[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

Aminoesters of Substituted Alicylic Carboxylic Acids[1]

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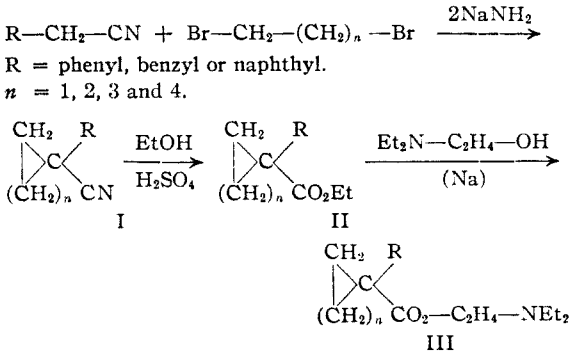
In the search for new compounds having antispasmodic and antihistamine activity, a series of aminoesters of substituted cycloalkanecarboxylic acids was investigated. The substituents attached to the ring were aryl, aralkyl, and cycloalkyl. All of these aminoesters are new compounds except β-diethylaminoethyl 1-phenylcyclohexanecarboxylate which has been reported recently.[1a]

The aminoesters of 1-substituted cycloalkanecarboxylic acids were prepared from the corresponding cyanides. Synthesis of the cyanides was accomplished in as high as 85% yields by a modification[2] of the procedure of Case.[3] Phenylacetonitrile was condensed with an alkylene dihalide using two equivalents of sodamide in a liquid ammonia and ether mixture at about −50°. Alcoholysis of the substituted cyanides by a sulfuric acid–ethanol mixture[4] usually resulted in the formation of the crude ethyl esters which were not usually purified. The crude esters (II) were re-



esterified[5] with the desired aminoalcohol using sodium as a catalyst and toluene or xylene as a solvent. The amino esters (III) thus obtained were isolated as crystalline hydrochlorides.

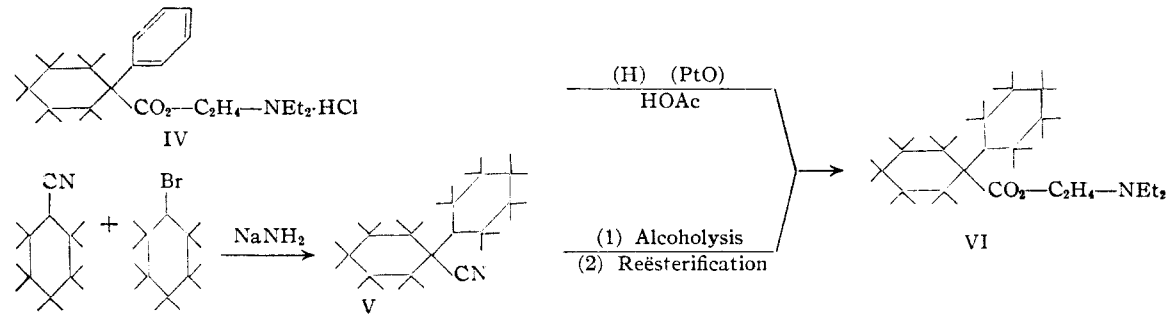
In cases where steric hindrance greatly reduced the activity of the cyanide group, alcoholysis was only partially successful. Thus it was necessary to heat 1-α-naphthylcyclopentyl cyanide with alcoholic potassium hydroxide[6] in an autoclave at 190° in order to obtain the acid. The acid was conveniently converted to the aminoester[7] by refluxing with β-diethylaminoethyl chloride in isopropanol.

The 1-phenyl aminoester hydrochlorides were reduced to the 1-cyclohexyl derivatives in excellent yields. In one case, the structure of the reduced compound (VI) was proved by an independent method of synthesis from V.

That the products from both reactions were identical was shown by a melting point of a mixture of the two substances.

2-Phenylbenzoic acid was reduced by sodium–*n*-butanol to 2-phenylcyclohexanecarboxylic acid.[8] Methyl 4-phenylcyclohexanecarboxylate was obtained by the reaction of methyl 1-cyclohexenecarboxylate with benzene in the presence of aluminum chloride.[9] The aminoester prepared from this methyl ester by the regular reësterification procedure was catalytically reduced in a good yield to the corresponding 4-cyclohexyl derivative.

The reaction of tetrahydrophthalic anhydride with phenylmagnesium bromide[10] and cyclohexyl-



magnesium bromide afforded a means of preparing 2-substituted cyclohexene (VII) and cyclohexanecarboxylates (VIII). In certain cases, the *cis* and *trans* isomers were isolated. The Clemmensen re-

(1) Presented at the 110th Meeting of the American Chemical Society, Medicinal Section, Chicago, September 12th, 1946.

(1a) Rubin and Wishinsky, THIS JOURNAL, **68**, 829 (1946). After this manuscript had been completed U. S. Patent 2,404,588 reported on 1-phenyl- and 1-tolyl-substituted cycloalkanes.

(2) Cloke, Anderson, Lachmann and Smith, *ibid.*, **53**, 2791 (1931).

(3) Case, *ibid.*, **56**, 715 (1934).

(4) Blicke and Feldkamp, *ibid.*, **66**, 1088 (1944)

(5) Sudborough and Karve, *J. Indian Inst. Sci.*, **3**, 1–14 (1919); U. S. Patent 2,394,770.

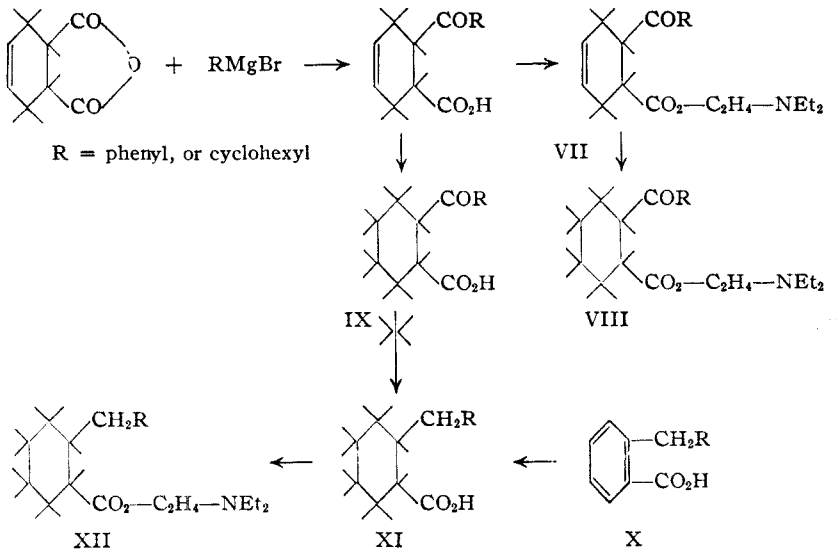
(6) Eisleb, *Ber.*, **74**, 1444 (1941).

(7) Burtner and Cusic, THIS JOURNAL, **65**, 262 (1943).

(8) Fujise, *Ber.*, **71B**, 2461 (1938).

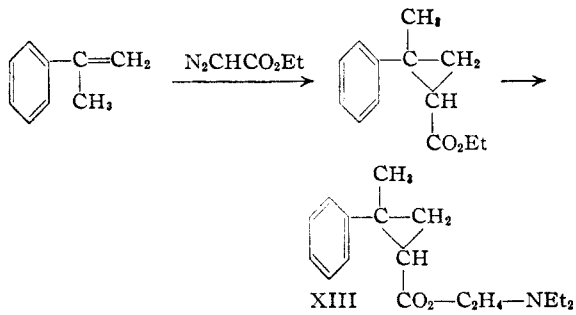
(9) Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945)

(10) Fieser and Novello, *ibid.*, **64**, 802 (1942).



duction of IX failed in an attempt to prepare XI, which was finally obtained from X by a sodium–*n*-butanol reduction.

A 2-disubstituted cyclopropane derivative XIII was readily prepared[11] from α-methylstyrene.



The pharmacological activities of the compounds of this study are listed in Table I. The most active compounds are 1-substituted cycloalkanecarboxylates having 4–6 carbon atoms in the alicyclic ring. Further substitution by a methyl group in the 2-position decreases activity; however, a methyl group in the 3-position (no. 22) of the cyclobutane derivative (no. 23) enhances activity. Hydrogenation of phenyl groups in the 1-positions decreases the activity except in the case of the 1-phenylcyclohexanecarboxylate (no. 5) where the activity against acetylcholine is apparently increased twofold.

No definite conclusions can be drawn in regard to relationship of structure and antihistamine activity. However, a cyclohexyl or benzyl group in the 1- or 2-position of the cyclohexane ring furnishes compounds of the greatest activity of this series.

In vivo tests have also shown the high activity of compounds nos. 4, 5, 14, and 22; no. 22 was effective when given intravenously in doses of 0.5–1 mg./kg. against acetylcholine on the anesthetized cat, and had an oral toxicity of 660 mg./kg. A pharmacological report will be given elsewhere.

Acknowledgment.—The pharmacological data were furnished by Dr. H. W. Werner, Miss B. B. Brown and Mr. E. Peters of this Laboratory

Experimental

1-Substituted Cycloalkyl Cyanides.—The general method of preparation was a modification of that of Case.[3] A detailed procedure is given using 1-phenylcyclopentyl cyanide as a representative example.

All of the alkylene dibromides are available commercially[12] except 1,4-dibromopentane, which was prepared in a 47% yield by the hydrogenation[13] of methylfuran using Adams catalyst and no solvent followed by direct treatment of the crude tetrahydromethylfuran with 40% hydrobromic acid[14]: b. p., 89–92 (18 mm.).

Phenylacetonitrile, α-naphthaleneacetonitrile and β-phenylpropionitrile are available from commercial sources. Cyclohexyl cyanide was conveniently prepared by a refluxing of cyclohexanecarboxamide with an excess of thionyl chloride[15] for six hours. The cyanide was distilled directly from the reaction mixture at 80–84° (18 mm.) to give 85–93% yields.

1-Phenylcyclopentyl Cyanide.—To 500 ml. of liquid ammonia containing 0.5 g. of ferric nitrate and cooled to −30° by a Dry Ice–bath was added 44 g. (1.92 mole) of sodium[16] during a period of about one-half hour with stirring. When the initial blue color had faded to gray, 110 g. (0.93 mole) of phenylacetonitrile was added in about twenty minutes. The mixture was cooled and maintained at about −50° during one to one and a half hours' addition of 195 g. (0.9 mole) of tetramethylene bromide in 500 ml. of dry ether. The Dry Ice-bath was removed and the ammonia was allowed to evaporate. The original volume was maintained by the addition of dry ether or toluene. Finally the mixture was refluxed on the water-bath for two hours. About 400 ml. of water[17] was added with cooling, followed by 500 ml. of benzene. The benzene–ether solution was separated from the aqueous layer and distilled. The desired cyanide was collected at 148–153° (20 mm.) and weighed 130 g. (85%).

Amino Esters.—The 1-substituted aminoesters were prepared from the cyanides. The general procedure is given for the 1-phenylcyclopentanecarboxylate.

β-Diethylaminoethyl 1-Phenylcyclopentanecarboxylate Hydrochloride (Method A).—To a solution of 130 g. (0.77 mole) of 1-phenylcyclopentyl cyanide in 1100 ml. of

(11) Wieland and Probst, *Ann.*, **530**, 274–290 (1937), reported a similar reaction using biphenylethylene.

(12) We are grateful to E. I. du Pont de Nemours and Co. for furnishing tetrahydrofuran and tetrahydropyran used in the preparation of two of the dihalides.

(13) Andrus and Johnson, "Organic Syntheses," **23**, 90 (1943); methylfuran substituted for dihydropyrane.

(14) Andrus, "Organic Syntheses," **23**, 67 (1943).

(15) Breslow and Hauser, THIS JOURNAL, **67**, 686 (1945).

(16) Hancock and Cope, "Organic Syntheses," **25**, 25 (1945).

(17) In the preparation of 1-substituted cyclohexyl cyanides, the addition of water was omitted since emulsions always formed. It was found best to remove the inorganic salts and insoluble polymer by filtration followed by a washing of the precipitate several times with benzene. The filtrate was distilled directly.

95% ethanol was added 300 ml. of concentrated sulfuric acid with cooling. The mixture was heated at 90–95° under vigorous refluxing for twenty-four to forty-eight hours. Near the end of the reaction, two layers always formed in the reaction mixture. At this point, if the temperature exceeds 115°, charring occurs and hence decreased yields are obtained.

The reaction mixture was poured into 2 liters of cracked ice and the crude ethyl ester was extracted three times with 300-ml. portions of xylene. (The distilled ester could be collected at 118–120° (0.75 mm.)). The combined xylene extract was placed in a flask having a short Vigreux column and 130 g. of β-diethylaminoethanol was added. Distillation was carried out till all the water was

TABLE I

SPASMOLYTIC ACTIVITY OF β-DIETHYLAMINOETHYL ESTER HYDROCHLORIDES

No.	Carboxylic acid	Formula	M. p., °C. (cor.)	% Chlorine Calcd.	% Chlorine Obs.	Method[a]	% Yield	Normal[b]	Acetylcholine[c]	Barium chloride[d]	Histamine, γ/cc.[e]
1	1-α-Naphthylcyclohexane	$C_{23}H_{31}O_2NCl$	181–185	9.17	9.25	B	30	0.05	0.5	0.5	20
2	1-Benzylcyclohexane	$C_{20}H_{31}O_2NCl$	148–150	10.06	9.97	B	30	.25	.25	.5	1
3	2-Methyl-1-phenylcyclohexane	$C_{20}H_{31}O_2NCl$	126–128	10.06	10.15	B	10	.1	.2	.2	5
4	1-Phenylcyclohexane	$C_{19}H_{29}O_2NCl$	159–161	10.42	10.40	A	74	1	5	.5	10
5	1-Cyclohexylcyclohexane	$C_{19}H_{35}O_2NCl$	165–166	10.28	10.25	D	80	0.1	10	.2	5
6	2-Phenylcyclohexane	$C_{19}H_{29}O_2NCl$	75–76	10.42	10.38	C	69	.25	0.5	.05	...
7	2-Cyclohexylcyclohexane	$C_{19}H_{35}O_2NCl$	105–109	10.28	10.40	D	75	.1	1	.1	0.5
8	2-Benzoyl-Δ_4-cyclohexene[f]	$C_{20}H_{27}O_3NCl$	130–133	9.70	9.75	C	58	.05	0.01	.05	5
9	2-Benzoylcyclohexane	$C_{20}H_{29}O_3NCl$	98–100	9.68	9.70	C	60	.5	.2	.5	20
10	2-Hexahydrobenzoyl-Δ_4-cyclohexene	(A) $C_{20}H_{33}O_3NCl$	118–122	9.56	9.52	C	10	.2	.02	.1	20
	(diastereoisomers)	(B)	103–108		9.60		65	.2	.02	.05	...
11	2-Hexahydrobenzoylcyclohexane	(A) $C_{20}H_{35}O_3NCl$	132–136	9.52	9.50	D	60	.1	.1	.05	5
	(diastereoisomers)	(B)	135–139		9.56		67	.1	0.5	.1	5
12	2-Benzylcyclohexane	$C_{20}H_{31}O_2NCl$	114–116	10.06	9.95	C	53	5	.5	.5	5
13	4-Phenylcyclohexane[g]	$C_{19}H_{29}O_2NCl$	160–162	10.42	10.42	C	68	0.01	.01	.10	5
14	4-Cyclohexylcyclohexane	$C_{19}H_{35}O_2NCl$	191–192	10.28	10.20	D	85	.1	.2	.2	10
15	1-α-Naphthylcyclopentane	$C_{22}H_{29}O_2NCl$	175–176	9.48	9.60	B	56	.01	.2	.2	5
16	2-Phenyl-2-indane	$C_{22}H_{27}O_2NCl$	158–162	9.52	9.60	A	8	.5	.5	.5	5
17	1-Benzylcyclopentane	$C_{19}H_{29}O_2NCl$	121–122	10.42	10.52	A	33	1	.2	.2	1
18	2-Methyl-1-phenylcyclopentane	$C_{19}H_{29}O_2NCl$	144–145	10.42	10.50	B	51	1	.5	.5	5
19	1-Phenylcyclopentane	$C_{18}H_{27}O_2NCl$	142–144	10.90	10.90	A	70	0.1	5	.5	5
20	2-Methyl-1-cyclohexylcyclopentane	$C_{19}H_{35}O_2NCl$	140–143	10.28	10.30	D	82	.2	0.2	.2	1
21	1-Cyclohexylcyclopentane	$C_{18}H_{33}O_2NCl$	127–128	10.70	10.75	D	84	.01	.5	.1	5
22	3-Methyl-1-phenylcyclobutane	$C_{18}H_{27}O_2NCl$	137–139	10.90	10.96	A	11	1	2	.5	5
23	1-Phenylcyclobutane	$C_{18}H_{25}O_2NCl$	145–146	11.40	11.45	A	42	1	2	.1	
24	1-Cyclohexylcyclobutane	$C_{17}H_{31}O_2NCl$	126–127	11.18	11.28	D	90	0.1	0.25	.05	10
25	2-Methyl-2-phenylcyclopropane	$C_{17}H_{25}O_2NCl$	78–81	11.40	11.50	B	30	.25	.1	.1	10
26	1-Phenylcyclopropane	$C_{16}H_{23}O_2NCl$	.....[h]	11.92	12.05	A	6	.1	.1	.25	
		β-Dimethylaminoethyl Ester Hydrochlorides[f]									
27	1-Phenylcyclohexane	$C_{17}H_{25}O_2NCl$	176–177	11.40	11.45	A	86	.5	1	1	5
28	2-Cyclohexylcyclohexane	$C_{17}H_{31}O_2NCl$	140–142	11.18	11.30	A	80	.25	.2	0.1	1
29	2-Methyl-1-phenylcyclopentane	$C_{17}H_{25}O_2NCl$	136–138	11.40	11.40	B	27	1	.1	.1	5
30	1-Phenylcyclopentane	$C_{16}H_{23}O_2NCl$	116–118	11.92	11.88	A	60	0.01	.05	.1	5
		1-Phenylcyclohexanecarboxylate Hydrochlorides									
	Amino alcohol										
31	β-Dimethylaminoethoxyethyl[i]	$C_{19}H_{29}O_3NCl$	128–130	9.95	9.95	A	30	2	.5	.5	10
32	γ-Piperidino-β-hydroxypropyl[j]	$C_{21}H_{31}O_3NCl$	141–145	9.34	9.40	A	29	0.01	.5	1	10
33	γ-Piperidino-β-phenylurethan propyl	$C_{28}H_{36}O_4N_2Cl$	162–164	7.12	7.36		35	.1	.01	0.1	50
34	β,β′-bis-(Diethylamino)-isopropyl	$C_{24}H_{40}O_2N_2Cl_2$	135–137	15.38	15.45	A	15	.5	.5	.5	5
35	1,2-Divinylene-1,4,5,6-tetrahydro-5-pyrimidyl	$C_{21}H_{25}O_2N_2Cl$	186–188	9.51	9.45	E	72	.01	.1	.1	5
36	β-bis-(Hydroxymethyl)-β-aminoethyl	$C_{17}H_{26}O_4NCl$	213–214	10.30	10.30	F	35	.1	.01	.1	5

TABLE I (*Continued*)

Standards for Comparison

No.	Amino alcohol		Normal[b]	Acetyl[c] choline	Barium[d] chloride	Histamine,[e] γ/cc.
37	Trasentin	(β-Diethylaminoethyl diphenylacetate hydrochloride)	.05	1	.2	5
38	Pavatrine	(β-Diethylaminoethyl 9-fluorenecarboxylate hydrochloride)	2.5	1	.5	5
39	Amethone	(3-β-Diethylaminoethyl-3-phenyl-2-benzofuranone hydrochloride)	0.5	5	.1	5
40	Atropine		10	80	.2	5
41	Papaverine		0.15	0.1	.1	. .
42	Benadryl	(β-Dimethylaminoethyl benzhydryl ether hydrochloride)	...	...	..	0.02

[a] Examples of these methods are given in the Experimental part, except Method C, which is the second step in Method B using the acid and dialkylaminoalkyl chloride as starting materials. [b] Dilutions in million parts of water that gave a minimal but definite relaxation of the normal isolated rabbit jejunum. [c] Dilutions in million parts of water that gave complete relief of spasm on isolated rabbit jejunum induced by a 1 to 1 million concentration of acetyl choline. [d] Dilutions in million parts of water that gave complete relief of spasm on isolated rabbit jejunum caused by a 1 to 10 thousand concentration of barium chloride. [e] Minimal dose of test compound necessary to antagonize 0.1 γ/cc. of histamine diphosphate on isolated guinea pig intestine. [f] For the preparation of the carboxylic acid see reference 6. [g] For the preparation of the carboxylic acid see reference 5. [h] Too hygroscopic to permit satisfactory melting point. See Weston, THIS JOURNAL, **68**, 2347 (1946). [i] β-Dimethylaminoethoxyethanol; Horne and Shriner, *ibid.*, **54** 2925 (1932). [j] 1-Piperidinopropanediol-2,3, Rider and Hill, *ibid.*, **52**, 1528 (1930).

TABLE II

	B. p., °C.	Mm.	Yield, %
1-α-Naphthylcyclohexyl	190–198	1	23
1-Benzylcyclohexyl	165–168	12	29
2-Methyl-1-phenylcyclohexyl	154–155	10	57
1-Phenylcyclohexyl[a]	160–163	18	72
1-Cyclohexylcyclohexyl[b]	158–162	16	38
1-α-Naphthylcyclopentyl	172–175	0.6	67
2-Phenyl-2-indyl[a]	160–180	1	25
1-Benzylcyclopentyl	155–157	12	23
2-Methyl-1-phenylcyclopentyl	153–155	15	85
1-Phenylcyclopentyl[a]	148–153	20	85
3-Methylcyclobutyl	140–142	14	16
1-Phenylcyclobutyl[a]	130–135	16	10
1-Phenylcyclopropyl[a]	120–122	16	65

[a] Reference 3. [b] Prepared from cyclohexyl cyanide and cyclohexyl bromide with one equivalent of sodamide.

removed from the mixture, and then about 2 g. of sodium was added. The temperature of the reaction mixture was maintained at 140–150°, and a xylene–ethanol azeotrope distilled at about 78–82°. The progress of the reaction was followed by shaking the distillate with 3 volumes of water, and the observed decrease in volume of the distillate was considered a measure of the amount of ethanol formed. After 80–90% of the theoretical amount of alcohol had been obtained, the reaction mixture was subjected to vacuum distillation until most of the xylene and unchanged diethylaminoethanol had been recovered (b. p. 50–100° (25 mm.)).

The residue was poured into 500 ml. of benzene and extracted twice with 500 ml. portions of water. The combined aqueous extracts were acidified with concd. hydrochloric acid and the precipitated by-product, 1-phenylcyclopentanecarboxylic acid, amounted to 28–40 g. (20–27%); m. p., 156–158° (reported[3] m. p., 158°).

The above washed benzene layer was diluted with 2–3 volumes of ether and alcoholic hydrochloric acid was added till the mixture was acid to congo red paper. The crystalline product was recrystallized from a methanol–ether or an ethanol–butanone mixture. The yield of white needles melting at 139–141° was 155–170 g. (about 70% based on the cyanide and the above recovered carboxylic acid[18]). An analytical sample melted at 142–144°.

Anal. Calcd. for $C_{18}H_{27}O_2N\cdot HCl$: Cl, 10.90. Found: Cl, 10.90.

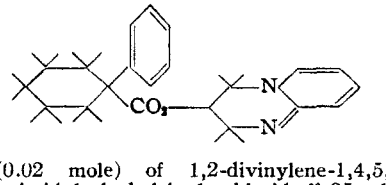
(18) See second part of Method B for conversion of an acid to an aminoester.

β-Diethylaminoethyl 1-α-Naphthylcyclopentanecarboxylate Hydrochloride (Method B).—The above alcoholysis and reësterification procedures were unsuccessful when applied to 1-α-naphthylcyclopentyl cyanide. A small amount of aminoester hydrochloride melting at 173–175° was obtained. Therefore, the cyanide was converted to the acid by heating 6 g. (0.027 mole) of the cyanide with 6 g. of potassium hydroxide in 20 ml. of methanol for eight hours at 190°. The methanolic solution was diluted with 3 volumes of water and acidified with dilute hydrochloric acid. The precipitate was collected at the filter and air dried. A mixture of this crude acid (3 g., 0.012 mole), 5 g. (0.029 mole) of β-diethylaminoethyl chloride hydrochloride, and 0.67 g. (0.029 mole) of sodium in 30 ml. of isopropanol was refluxed twelve hours. About 25 ml. of a saturated sodium bicarbonate solution was added and the mixture was evaporated on the steam-bath at 15–20 mm. to a residue. The crude amino ester was taken up in benzene, washed with water, and converted to the hydrochloride as above. The yield of white crystals was 2.5 g. (56%); m. p., 175–176°.

β-Diethylaminoethyl 1-Cyclohexylcyclohexanecarboxylate Hydrochloride (Method D).[19]—A mixture of 20 g. (0.058 mole) of β-diethylaminoethyl 1-phenylcyclohexanecarboxylate hydrochloride, 160 ml. of glacial acetic acid and 0.4 g. of Adams catalyst was shaken with hydrogen at 70–80° under a pressure of 50 pounds till 90–100% of the theoretical amount was absorbed (two to four hours). The mixture was filtered and the acetic acid was removed by vacuum distillation. The residue was recrystallized from butanone to give a white crystalline product melting at 164–166° and weighing 17 g. (80%).

A product obtained from 1-cyclohexylcyclohexyl cyanide by the regular alcoholysis and reësterification procedures melted at 164–166°. A melting point of an equal mixture of substances from the two different reactions was 164–166°.

1,2-Divinylene-1,4,5,6-tetrahydro-5-pyrimidyl 1-Phenylcyclohexanecarboxylate (Method E).—A mixture of



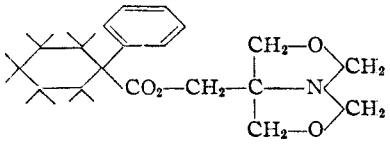
3.5 g. (0.02 mole) of 1,2-divinylene-1,4,5,6-tetrahydro-5-pyrimidyl alcohol hydrochloride,[20] 35 ml. of dry pyridine and 5 g. (0.025 mole) of 1-phenylcyclohexanecarbonyl chloride (prepared in 88% yield from the acid using

(19) British Patent No. 536,211.

(20) Knunyanz, *Ber.*, **68B**, 397 (1935).

thionyl chloride; b. p. 145–148° (11 mm.)) was heated on the steam-bath twelve hours with the exclusion of moisture. The mixture was poured into 500 ml. of water and extracted with 100 ml. of benzene. The benzene solution was subjected to distillation on the steam-bath under a water pump vacuum to remove volatile substances. The residue was converted to the hydrochloride, which was recrystallized from a butanone–ethanol mixture. The yield of white crystals melting at 186–188° was 5 g. (72%).

β-Bis-(Hydroxymethyl)-β-Aminoethyl 1-Phenylcyclohexanecarboxylate Hydrochloride (Method F).—The regular reësterification procedure as described in Method A was carried out using 35 g. (0.15 mole) of ethyl 1-phenylcyclohexanecarboxylate, 44 g. (0.3 mole) of 4-hydroxymethyl-3,4-oxydimethyleneoxazolidine,[21] 200 ml. of xylene and 0.2 g. of sodium. A yield of 21 g. (38%) of a white crystalline oxazolidine hydrochloride melting at 166–168° of the following structure was obtained



Anal. Calcd. for $C_{19}H_{26}O_4NCl$: Cl, 9.63. Found: Cl, 9.60.

A mixture of 5 g. (0.013 mole) of the above amino ester hydrochloride and 300 ml. of distilled water was heated on the steam-bath for twenty-four hours in an open flask. The volume was maintained by the occasional addition of water. The formaldehyde that was formed by hydrolysis of the oxazolidine was totally removed by the end of this period. Finally the water was distilled under vacuum and the residue was recrystallized from butanone to yield 4.2 g. (90%) of a white crystalline hydrochloride melting at 213–214°.

2-Hexahydrobenzoyl-Δ⁴-cyclohexenecarboxylic Acid.—An ether solution of cyclohexylmagnesium bromide was prepared in an 87% yield from 50 g. (0.3 mole) of bromocyclohexane, 10 g. (0.41 mole) of magnesium turnings and 270 ml. of dry ether. This solution was added to 40 g. (0.26 mole) of tetrahydrophthalic anhydride in 400 ml. of a 1:1 mixture of ether and benzene over a period of an hour at about −10°. The mixture was decomposed in the usual manner, and the ether solution was extracted with dilute alkali. Acidification of this aqueous extract gave an oil that could not be crystallized from ether, benzene, or a mixture of these with petroleum ether. However, a crude separation of the diastereoisomers was obtained by cooling a petroleum ether solution of the oil to −20°; 13 g. (18%) of one isomer and, upon evaporation of the ether, 18 g. (25%) of another isomer were obtained. These crude fractionally precipitated acids were then individually converted to the diethylaminoethyl ester hydrochlorides, which gave correct analyses and had different melting points. A mixture of the two hydrochlorides melted lower than either isomer, thus substantiating the assumption that the two above acid fractions were isomeric.

2-Methyl-2-phenylcyclopropanecarboxylic Acid.—A mixture of 25 g. (0.22 mole) of ethyl diazoacetate[22] and 18 g. (0.15 mole) of α-methylstyrene was heated at 130–140° for twelve hours and distilled. At 60–70° (20 mm.), 10 g. of unchanged methylstyrene distilled; at 135–138° (20 mm.), 6 g. (75% based on the recovered methylstyrene) of the desired ester was obtained. The hydrolysis of the ester by refluxing it with 5 g. of potassium hydroxide in 50 ml. of 50% ethanol for three hours gave upon acidification and ether extraction 5 g. (97%) of a crude oil having a neutral equivalent of 173 as compared to a theoretical of 176. The acid was converted to a pure crystalline amino ester by Method B.

β-Diethylaminoethyl 1-Phenylcyclohexanecarboxylate Ethobromide.—A mixture of 10 g. (0.033 mole) of β-diethylaminoethyl 1-phenylcyclohexanecarboxylate and 20 g. of ethyl bromide was heated in a closed container at 80° for twenty-four hours. The solid was recrystallized from butanone to yield 11 g. (82%) of white crystals melting at 158–160°.

Anal. Calcd. for $C_{21}H_{34}O_2NBr$: Br, 19.40. Found: Br, 19.40.

β-Diethylaminoethyl 1-Phenylcyclopentanecarboxylate Ethobromide.—Prepared by the above procedure, the white crystalline product melted at 150–152°.

Anal. Calcd. for $C_{20}H_{32}O_2NBr$: Br, 20.06. Found: Br, 20.00.

2-Benzylcyclohexanecarboxylic Acid.—The Clemmensen reduction of 2-benzoylcyclohexanecarboxylic acid did not prove to be satisfactory. Therefore, because of the availability of 2-benzylbenzoic acid from 2-benzoylbenzoic acid, the following preparation was found convenient. To a solution of 20 g. (0.095 mole) of 2-benzylbenzoic acid[23] in 500 ml. of butanol was added 46 g. (2 mole) of sodium with vigorous stirring and refluxing during a period of thirty minutes. The butanol was removed by steam distillation and the residue was treated with dilute hydrochloric acid. The crude acid was collected at the filter and recrystallized twice from 75–90° petroleum ether. A yield of 5 g. (23%) of white needles melting at 133–135° was isolated.

Anal. Calcd. for $C_{14}H_{16}O_2$: neut. equiv., 218. Found: neut. equiv., 221.

From the mother liquors was obtained 5 g. (23%) of a diastereoisomer melting at 88–92° and having a neutral equivalent of 219. Two such isomers, one melting at 133–134° (*trans*) and the other at 86–88° (*cis*), have been reported isolated from the reaction of 2-benzylcyclohexylmagnesium chloride and carbon dioxide.[24] The diethylaminoethyl ester was prepared from the above higher melting isomer.

γ-Piperidino-β-phenylurethanpropyl 1-Phenylcyclohexanecarboxylate Hydrochloride.—A mixture of 4 g. (0.012 mole) of γ-piperidino-β-hydroxypropyl 1-phenylcyclohexanecarboxylate, 1.6 g. (0.015 mole) of phenyl isocyanate and 100 ml. of dry benzene was refluxed for three hours. Alcoholic hydrochloric acid was added and the mixture was cooled and filtered. The solid hydrochloride thus obtained was recrystallized from butanone to give 1.5 g. (28%) of white crystals melting at 162–164°.

Summary

1. A series of aminoesters of substituted alicyclic carboxylic acids has been prepared, and their antispasmodic and antihistamine activity reported.

2. A method reported in the literature for the cyclization of alkylene dihalides with substituted acetonitriles using sodamide as the condensing agent was modified and increased yields were obtained. The cyanides thus formed were conveniently converted to aminoesters by an alcoholysis and a reësterification procedure.

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(21) British Patent 564,506.

(22) Womack and Nelson, "Organic Syntheses," **24**, 56 (1944).

(23) Barrett, Cook and Nixon, *J. Chem. Soc.*, 504 (1927).

(24) Cook, Hewett and Lawrence, *ibid.*, 71 (1936).

(25) Original manuscript received October 16, 1946.