Method F. Aluminum Bromide Catalyzed Isomerization of *t*-Butyltoluenes (Expts. 37, 38).—The aluminum bromide was added to the mixture of *t*-butyltoluenes and toluene contained in a dry flask equipped with calcium chloride tube. The mixtures were shaken eight hours each day and allowed to stand at room temperature the rest of the time. At intervals, 100-ml. samples were pipetted from the hydrocarbon phase, shaken with dilute hydrochloric acid, washed with water, dried over anhydrous potassium carbonate and the *t*-butyltoluene fraction, distilling from 185–195°, isolated by distillation through a small twenty-plate column using biphenyl to minimize losses due to column hold-up.

Method G. Aluminum Bromide Catalyzed Isomerization of *t*-Butyltoluenes (Expt. 39).—The isomerization was carried out in a borosilicate glass reaction vessel equipped with stirrer and baffles[22] and provided with a drying tube. The *t*-butyltoluenes and aluminum bromide were stirred eight hours during each 24-hour period. The isomerization was carried out at room temperature for the first three days and at 25 ± 1° during the rest of the six-day period. The heavy catalyst layer was separated, the hydrocarbon layer clarified by centrifuging, washed with dilute hydrochloric acid and water, dried over potassium carbonate and fractionally distilled. The transition cuts and main *t*-butyltoluene fraction were analyzed separately: 109.3–120.2° at 100 mm. (6.4 g.), 120.2–122.0° at 100 mm. (165.9 g.), 122.0–160.2° at 100 mm. (6.4 g.).

RICHMOND, CALIFORNIA

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Synthesis of Some Tertiary Carbinamines as Vasopressor Agents

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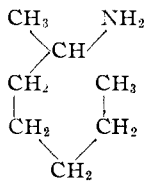
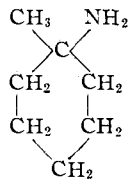
The synthesis of a series of tertiary carbinamines as vasopressor agents has been accomplished by two methods. The hydrogenation of tertiary nitrocyclanes afforded certain of these amines. In addition, sodium amide cleavage of tertiary alkyl phenyl ketones yielded tertiary carboxamides which were converted by sodium hypobromite to tertiary carbinamines. N-Alkylation of these compounds by a variety of methods is described.

It has been well established that vasopressor action is not confined to members of the phenethylamine series. Indeed, examination of a large group of aliphatic amines has indicated that practical pressor activity is found in those compounds with seven or eight carbon atoms having the amino group in the 2-position.[1a,b] Such pharmacologic effects may also be found in certain alicyclic amines. While cyclohexylamine itself has only mild pressor activity, recently both 1-cyclohexyl- and 1-cyclopentyl-2-methylaminopropane have proved to be valuable medicinal agents in this field.[2a,b] These facts suggested the investigation of certain cyclized analogs of the 2-aminoalkanes (I), *i.e.*, 1-amino-1-methylcyclanes (II) and their derivatives as vasopressor agents. In addition, such com-



I

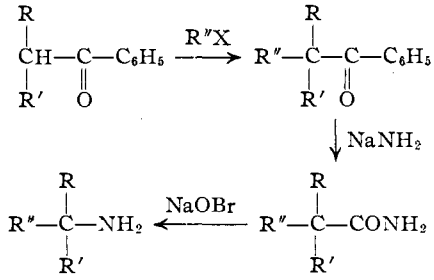


II

pounds may be regarded as tertiary carbinamines, certain examples of which have been found to be useful agents in this field.[3a,b]

The most direct method of preparation of such amines appeared to be the nitration of the appropriate hydrocarbon followed by catalytic hydrogenation of the tertiary nitrocyclane. Several procedures are available whereby hydrocarbons can be nitrated satisfactorily at the tertiary position. Thus 1-methyl-1-nitrocyclohexane has been prepared by Nametkin[4] by nitrating methylcyclohexane with aluminum nitrate. The secondary nitro products were removed by alkali extraction. With minor modifications, this method was used to nitrate the isomeric dimethylcyclohexanes, and hydrogenation using a Raney nickel catalyst provided the corresponding tertiary carbinamines (method A).

This procedure, however, had serious limitations. The synthesis of additional members of the series was necessarily restricted by the available pure hydrocarbons. Also, after conducting numerous nitrations with no untoward effects, during one experiment there resulted a violent exothermic reaction causing considerable damage to the autoclave. As a result, the general method of Haller[5] for the preparation of tertiary carboxamides was investigated. This procedure involves the cleavage of a tertiary alkyl phenyl ketone with sodium amide. The complete reaction sequence may be depicted as



In a model experiment, isobutyrophenone was alkylated with *n*-amyl bromide and the resulting tertiary ketone, where R and R′ represent methyl and R″ represents *n*-amyl, was cleaved with sodium amide in refluxing toluene. The resulting

(1) (a) E. Rohrmann and H. A. Shonle, THIS JOURNAL, **66**, 1516 (1944); (b) E. E. Swanson and K. K. Chen, *J. Pharmacol.*, **88**, 10 (1946).

(2) (a) E. Macko and E. J. Fellows, *Federation Proc.*, **8**, 318 (1949); (b) E. E. Swanson and K. K. Chen, *J. Pharmacol.*, **93**, 423 (1948).

(3) (a) R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,408,345 (1942); (b) R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,482,377 (1946).

(4) S. Nametkin, *J. Russ. Phys. Chem. (Ger.)*, **42**, 691 (1909); *Chem. Zentr.*, **81**, II, 1377 (1910).

(5) A. Haller, *Bull. soc. chim.*, **31**, 1073 (1922).

α,α-dimethylenanthamide was converted to 2-amino-2-methylheptane by means of sodium hypobromite. In like manner (method B), additional 1-alkyl-1-aminocyclanes were synthesized from the 1-alkylcyclohexyl and -cyclopentyl phenyl ketones and their corresponding carboxamides.

The alkylation of the cycloalkyl phenyl ketones was accomplished by first forming the sodio derivatives by means of sodium amide and then adding the necessary alkyl iodide. It was significant that in each instance, traces of cyclohexanecarboxamide were isolated. This closely parallels the experience of Wash, Shive and Lochte[6] in their work with 2-methylcyclopentyl phenyl ketone where 2-methylcyclopentanecarboxamide was formed during the alkylation of this ketone with isopropyl iodide by means of sodamide. These workers cited this side reaction as the first example of the sodium amide cleavage of a ketone having an α-hydrogen atom. However, the direct action of sodium amide on 2-methylcyclopentyl phenyl ketone was not described. Although it seemed unlikely that in these experiments the cyclohexanecarboxamide and 2-methylcyclopentanecarboxamide could arise by any other means,[7] cyclohexyl phenyl ketone and 2-methylcyclopentyl phenyl ketone were subjected to the action of sodium amide in boiling xylene. Cyclohexylcarboxamide and 2-methylcyclopentanecarboxamide were formed in 1 and 8%, respectively. These results directly confirm the observation of Wash and co-workers; they afford as well an additional example of the sodium amide cleavage of a ketone having an α-hydrogen atom.

Certain technical difficulties were encountered in the alkylation of these ketones since, depending on the conditions, either C-alkylation or O-alkylation may occur. This was particularly true when the entering group was methyl, in which case inseparable isomers were formed under a variety of conditions. However, it was found that a high yield of 1-methylcyclohexyl phenyl ketone could be obtained if the required methyl iodide were added in one portion to the sodio derivative of cyclohexyl phenyl ketone in dry benzene. With larger alkyl groups, although the yield of substituted phenyl ketone became progressively lower, there was little evidence of O-alkylation.

N-Alkylation of these primary amines was accomplished in a variety of ways. Monomethylation by the Decker method[8] was first attempted. In order to prepare the intermediate methiodides, it was found necessary to treat the required benzylidene amines with methyl iodide under autoclave conditions (method C). Hydrolysis of the quaternary salts yielded the N-methyl derivatives in the usual fashion. However, in the case of 1,2-dimethylcyclohexylamine, hydrolysis of the intermediate salt afforded only the starting benzylidene amine.[9] Here the desired N,1,2-trimethylcyclohexylamine was obtained by the catalytic debenzylation of N-benzyl-N,1,2-trimethylcyclohexylamine. Other sterically hindered primary amines were monomethylated by a second procedure. Formylation of the primary amines followed by lithium aluminum hydride reduction of corresponding formamide proved to be a highly successful method (method D).

Dimethylation of the nitrogen atom was simply accomplished by treatment of the primary amines with formaldehyde and formic acid[10] (method E). The aforementioned benzylidene amines were hydrogenated using a Raney nickel catalyst and thus served as intermediates in the preparation of the corresponding N-benzyl derivatives (method F). Methylation of the N-benzyl-1-methylcyclohexylamines was also carried out by means of formaldehyde and formic acid to provide the N-benzyl-N,1-dimethylcyclohexylamines.

A preliminary pharmacological examination of the tertiary carbinamines listed in Table I was carried out. The primary amines and their N-methyl derivatives all showed a vasopressor response upon administration to anesthetized cats. However, although these drugs were found to be of a low order of toxicity, none was more potent than 2-aminoheptane. The remainder of the group showed little activity as vasopressor agents.

Experimental

Cyclohexanes.—The methylcyclohexane was a commercial grade obtained from the Dow Chemical Company. The 1,2-,[11] 1,3-[12] and 1,4-[13] dimethylcyclohexanes were prepared by hydrogenation of the corresponding xylenes using Raney nickel catalyst. No attempt was made to separate *cis–trans* isomers where present.

Nitro Compounds. 1-Methyl-1-nitrocyclohexane.—The method of Nametkin[4] which describes the nitration of methylcyclohexane by means of aluminum nitrate was modified and used as a general procedure. Thus, a mixture of 2.0 moles of the methylcyclohexane and 1.0 mole of aluminum nitrate nonahydrate was heated in a stainless steel autoclave at 120–140° for six hours. The reaction mixture was cooled and then stirred well with a mixture of 20% sodium hydroxide solution and ether. The ether extract was dried and the ether was removed by distillation. The residual pale yellow oil was carefully fractionated to obtain the desired 1-methyl-1-nitrocyclohexane which boiled at 88–91° at 15 mm., $n^{25}D$ 1.4594, yield 83 g. (29%).

The nitrocyclohexanes prepared in this manner were of sufficient purity to be used in the next step. However, analyses indicated the presence of about 0.5% of an impurity. This was shown to be ketonic in character and could be removed for analytical purposes by treatment with large excesses of 2,4-dinitrophenylhydrazine.

A small sample of 1-methyl-1-nitrocyclopentane was kindly furnished by L. O. Dubois, Eastern Laboratory, E. I. du Pont de Nemours and Co.

1,2-Dimethyl-1-nitrocyclohexane.—In the manner outlined above, 152 g. (1.35 moles) of 1,2-dimethylcyclohexane was treated with 260 g. (0.7 mole) of aluminum nitrate nonahydrate. The product was distilled at 89–90° at 7 mm., $n^{25}D$ 1.4668, yield 64 g. (30%). This material was analyzed without further purification.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.82; H, 9.60; N, 8.43.

(6) G. Wash, B. Shive and H. L. Lochte, THIS JOURNAL, **63**, 2975 (1941).

(7) The enol ethers resulting from O-alkylation of the phenyl ketone conceivably could be the source of this amide. However, the enol ether blocking technique employed by W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947), for the introduction of an angular methyl group into a polycyclic ketone indicates the stability of such compounds to sodium amide in refluxing ether.

(8) H. Decker and P. Becker, *Ann.*, **395**, 362 (1913).

(9) Professor Roger Adams in a private communication reported similar results for the monomethylation of certain sterically hindered aromatic amines.

(10) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(11) N. Zelinsky, *Ber.*, **57**, 50 (1924).

(12) R. Adams and J. R. Marshall, THIS JOURNAL, **50**, 1970 (1928).

(13) F. K. Signaigo and P. L. Cramer, *ibid.*, **55**, 3326 (1933).

1,3-Dimethyl-1-nitrocyclohexane.—Following the general method described above, 152 g. (0.35 mole) of 1,3-dimethylcyclohexane was treated with 340 g. (0.9 mole) of aluminum nitrate nonahydrate. After fractionation and removal of ketonic impurities, the nitroalkane boiled at 80° at 6 mm., $n^{25}D$ 1.4538.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.29; H, 9.51; N, 8.88.

The yield of material suitable for catalytic hydrogenation was 51 g. (24%).

1,4-Dimethyl-1-nitrocyclohexane.—A mixture of 165 g. (1.45 moles) of 1,4-dimethylcyclohexane and 284 g. (0.78 mole) of aluminum nitrate nonahydrate was heated to 120° under autoclave conditions as described above. The product was distilled at 79–81° at 7 mm. to yield 48 g. (21%) of material, $n^{25}D$ 1.4541.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.43; H, 9.40; N, 8.60.

Ketones.—Isobutyrophenone,[14] cyclohexyl phenyl ketone[15] and 2-methylcyclopentyl phenyl ketone[16] were prepared by condensation of the corresponding acid chloride with benzene in the presence of anhydrous aluminum chloride in the usual manner.

α,α-Dimethylenanthophenone.—A suspension of 47 g. (1.2 moles) of sodamide in 200 cc. of anhydrous toluene was stirred while 180 g. (1.2 moles) of isobutyrophenone was added dropwise. The mixture was refluxed for one hour and 184 g. (1.2 moles) of *n*-amyl bromide was added dropwise. Refluxing was continued for four hours. The reaction mixture was cooled and washed with water. The toluene was removed *in vacuo* and the product was distilled. The resulting α,α-dimethylenanthophenone boiled at 120–130° at 1 mm. and weighed 193 g. (75%).

1-Methylcyclohexyl Phenyl Ketone.—The sodio derivative was prepared in toluene from 282 g. (1.5 moles) of cyclohexyl phenyl ketone and 59 g. (1.5 moles) of sodium amide. This mixture was stirred and cooled in an ice-bath while 425 g. (3.0 moles) of methyl iodide was added in one portion. A sudden surge of heat after five minutes caused rapid refluxing of the mixture. Stirring at room temperature was continued for 24 hours after which the product was isolated in the usual manner. The 1-methylcyclohexyl phenyl ketone distilled at 134–140° at 5 mm., $n^{25}D$ 1.5316, yield 243 g. (80%).

Small amounts of an amide melting at 186–187° after recrystallization from water were isolated from the distillate. This proved to be identical with an authentic sample of hexahydrobenzamide, melting at 185–186°.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.41; H, 8.94.

1,2-Dimethylcyclopentyl Phenyl Ketone.—In the manner outlined above, 2-methylcyclopentyl phenyl ketone was converted to 1,2-dimethylcyclopentyl phenyl ketone in 60% yield. This product distilled at 110° at 1 mm., $n^{25}D$ 1.5331. Wash and co-workers[6] report a boiling point of 288° and $n^{20}D$ 1.5368.

1-Ethylcyclohexyl Phenyl Ketone.—A suspension of the sodio derivative of 56.5 g. (0.3 mole) of cyclohexyl phenyl ketone in toluene, prepared as in the example above, was stirred at 50° while 46.8 g. (0.3 mole) of ethyl iodide was added dropwise. The mixture was then heated at 75–80° for eight hours, was washed with water and was distilled. The desired 1-ethylcyclohexyl phenyl ketone distilled at 159–160° at 11 mm., $n^{25}D$ 1.5348, yield 49.5 g. (77%).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.56; H, 9.18.

1-*n*-Propylcyclohexyl Phenyl Ketone.—In the manner outlined above, 1-*n*-propylcyclohexyl phenyl ketone was prepared from cyclohexyl phenyl ketone and *n*-propyl iodide. This product distilled at 105° at 0.3 mm., $n^{25}D$ 1.5271, yield 60%.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.44; H, 9.63. Found: C, 83.86; H, 9.60.

1-*n*-Butylcyclohexyl Phenyl Ketone.—In a similar fashion, 1-*n*-butylcyclohexyl phenyl ketone was prepared in a 34% yield. This material was distilled at 123° at 1 mm., $n^{25}D$ 1.5245.

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.65; H, 9.93.

Amides.—3-Isopropyl-1-methylcyclopentanecarboxamide, fencholamide, was prepared according to the directions of Wallach[17] from the acid chloride and ammonia.

1-Methylcyclohexanecarboxamide.—A suspension of 15.5 g. (0.4 mole) of freshly prepared sodium amide in 200 cc. of anhydrous toluene was treated with 42 g. (0.2 mole) of 1-methylcyclohexyl phenyl ketone. The mixture was refluxed while stirring for six hours, then was cooled to room temperature. The toluene mixture was washed with water and was distilled. The product boiled at 151–154° at 15 mm. and solidified on cooling. After recrystallization from pentane, the 1-methylcyclohexanecarboxamide melted at 65° and weighed 25 g. (yield 88%).

Anal. Calcd. for $C_8H_{15}NO$: N, 9.92. Found: N, 10.15.

1-Ethylcyclohexanecarboxamide.—In the manner described above, 1-ethylcyclohexyl phenyl ketone was cleaved with sodium amide to afford a 65% yield of 1-ethylcyclohexanecarboxamide, m.p. 72° from pentane.

Anal. Calcd. for $C_9H_{17}NO$: N, 9.02. Found: N, 9.06.

1-*n*-Propylcyclohexanecarboxamide.—Similarly, 1-*n*-propylcyclohexanecarboxamide was obtained in a 65% yield from 1-*n*-propylcyclohexyl phenyl ketone. This amide after recrystallization from Skelly B melted at 91–93°.

Anal. Calcd. for $C_{10}H_{19}NO$: N, 8.27. Found: N, 8.41.

1-*n*-Butylcyclohexanecarboxamide.—In the manner outlined above, 1-*n*-butylcyclohexanecarboxamide was prepared in a 66% yield from the corresponding ketone. After recrystallization from pentane, this amide melted at 83–84°.

Anal. Calcd. for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.73.

1,2-Dimethylcyclopentanecarboxamide.—1,2-Dimethylcyclopentyl phenyl ketone was similarly converted to 1,2-dimethylcyclopentanecarboxamide, melting at 97–98°, in a 71% yield. Wash, Shive and Lochte[6] report 98.5–99.5° as the melting point of this amide.

1,1-Dimethylenanthamide.—As described above, 1,1-dimethylenanthophenone was converted to 1,1-dimethylenanthamide in an 80% yield. After recrystallization from Skelly B, this amide melted at 101.5–102.5°. Leers[18] reports a melting point of 101–102° for this material.

Tertiary Carbinamines. Method A. 1-Methylcyclohexylamine.—A mixture of 70 g. (0.49 mole) of 1-methyl-1-nitrocyclohexane, 45 cc. of glacial acetic acid, 7 g. of Raney nickel catalyst and 500 cc. of methanol was subjected to a hydrogen pressure of 1400 p.s.i. at 75°. After the mixture was shaken under these conditions for one hour, the material was cooled, filtered and evaporated *in vacuo*. The crystalline residue was treated with 20% sodium hydroxide and the liberated base was extracted with ether. The ether extracts were dried and the solution was distilled. The 1-methylcyclohexylamine, thus obtained, distilled at 140–145°, $n^{25}D$ 1.4522, yield 35 g. (63%). A hydrochloride prepared from the base melted at 285° with decomposition.

Method B. 1-Methylcyclohexylamine.—The well known Hofmann reaction[19] was used to convert the tertiary carboxamides to the desired amines given in Table I. The following example is illustrative of the method.

A solution of 85 g. (0.52 mole) of bromine in 1450 cc. of 20% potassium hydroxide solution was stirred and cooled in an ice-bath while 74 g. (0.52 mole) of 1-methylcyclohexanecarboxamide was added as a fine powder. After stirring for an additional one-half hour, the resulting isocyanate was extracted from the alkaline mixture with ether. The ether extract was added dropwise while stirring to 200 cc. of boiling concentrated hydrochloric acid. After the liberation of carbon dioxide had ceased, the hydrochloric acid solution was concentrated *in vacuo*. The crystalline residue was recrystallized from absolute ethanol–ether; m.p. 285° with decomposition, yield 62 g. (80%).

The free base was obtained in the usual manner by treating an aqueous solution of the hydrochloride with alkali, extracting with ether and distilling.

Condensation of the appropriate primary amine with benzaldehyde in equimolecular quantities using ethanol as a solvent afforded the benzylidene amines. These products

(14) C. Schmidt, *Ber.*, **22**, 3250 (1889).

(15) V. Meyer and W. Scharvin, *ibid.*, **30**, 1942 (1897).

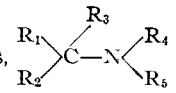
(16) Nenitzescu and Ionescu, *Ann.*, **491**, 209 (1931).

(17) O. Wallach, *ibid.*, **369**, 76 (1909).

(18) L. Leers, *Bull. soc. chim.*, **39**, 655 (1926).

(19) E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 267.

TABLE I

TERTIARY CARBINAMINES, 

R_1	R_2	R_3	R_4	R_5	B.p. °C.	Mm.	Refractive index $n^{25}D$	Method	Nitrogen, % Calcd.	Nitrogen, % Found	Salt M.p., °C.	Salt Formula	Nitrogen, % Calcd.	Nitrogen, % Found
$-C_5H_{10}-$[a,b]		CH_3	H	H	135–139	[c]	1.4522	A & B	12.37	12.52	285[d]	$C_7H_{15}N\cdot HCl$	9.36	9.77
$-C_5H_{10}-$		CH_3	CH_3	H	148–150		1.4512	C	11.01	11.18	157–159	$C_8H_{17}N\cdot(COOH)_2$	6.45	6.48
$-C_5H_{10}-$		CH_3	CH_3	CH_3	165–167		1.4551	E	9.92	10.12	182–183	$C_9H_{19}N\cdot HCl$	7.88	7.92
$-C_5H_{10}-$		CH_3	$C_6H_5CH_2$	H	160–162	18	1.5208	F	6.89	6.87	250–251	$C_{14}H_{21}N\cdot HCl$	5.84	5.85
$-C_5H_{10}-$		CH_3	$C_6H_5CH_2$	CH_3	152	12	1.5212	E	6.45	6.54	175.5–177	$C_{15}H_{23}N\cdot HCl$	5.52	5.51
2-CH_3–C_5H_9-[e]		CH_3	H	H	163		1.4565	A	11.01	10.86	315–316[d]	$C_8H_{17}N\cdot HCl$	8.56	8.55
2-CH_3–C_5H_9-		CH_3	CH_3	H	172–173		1.4582	..	9.92	9.88	184–185[d]	$C_9H_{19}N\cdot(COOH)_2$	6.05	6.25
2-CH_3–C_5H_9-		CH_3	CH_3	CH_3	191–193		1.4659	E	9.02	9.33	219–221	$C_{10}H_{21}N\cdot C_6H_3N_3O_7$[f]	14.58	14.53
2-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	H	118–120	1	1.5218	F	6.45	6.26	234–235	$C_{15}H_{23}N\cdot HCl$	5.52	5.43
2-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	CH_3	127–128	1	1.5249	E	6.05	6.07	193–194[d]	$C_{16}H_{25}N\cdot HCl$	5.23	5.32
3-CH_3–C_5H_9-		CH_3	H	H	154		1.4466	A	11.01	10.80	303[d]	$C_8H_{17}N\cdot HCl$	8.56	8.40
3-CH_3–C_5H_9-		CH_3	CH_3	H	153–155		1.4480	C	9.92	10.02	215–216	$C_9H_{19}N\cdot{}^1/_2(COOH)_2$	7.52	7.33
3-CH_3–C_5H_9-		CH_3	CH_3	CH_3	186–187		1.4520	E	9.02	9.14	159–161	$C_{10}H_{21}N\cdot HCl$	7.31	7.61
3-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	H	160–162	15	1.5062	F	6.45	6.77	184–185	$C_{15}H_{23}N\cdot HCl$	5.52	5.74
3-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	CH_3				E			174.5–175.5	$C_{16}H_{25}N\cdot HCl$	5.23	5.26
4-CH_3–C_5H_9-		CH_3	H	H	157–158		1.4465	A	11.01	11.22	248–249[d]	$C_8H_{17}N\cdot HCl$	8.56	8.33
4-CH_3–C_5H_9-		CH_3	CH_3	H	150–152		1.4480	C	9.92	10.03	269–271[d]	$C_9H_{19}N\cdot{}^1/_2(COOH)_2$	7.52	7.41
4-CH_3–C_5H_9-		CH_3	CH_3	CH_3	175–180		1.4541	E	9.02	9.18	212–213	$C_{10}H_{21}N\cdot HCl$	7.31	7.45
4-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	H	107	1	1.5112	F	6.45	6.31	252–253	$C_{15}H_{23}N\cdot HCl$	5.52	5.57
4-CH_3–C_5H_9-		CH_3	$C_6H_5CH_2$	CH_3	165–170	15	1.5133	E	6.05	6.24	217[d]	$C_{16}H_{25}N\cdot HCl$	5.23	5.65
$-C_5H_{10}-$[a]		C_2H_5	H	H	160–162		1.4582	B	11.01	11.03	302[d]	$C_8H_{17}N\cdot HCl$	8.56	8.89
$-C_5H_{10}-$		C_2H_5	CH_3	H				D			129–130	$C_9H_{19}N\cdot(COOH)_2$	6.05	6.00
$-C_5H_{10}-$		n-C_3H_7	H	H	73–74	10	1.4583	B	9.92	10.08	300[d]	$C_9H_{19}N\cdot HCl$	7.88	7.97
$-C_5H_{10}-$		n-C_4H_9	H	H	133	9	1.4597	B	9.02	9.13	294[d]	$C_{10}H_{21}N\cdot HCl$	7.31	7.59
$-C_5H_{10}-$		n-C_4H_9	CH_3	H				D			112–113	$C_{11}H_{23}N\cdot1^1/_2(COOH)_2$	4.60	4.71
$-C_4H_8-$[g]		CH_3	H	H	108–115		1.4408	A	14.13	13.78	262–263[d]	$C_6H_{13}N\cdot HCl$	10.33	10.33
$-C_4H_8-$		CH_3	CH_3	H	115–118		1.4431	C	12.37	12.34		$C_7H_{15}N$		
2-CH_3–C_4H_7-[h]		CH_3	H	H	135		1.4432	B	12.37	12.49	310–312[d]	$C_7H_{15}N\cdot HCl$	9.36	9.42
2-CH_3–C_4H_7-		CH_3	CH_3	H	154		1.4472	D	11.01	10.90	170–171	$C_8H_{17}N\cdot(COOH)_2$	6.45	6.59
3-i-C_3H_7–C_4H_7-[i]		CH_3	H	H	170–172		1.4432	B			166–167	$C_9H_{19}N\cdot HCl$		
3-i-C_3H_7–C_4H_7-		CH_3	CH_3	H	183–185		1.4475	C	9.02	9.00	119–121	$C_{10}H_{21}N\cdot HCl$	7.31	7.55
n-C_5H_{11}	CH_3	CH_3	H	H	148–150		1.4192	B	10.84	11.03	239–240[d]	$C_8H_{17}N\cdot{}^1/_2(COOH)_2$	8.04	7.97
n-C_5H_{11}	CH_3	CH_3	CH_3	H	158–161		1.4202	D	9.78.	9.66	238–241	$C_9H_{19}N\cdot{}^1/_2(COOH)_2$	7.44	7.32

[a] Pentamethylene. [b] Previously reported by Nametkin.[4] [c] Where figures are not given, the distillation was conducted at atmospheric pressure. [d] Melted with decomposition. [e] Monosubstituted pentamethylene. [f] Picrate. [g] Tetramethylene. Previously reported by W. Markownikoff, *Ann.*, **307**, 355 (1898). [h] Monosubstituted tetramethylene. [i] O. Wallach[17] reported the following data for this amine: b.p. 173°, $n^{21}D$ 1.4450, hydrochloride, m.p. 169–170°.

obtained by distillation of the reaction mixture are given with their physical constants under the heading of the parent amine. 1-Methylcyclohexylamine, b.p. 144° at 10 mm., $n^{25}D$ 1.5429. *Anal.* Calcd. for $C_{14}H_{19}N$: N, 6.96. Found: N, 7.10. 1,2-Dimethylcyclohexylamine, b.p. 118° at 1.5 mm., $n^{25}D$ 1.5384. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.52. 1,3-Dimethylcyclohexylamine, b.p. 100° at 1 mm., $n^{25}D$ 1.5324. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.64. 1,4-Dimethylcyclohexylamine, b.p. 101–103° at 1 mm., $n^{25}D$ 1.5310. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.60. 1-Methylcyclopentylamine, b.p. 148° at 18 mm., $n^{25}D$ 1.5432. *Anal.* Calcd. for $C_{13}H_{17}N$: N, 7.48. Found: N, 7.32. 3-Isopropyl-1-methylcyclopentylamine, b.p. 122–123° at 1 mm., $n^{25}D$ 1.5263. *Anal.* Calcd. for $C_{16}H_{23}N$: N, 6.11. Found: N, 6.14. 1,1-Dimethyl-*n*-hexylamine, b.p. 159–160° at 18 mm., $n^{25}D$ 1.5088. *Anal.* Calcd. for $C_8H_{19}N$: N, 6.45. Found: N, 6.52.

Method C. N-1-Dimethylcyclohexylamine.—With a few modifications, the method of Decker[8] was used for monomethylation of most of the primary amines given in Table I.

A mixture of 38 g. (0.19 mole) of benzylidene-1-methylcyclohexylamine and 27 g. (0.19 mole) of methyl iodide was heated at 125° for six hours in an autoclave. The red viscous material thus obtained was dissolved in 100 cc. of 85% methanol and the mixture was boiled for one hour. After the addition of 150 cc. of water, the liberated benzaldehyde was steam distilled. The residual mixture was evaporated to dryness *in vacuo* and then was made alkaline with 20% sodium hydroxide solution. The resulting base was extracted with ether, the ether extracts were dried and the solution was distilled. The physical data for this base and its salt are included in Table I.

Method D. 1-*n*-Butyl-N-methylcyclohexylamine.—A mixture of 1.5 g. (0.01 mole) of 1-*n*-butylcyclohexylamine and 2 cc. of 98% formic acid was heated at 180–190° for two hours and then cooled. This material was dissolved in ether and the ether solution was extracted with diluted hydrochloric acid and water. After the ether solution was dried over anhydrous magnesium sulfate, it was added dropwise to a solution of 1.52 g. (0.04 mole) of lithium aluminum hydride in ether. After the addition of the amide, the mixture was refluxed an additional six hours. Water was added until the complex and excess lithium aluminum hydride were decomposed. After filtration, the inorganic material was washed with ether and this filtrate was extracted well with ether. The ether extracts were combined, dried and then treated with a solution of anhydrous oxalic acid in ether. In this manner, 2.2 g. (83% yield) of the sesquioxalate of 1-*n*-butyl-N-methylcyclohexylamine was prepared; m.p. from ethyl acetate, 112–113°. This compound is further described in Table I. For additional confirmation of the structure of this amine, the picrate was formed in water. The yellow crystalline material was recrystallized from benzene, m.p. 122–123°. *Anal.* Calcd. for $C_{17}H_{26}N_4O_7$: N, 14.06. Found: N, 14.06.

Method E. N,N,1-Trimethylcyclohexylamine.—A mixture of 11.3 g. (0.1 mole) of 1-methylcyclohexylamine, 70 cc. of 90% formic acid and 13 cc. of formalin was boiled for four hours. After the mixture was evaporated to dryness *in vacuo*, the residue was made alkaline with 20% sodium hydroxide solution. The base which was formed in this manner was extracted with ether and the ether extracts were dried. After distillation, the desired N,N,1-trimethylcyclohexylamine was obtained in 85% yield (12 g.). Physical constants for this base and its salt are found in Table I.

Method F. N-Benzyl-1-methylcyclohexylamine.—A mixture of 25 g. (0.115 mole) of benzylidene-1-methylcyclohexylamine, 3 g. of Raney nickel catalyst and 75 cc. of methanol was subjected to a hydrogen pressure of 25 p.s.i. After the mixture was shaken for 12 hours, the catalyst was filtered and the filtrate was distilled. In this manner, 20.5 g. of N-benzyl-1-methylcyclohexylamine was obtained (80% yield). See Table I for physical data for this base and its salt.

N,1,2-Trimethylcyclohexylamine.—A mixture of 15 g. (0.065 mole) of N-benzyl-N,1,2-trimethylcyclohexylamine, 1.5 g. of 10% palladium–charcoal catalyst and 60 cc. of glacial acetic acid was subjected to a hydrogen pressure of 30 p.s.i. After the mixture was shaken for 12 hours, the catalyst was filtered and the filtrate was taken to dryness *in vacuo*. The residue was made strongly alkaline with 20% sodium hydroxide solution and the liberated base was extracted with ether. The ether extracts were dried and distilled. In this way, N,1,2-trimethylcyclohexylamine was obtained in an 87% yield (8 g.). Physical data for this amine and its salt are included in Table I.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

Anticonvulsants. III. A Study of N,α,β-Alkylsuccinimides

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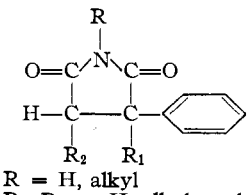
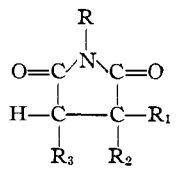
A third series of substituted succinimides has been synthesized and examined for anticonvulsant properties. Many of these alkyl derivatives exhibit a considerable degree of activity in preventing metrazol-induced convulsions in laboratory animals. However, at the dosage employed they are ineffective against electrically-induced convulsions.

The preparation and anticonvulsant properties of a number of substituted succinimides have been reported.[1,2] Each of these derivatives contained at least one phenyl group and may be represented by structure I. Certain members of this series are useful in the treatment of petit mal epilepsy. Indeed, N-methyl-α-phenylsuccinimide (Milontin)[3] is quite potent[4] against this type of convulsive disorder and is relatively non-toxic.



R = H, alkyl
R_1, R_2 = H, alkyl, aryl
I



R, R_1, R_2, R_3 = H, alkyl
II

Since an appreciable number of the compounds I proved to be particularly effective in preventing metrazol-induced convulsions,[5] it is important

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(3) Parke, Davis and Co. trademark for N-methyl-α-phenylsuccinimide.

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