D. F. Marsh of the University of West Virginia. Dr. L. D. Seager of the University of Arkansas will report separately on the 2-amino alkenes.

Acknowledgment: We wish to express our appreciation to Mr. C. W. Bell and Miss Olga Hawrylak for the analytical data reported here, to Dean James A. Bradley of Newark College of Engineering for his interest in the work, and to Dr. Rudolf O. Hauck of E. Bilhuber, Inc. for the benefit of many helpful discussions.

EXPERIMENTAL

METHOD A. ZINC AND ACETIC ACID REDUCTION OF NITRO ALCOHOLS

2-Amino-4-methyl-3-pentanol (EA-135). This reduction was adapted from the work of Zenitz, Macks, and Moore (7). Zinc dust (315 g., 4.8 gram-atoms) was added portionwise over 2 hours to a solution of 118 g. (0.8 mole) of 2-nitro-4-methyl-3-pentanol (14), 600 ml. of 87% 2-propanol, 660 ml. of glacial acetic acid, and 810 ml. of water at such a rate that the mixture refluxed gently and refluxing was continued for an additional 24 hours. After cooling, the voluminous white precipitate which separated was removed and washed on the funnel with 1000 ml. of ethyl acetate. The combined filtrates were acidified with conc'd hydrochloric acid, concentrated under reduced pressure to a final volume of about 300 ml., and made strongly alkaline with 50% caustic soda solution. The resulting sludge was steam-distilled until about 600 ml. of distillate had been collected. The distillate was acidified with conc'd hydrochloric acid, concentrated to a final volume of about 100 ml., made strongly alkaline with 50% caustic soda solution, and filtered to remove the precipitated solids. The organic layer was taken up in ether and dried. Fractionation yielded 39.4 g. or 42% of product, b.p. 78–84°/18 mm. The distillate crystallized to a white, oily solid.

METHOD B. SODIUM AND METHANOL REDUCTION OF OXIMES OF KETO ALCOHOLS

3-Methyl-4-hexanol-2-one (15), 4-heptanol-2-one (16), 3-methyl-4-heptanol-2-one (17), 5-methyl-4-hexanol-2-one (18), and 4-methoxy-4-methyl-2-pentanone (19) were converted to their oximes in yields of 60–86% by reaction with hydroxylamine hydrochloride in 50% aqueous methanolic potassium carbonate solution. Reaction of butylmagnesium bromide with isonitroso methyl ethyl ketone by the procedure of Freon (20) yielded 3-methyl-3-heptanol-2-one oxime directly. All of these oximes were reduced to the corresponding amino alcohols (EA-134, 131, 136, 141, and 144) by the process illustrated below with EA-132.

2-Amino-3-methyl-4-hexanol (EA-132). To a vigorously stirred and refluxing solution of 167 g. (1.15 moles) of 3-methyl-4-hexanol-2-one oxime in 2500 ml. of anhydrous methanol, 288 g. (12.5 gram-atoms) of sodium was added in long thin strips, vigorous refluxing being maintained until all the sodium dissolved. After cooling and with the addition of 1000 ml. of water, the reaction mixture was steam-distilled, collecting about 7 liters of distillate. The distillate was acidified with conc'd hydrochloric acid, concentrated under reduced pressure to a final volume of about 300 ml., and made strongly alkaline with 50% caustic soda solution. The organic layer which separated was taken up in ether, dried, and distilled to yield 58.0 g. or 38.4% of material boiling at 95–99°/16 mm., n_D^{25} 1.4517.

METHOD C. REDUCTIVE AMINATION OF KETONES

The reductive amination procedure of Klavehn (11) was found to work equally well with hydroxy ketones, methoxy ketones, and unsaturated ketones other than those possessing α,β-unsaturation. Examples of all these types are given below:

(*a*) *Amination of a hydroxy ketone. 2-Methylamino-7-heptanol* (EA-151). To a solution containing 124 g. (0.95 mole) of 7-hydroxy-2-heptanone (21), 135 g. of 30% monomethylamine solution, and 122 ml. of 87% 2-propanol was added 73 g. (2.7 gram-atoms) of aluminum turnings (activated with 20 ml. of a hot, saturated solution of mercuric chloride in 87% 2-propanol and 220 ml. of boiling water just prior to reaction) followed by 555 ml. of a warm 33% aqueous 2-propanol solution. Sufficient external heat was supplied to maintain an internal temperature of 60–70° for 8 hours. The cooled reaction mixture was filtered, the filtrate made faintly acid with 4 *N* hydrochloric acid and subjected to continuous ether extraction for 4 hours. The aqueous phase was separated, made strongly alkaline with 50% caustic soda solution, and again subjected to continuous ether extraction for 8 hours. After drying, the residue obtained from the ether extract was distilled. Yield, 98.4 g. or 71%; b.p. 101–106°/2 mm., n_D^{25} 1.4570.

By the same procedure 8-octanol-2-one (24) yielded EA-159. Similarly, 3-methyl-7-heptanol-2-one, prepared as described below, was converted into EA-156.

3-Methyl-7-heptanol-2-one. This ketone was prepared by the procedure of Franke and co-workers (21). A sodium ethoxide solution prepared from 37 g. (1.61 gram-atoms) of sodium and 770 ml. of absolute ethanol was added dropwise to 232 g. (1.16 moles) of ethyl α-methylacetoacetate and stirring was continued for one hour after addition was completed. To the resulting semi-solid mass 388.7 g. (1.51 moles) of δ-bromobutyl benzoate (22) was added dropwise. The reaction mixture was stirred at room temperature overnight, refluxed for one hour, cooled, and filtered to remove the precipitated sodium bromide. After removal of the alcohol, the residue was refluxed for 26 hours with a solution of 173 ml. of conc'd hydrochloric acid in 1080 ml. of water. The organic layer was separated from the cooled reaction mixture. The aqueous phase was neutralized and saturated with potassium carbonate and extracted with ether. The residue obtained by distillation of the ether from the combined organic layers was treated with a solution of 151 g. of potassium hydroxide in 1425 ml. of 50% aqueous ethanol and refluxed for 2 hours. Carbon dioxide was passed into the cooled reaction mixture until potassium bicarbonate began to separate. The alcohol was removed by atmospheric distillation and the residue was subjected to continuous ether extraction for 8 hours. After drying, fractionation of the residue obtained from the ether yielded 17.3 g. or 8% of product, b.p. 127–136°/16.5 mm., n_D^{25} 1.4488.

(*b*) *Amination of a methoxy ketone.* The 6-methoxy-6-methyl-2-heptanone and 5-methoxy-5-methyl-2-hexanone required as intermediates were obtained in low yield from methyl heptenone and methallyl acetone respectively by the processes described below.

6-Methoxy-6-methyl-2-heptanone. A solution of 252 g. (2 moles) of methyl heptenone in 194 g. (6 moles) of methanol was treated all at once with 20 g. of conc'd sulfuric acid. The solution immediately turned dark brown and some heat was evolved. The reaction mixture was warmed to 75° in a water-bath for 2.5 hours, poured into 500 ml. of cold water, and neutralized by the addition of solid sodium carbonate. The organic layer which separated was taken up in ether, dried, and fractionated to yield 112.3 g. or 35% of product, b.p. 87–89°/11 mm., n_D^{25} 1.4290–1.4295.

5-Methoxy-5-methyl-2-hexanone. Application of the procedure described above to methallyl acetone (23) gave only a 13% yield of 5-methoxy-5-methyl-2-hexanone, b.p. 71–74°/15 mm., n_D^{20} 1.4269–1.4278.

2-Methylamino-6-methoxy-6-methyl heptane (EA-149). To a solution containing 205 g. (1.3 moles) of 6-methoxy-6-methyl-2-heptanone, 183 g. of 30% monomethylamine solution, and 170 ml. of 87% 2-propanol was added 100 g. (3.7 gram-atoms) of aluminum (activated as described for EA-151) which was washed into the reaction flask with 750 ml. of warm 33% aqueous 2-propanol. When the spontaneous reaction had subsided the reaction mixture was warmed to 60–65° on a water-bath for 7 hours. The cooled reaction mixture was decanted from the unreacted aluminum, neutralized with 4 *N* hydrochloric acid, and steam-distilled to remove 2-propanol and unreacted ketone. The residue in the still pot was then made strongly alkaline with 50% caustic soda solution and again steam-distilled, collecting about 2 liters of distillate. After saturation with potassium carbonate, the organic layer

was extracted with ether, dried, and distilled to yield 142.5 g. (63%) of product boiling 96–97°/17.5 mm., n_D^{25} 1.4356.

Substitution of isopropylamine for methylamine in this procedure yielded EA-152. Similarly, 5-methoxy-5-methyl-2-hexanone gave EA-160. Methylation of EA-149 with formic acid and formaldehyde as described by Clarke, *et al.* (25) led to EA-155.

(*c*) *Amination of an unsaturated ketone. 2-Methylamino-3,6-dimethyl-5-heptene* (EA-153). To a solution of 159.6 g. (1.14 moles) of 3,6-dimethyl-5-heptene-2-one (26), 151.5 g. of 30% monomethylamine solution, and 145 ml. of 87% 2-propanol was added 87.5 g. (3.24 gram-atoms) of aluminum, activated in the usual manner. This was rinsed into the flask with 660 ml. of warm 33% aqueous 2-propanol and the reaction mixture was heated to an inside temperature of 65–70° for 7 hours. Solid materials were removed and the filtrate was just neutralized with 4 *N* hydrochloric acid. An excess of acid at this point led to the production of amino alcohols as described below under Method D. The neutral filtrate was steam-distilled to remove 2-propanol and unreacted ketone. The residue in the still pot was then made strongly alkaline with 50% caustic soda solution and again steam-distilled, collecting about 2.5 liters of distillate. The organic layer of the distillate was taken up in ether, dried, and distilled. Yield, 79.8 g. (45%) of product, b.p. 70.5–74.5°/10 mm., n_D^{25} 1.4480.

In an analogous manner allyl acetone (23), methallyl acetone (23), and 4,6-dimethyl-5-heptene-2-one (27) were converted to EA-137, 138, and 146 respectively.

METHOD D. HYDRATION OF UNSATURATED AMINES

The process of converting an unsaturated amine containing the grouping $\begin{matrix} & & C \\ & & | \\ C & - & C = C \end{matrix}$ into an amino tertiary alcohol is illustrated below.

2-Methylamino-5-methyl-5-hexanol (EA-139). A solution of 25.4 g. (0.2 mole) of 2-methylamino-5-methyl-5-hexene (EA-138) in 175 g. of 20% hydrochloric acid was heated on a steam-bath for 3 hours, cooled, made strongly alkaline with 50% caustic soda solution, and allowed to stand for 3 hours with occasional shaking. The organic layer was taken up in ether, dried, and distilled. The yield was 18.6 g. (64%) of product, b.p. 105–108°/25.5 mm., n_D^{25} 1.4489.

By a similar process EA-146 and 153 gave rise to EA-147 and 154 respectively. Compound EA-158 was obtained directly from 4,7-dimethyl-7-octene-2-one, whose preparation is described below, by a combination of Methods C and D. The reaction mixture containing the crude 2-methylamino-4,7-dimethyl-7-octene obtained by treating the ketone with methylamine by Method C was made excessively acid during the isolation procedure and yielded EA-158 which was isolated directly.

Synthesis of 4,7-dimethyl-7-octene-2-one (outlined in Flow Sheet I). (*A*). *2-Methyl-1-hexene-5-ol.* A 1-liter, 3-necked flask equipped with a sealed-stirrer, dropping-funnel, and a packed glass column attached to a condenser set for downward distillation (entire system protected from moisture) was charged with 130 g. of aluminum isopropoxide and 490 ml. of absolute 2-propanol which had been freshly distilled over aluminum isopropoxide. The mixture was brought to slow distillation such that the head temperature remained between 77–78°. To this slowly distilling mixture a solution of 112 g. (1 mole) of 5-methyl-5-hexene-2-one (methallyl acetone) (23) in 110 ml. of absolute 2-propanol was added dropwise over a period of 4 hours. After all the ketone solution had been added, absolute 2-propanol was added dropwise at such a rate as to maintain a constant reaction volume. After 6 hours the distillate gave a negative test for acetone with 2,4-dinitrophenylhydrazine and reaction was assumed to be complete. The 2-propanol was removed by distillation under slightly reduced pressure, the residue poured into 1 liter of ice-water, and the resulting mixture steam-distilled until about 2 liters of distillate were collected. The organic layer was removed, combined with the ether extracts of the aqueous phase, dried, and distilled to yield 101.7 g. (89%) of product, b.p. 73–74°/26.5–28.5 mm., n_D^{25} 1.4378.

(*B*). *5-Bromo-2-methyl-1-hexene.* Phosphorus tribromide (218.5 g., 0.806 mole) containing

7 drops of dry pyridine was cooled in an ice-salt bath and a mixture of 235.5 g. (2.06 mole) of 2-methyl-1-hexene-5-ol and 38.4 g. of pyridine was added dropwise over a period of 4 hours. When addition was completed the reaction mixture was allowed to stir at room temperature for 1 hour and the contents of the reaction flask were then distilled under reduced pressure. Fractionation of the crude distillate through a packed glass column gave a yield of 189 g. (53%), b.p. 50–53°/12 mm., n_D^{25} 1.4700.

(C). Ethyl 2-acetyl-3,6-dimethyl-6-heptene-1-oate. A cold sodium ethoxide solution prepared from 26.7 g. (1.16 gram-atoms) of sodium in 680 ml. of absolute ethanol was added dropwise over 1.5 hours to 157 g. (1.21 moles) of ethyl acetoacetate which was chilled in an ice-bath. Then 189 g. (1.06 moles) of 5-bromo-2-methyl-1-hexene was added, with continued cooling, over a period of 2 hours. The reaction mixture was stirred at room temperature overnight, heated to reflux for 32 hours, cooled, and filtered to remove sodium bromide. The alcohol was removed from the filtrate by distillation and the residue was poured into water. The organic layer which separated was extracted with ether, dried, and distilled. The yield was 77.5 g. or 32%, b.p. 101–107°/3 mm., n_D^{25} 1.4515.

(D). 4,7-Dimethyl-7-octene-2-one. A mixture of 64.8 g. (0.287 mole) of ethyl 2-acetyl-3,6-dimethyl-6-heptene-1-oate, 890 ml. of water, 194 ml. of methanol, and 64.4 g. (0.344 mole) of barium hydroxide monohydrate was refluxed for 24 hours, cooled, and acidified with 4 *N* hydrochloric acid. The combined organic layer and ether extracts of the aqueous phase were washed with 10% sodium hydroxide, then with water, and dried over sodium sulfate. On fractionation there was obtained 29.6 g. or 67.5% of product, b.p. 72–75°/11 mm., n_D^{25} 1.4367.

Preparation of intermediates for the Ritter reaction. (method e)

The intermediates required for the Ritter reaction were obtained as follows.

2,5-Dimethyl-2-heptene-6-ol. Aluminum isopropoxide reduction of 3,6-dimethyl-5-heptene-2-one (26) by the procedure described for the preparation of 2-methyl-1-hexene-5-ol (see under Method D) was accomplished in 90% yield, b.p. 82–83°/11.5 mm., n_D^{25} 1.4531.

2,4-Dimethyl-2-heptene-6-ol. The same process as above was used to reduce 4,6-dimethyl-5-heptene-2-one (27) to the corresponding alcohol in 80% yield. The product boiled 86–90°/41 mm., n_D^{25} 1.4449.

2,5-Dimethyl-2-heptene-6-ol acetate. A mixture of 126.4 g. (0.89 mole) of 3,6-dimethyl-5-heptene-2-ol and 182.0 g. (1.78 moles) of acetic anhydride was refluxed for 5 hours, cooled, poured into 500 ml. of ice-water, and neutralized with solid potassium carbonate. The organic layer and the ether extracts of the water layer were combined, dried, and distilled. The yield was 138.4 g. or 85%, b.p. 87.5–88°/11.5 mm., n_D^{25} 1.4363.

In a similar manner the following were obtained: *2,4-Dimethyl-2-heptene-6-ol acetate.* Yield 80%, b.p. 83.5–85°/16.5 mm., n_D^{25} 1.4306. *2-Methyl-1-hexene-6-ol acetate.* Yield 76%, b.p. 64–66°/13 mm., n_D^{25} 1.4233. *2-Methyl-2-heptene-6-ol acetate.* Yield 88%, b.p. 85–86°/17 mm., n_D^{25} 1.4291.

Method E. Ritter reaction with derivatives of unsaturated alcohols

The acetates listed above and citronellyl acetate were converted to the corresponding hydroxy tertiary-carbinamines listed in Table I as EA-157, 148, 145, 143, and 140 respectively by the process illustrated in detail below for EA-143.

2-Amino-2-methyl-6-heptanol (EA-143). A 2-liter, 3-necked flask equipped with a reflux condenser (lightly stoppered), dropping-funnel, sealed-stirrer, and inside thermometer was charged with 101 g. (0.60 mole) of 2-methyl-2-heptene-6-ol acetate, 74 ml. of glacial acetic acid, and 32.7 g. (0.60 mole) of sodium cyanide. On turning the stirrer by hand these components formed a pasty white sludge. A cold mixture of 149 g. of conc'd sulfuric acid and 74 ml. of glacial acetic acid was added dropwise at such a rate as to maintain an inside temperature of 50–60°. The stirrer was not used except to be occasionally turned by hand. When pressure developed within the system the condenser was unstoppered momentarily in order to release it. When addition was completed (about 2 hours) the condenser was

stoppered tightly and the mixture allowed to stand overnight. A solution of 356 g. of sodium hydroxide in 740 ml. of water was then added and the reaction mixture was refluxed for 7 hours. The organic layer and the ether extracts of the aqueous phase were combined and dried. On distillation there was obtained 40.3 g. (47%) of product, b.p. 119–122°/22 mm., n_D^{25} 1.4538.

Application of this process to 2-methyl-6-methoxy-2-heptene (28) yielded EA-150.

SUMMARY

The syntheses of 17 new and 3 previously known 2-amino alkanols and 6 new methoxy derivatives of 2-amino alkanols representing simple structural variations of the cardiac stimulant (EA-83), 2-methylamino-6-methyl-6-heptanol (Aranthol), are described.

Four previously unreported unsaturated aliphatic amines related to the antispasmodic agent 2-methylamino-6-methyl-5-heptene (Octin) were also prepared.

During the course of the work several intermediates were prepared for the first time, namely 6-methoxy-6-methyl-2-heptanone, 5-methoxy-5-methyl-2-hexanone, 3-methyl-7-heptanol-2-one, 2,4-dimethyl-2-heptene-6-ol, 2,5-dimethyl-2-heptene-6-ol, 5-bromo-2-methyl-1-hexene, ethyl 2-acetyl-3,6-dimethyl-6-heptene-1-oate and 4,7-dimethyl-7-octene-2-one.

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