methyl-2-thiourea which could be isolated by extraction of the dry mixture with warm benzene. The aqueous filtrate from the potassium perchlorate and the trimethylthiourea was now evaporated to dryness on the water-bath and left a solid residue which upon extraction with hot benzene gave an additional 4.15 g. of 1,1,3-trimethyl-2-thiourea. The total crude yield of this thiourea corresponded to 0.05 mole. The salt mixture which was left from the benzene extraction contained sulfate, thiosulfate, carbonate and a little perchlorate.

BOUND BROOK, N. J.

[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

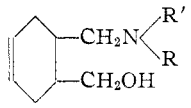
Hypotensive Agents. II.[1] Alicyclic Amino Alcohols[2a,b]

BY LEONARD M. RICE, CHARLES H. GROGAN, C. F. GESCHICKTER AND E. EMMET REID[3]

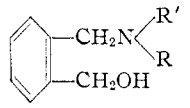
RECEIVED SEPTEMBER 4, 1952

Nine new mono- and di-N-substituted aminomethyl-2-hydroxymethyl-*cis*-Δ^4-cyclohexenes have been prepared by the reduction of the corresponding tetrahydrophthalamic acids with excess lithium aluminum hydride. These compounds have been screened for hypotensive activity in dogs. Three new N-substituted-*cis*-Δ^4-tetrahydrophthalamic acids are reported.

Because of the widespread use of amino alcohol residues in many substances of high physiological activity, it was desirable to be able to obtain readily a series of these compounds in which the two carbon atoms holding the fixed and variable substituents are rigidly held in place. In the series of compounds prepared, two of the carbon atoms are part of an alicyclic ring system, *i.e.*, cyclohexene (I).



I

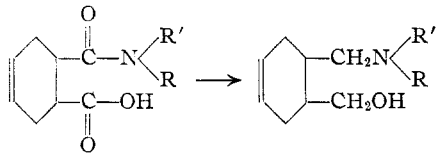


II

The substituent, R, in the compounds may represent hydrogen, an alkyl group or it may be a heterocyclic ring system. R′ may be the same as R, or it may represent a different, although similar type of group. It is of interest to note that these compounds may be considered the cyclic analogs of the dialkylaminobutyl alcohols.

By a rather involved sequence of reactions Funke and Rougeaux[4] have prepared a similar type of compound in which two of the carbon atoms are part of the benzene ring system (II).

We believe that the method used in our investigation offers a more direct synthesis for these types of compounds and is applicable to the phthalamic acids derived from other ring systems, such as phthalic, hexahydrophthalic and related compounds. We have prepared the alicyclic compounds in yields up to 92% by the reduction of 50 g. of the corresponding tetrahydrophthalamic acids with an excess of lithium aluminum hydride in anhydrous ether. Under the conditions in which we carried out our reactions all reductions were very smooth and when judged by the yields and the purity of materials obtained were relatively free of side reactions. The various hydroxymethyl-2-mono- or dialkylaminomethyl-*cis*-Δ^4-cyclohexenes prepared are shown in Table I. The several variations in R and R′ show the wide applicability and general nature of the reaction.



It may be noted that not only the amide group but, also, the carboxyl group is reduced. The structures of the reduction products were proven experimentally. From the compound in which R and R′ were ethyl, the *p*-nitrobenzoate ester was prepared. Subsequently, the formation of a methiodide and hydrochloride demonstrated the amine function. When this compound was hydrogenated at room temperature using platinum oxide catalyst one mole of hydrogen was absorbed. Ordinary tests for unsaturation, decolorization of aqueous permanganate and bromine in carbon tetrachloride, were also positive.

The tetrahydrophthalamic acids used in the present work, with the exception of those derived from diethylamine, isopropylamine and pyrrolidine, have been described in previous papers.[1,5] Three new tetrahydrophthalamic acids are listed in Table II.

Compound one, in Table I, on injection into dogs produced a moderate fall in blood pressure with a simultaneous increase in respiratory rate.

Experimental

N,N-Disubstituted-*cis*-Δ^4-tetrahydrophthalamic Acids.—The tetrahydrophthalamic acids were prepared by treating equimolecular quantities of the appropriate amine and tetrahydrophthalic anhydride. Benzene was used as a solvent to prevent loss of the low boiling amines, since the reaction is exothermic. When isopropylamine was used the reaction mixture was permitted to stand for several hours at room temperature with occasional stirring. When diethylamine and pyrrolidine were used the mixture was maintained at 100° for one hour after the benzene had boiled off. After cooling to room temperature, the products were recrystallized from suitable solvents.

Reductions: The Preparation of Diethylaminomethyl-2-hydroxymethyl-*cis*-Δ^4-cyclohexene.—The following general method was used for all of the lithium aluminum hydride

(1) For the first paper in this series see L. M. Rice, A. Popovici, M. Rubin, C. F. Geschickter and E. E. Reid, THIS JOURNAL, **74**, 3025 (1952).

(2) (a) Presented at the Meeting of the American Chemical Society, Medicinal Section, Atlantic City, N. J., September 15, 1952. (b) Supported in part by the Geschickter Fund for Medical Research, Inc.

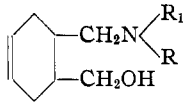
(3) Professor Emeritus, Johns Hopkins University, Baltimore 18, Md.

(4) M. A. Funke and O. Rougeaux, *Bull. soc. chim.*, **12**, 1050 (1945).

(5) L. M. Rice, M. Rubin, J. Scholler and E. E. Reid, *J. Org. Chem.*, **16**, 501 (1951).

TABLE I

1-DIALKYLAMINOMETHYL-2-HYDROXYMETHYL-Δ^4-CYCLOHEXENES

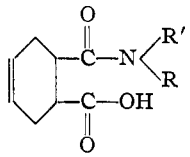


	R	R′	Formula	B.p., °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Oxygen, % Calcd.	Oxygen, % Found	M.p., °C. HCl
1	C_2H_5	C_2H_5	$C_{12}H_{23}NO$	101–103	3	73.04	73.75	11.75	11.81	7.10	6.75	8.11	7.81	82–83
			$C_{23}H_{24}NOCl$[a]			61.65	62.15	10.35	10.19	5.98	5.68	6.84	6.79	82–83
2	CH_3CHCH_3	H	$C_{11}H_{21}NO$	104–108	3	72.08	72.03	11.54	11.26	7.64	7.61	8.73	8.90	138–140
3	$C_{10}H_{21}$	H	$C_{18}H_{35}NO$	163–168	2	76.80	77.14	12.53	12.49	4.98	5.06	5.68	5.78	138–139
4	$C_6H_5CH_2$[b]	H	$C_{15}H_{21}NO$	152–156	2	77.87	78.43	9.17	9.11	6.06	6.08	6.92	6.90	130–132
5	C_6H_{11}[c]	H	$C_{14}H_{25}NO$	135–140	2	75.28	75.75	11.28	11.06	6.27	6.21	7.16	7.04	195[d]
6	C_4H_9	C_4H_9	$C_{16}H_{31}NO$	122–126	2	75.83	75.82	12.33	12.20	5.53	5.79	6.31	6.59	74–76
7	C_4H_9	H	$C_{12}H_{23}NO$	114–118	2	73.05	73.30	11.74	11.58	7.10	6.91	8.11	8.12	163–165[g]
8	C_4H_8[e]	..	$C_{12}H_{21}NO$	86–88	2	73.79	74.16	10.83	10.66	7.17	7.22	8.19	7.94	151–152
9	$C_6H_5CH_2CH_2$	H	$C_{16}H_{24}NOCl$[f]	.....		68.22	68.44	8.57	8.31	4.97	4.73	5.67	5.63	158–159

[a] Hydrochloride of 1. Calcd., Cl, 15.16; found Cl, 15.38. [b] Benzyl. [c] Cyclohexyl. [d] Decomposition, put in bath at 190°. [e] Pyrrolidine. [f] Hydrochloride. [g] Decomposed.

TABLE II

TETRAHYDROPHTHALAMIC ACIDS



	R	R′	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Acid number Calcd.	Acid number Found
1	C_2H_5	C_2H_5[a]	$C_{12}H_{19}NO_3$	104–106	6.22	6.35	225	216
2	H	$(CH_3)_2CH$[b]	$C_{11}H_{17}NO_3$	151–153	6.63	6.49	211	206
3	C_4H_8[c,d]	.....	$C_{12}H_{17}NO_3$	175–176	6.27	6.26	223	218

[a] Recrystallized from dilute alcohol. [b] Recrystallization from acetone. [c] Recrystallized from alcohol. [d] Pyrrolidine.

reductions in the present work: In a two-liter, three-necked flask, fitted with a mechanical stirrer, dropping funnel and reflux condenser with calcium chloride drying tube, was placed 19 g. of lithium aluminum hydride and a liter of anhydrous ether. When solution had been effected, a slurry of 50 g. of finely powdered N-diethyl-*cis*-Δ^4-tetrahydrophthalamic acid in anhydrous ether was slowly added with vigorous stirring. In some cases it was more convenient to use a Soxhlet extractor arrangement to transfer the tetrahydrophthalamic acid to the reaction mixture. The rate of addition of the tetrahydrophthalmic acid was regulated so as to just maintain reflux. After addition had been completed, the mixture was stirred for an additional four hours and then allowed to stand overnight.

While stirring, the reaction mixture was then decomposed by the dropwise addition of water. The addition of the water was regulated so as to just maintain reflux. Stirring was continued for another hour and the mixture was filtered. The residue was pressed and washed with three portions of ether. After drying the filtrate over anhydrous sodium sulfate, the ether was stripped off and the residual oil isolated by vacuum distillation. The product distilled as a colorless oil, b.p. 101–103° at 3 mm.

The *p*-Nitrobenzoate Hydrochloride.—This was prepared in the usual manner and had m.p. 152–154°.

Anal. Calcd. for $C_{19}H_{26}N_2O_4HCl$: N, 7.32. Found: N, 7.07.

The methiodide was prepared by mixing equimolecular amounts of the amino alcohol and methyl iodide in absolute ethanol. After standing for two days at room temperature in a closed system, the addition of anhydrous ether just to a permanent cloudiness and refrigeration produced the methiodide in crystalline form, m.p. 104–106°. After recrystallization from an absolute ethanol–ether mixture the compound melted at 106–107°.

Anal. Calcd. for $C_{13}H_{28}NOI$: N, 4.12; I, 37.41. Found: N, 3.95; I, 37.55.

WASHINGTON 7, D. C.