Pentaacetyl-N-methyl-L-mannosaminic Acid Nitrile.—Dry hydrogen chloride was passed through the ethanolic mother liquor from the preparation of N-methyl-L-glucosaminic acid nitrile[1] (from 100 g. of L-arabinose), while maintaining the temperature near 25° by appropriate cooling, until a maximum precipitation of sirupy material occurred. The supernatant liquor was removed by decantation and the sirup was washed with ether by trituration and decantation. The sirup was placed under reduced pressure until the residual ether and ethanol were removed, whereupon it was acetylated (initial cooling) with acetic anhydride (300 cc.) and pyridine (150 cc.) as described above for the acetylation of N-methyl-L-glucosamine hydrochloride. The sirup obtained on solvent removal was dissolved in 30 cc. of benzene and pentaacetyl-N-methyl-L-glucosaminic acid nitrile (18 g.) separated on nucleation and was removed by filtration. The filtrate was concentrated under reduced pressure to a sirup which was crystallized from benzene-ether-petroleum ether; yield 25 g., m. p. 100–105°. Pure material was obtained on further crystallization from the same solvent mixture and from absolute ethanol; m. p. 111–112°, $[\alpha]^{23}D$ −28° (*c* 3.8, chloroform).

In another experiment, 3.5 g. of a sirup containing the crude product was dissolved in 50 cc. of benzene and placed on a column (80 mm. diam. × 180 mm.) containing 300 g. of Magnesol-Celite (5:1)[9] and developed with 2.5 liters of benzene–ethanol (100:1). The principal zone near the center of the chromatogram was sectioned and eluted with acetone; yield 0.9 g., m. p. 110–112°. After one recrystallization from ethanol the material exhibited the constants: m. p. 112–113.5°, $[\alpha]^{26}D$ −27.5° (*c* 4.1, chloroform).

Anal. Calcd. for $C_{17}H_{24}O_9N_2$: C, 50.99; H, 6.04; N, 7.00. Found: C, 50.85; H, 6.33; N, 7.30.

N-Methyl-L-mannosaminic Acid.—Pentaacetyl-N-methyl-L-mannosaminic acid nitrile (10 g.) was suspended in 20 cc. of 2 *N* hydrochloric acid and heated in a boiling water-bath for thirty minutes. The sirup obtained by solvent removal under reduced pressure was dissolved in water containing 19 g. of barium hydroxide octahydrate and boiled for thirty minutes. The barium ion was then removed as sulfate by the addition of the equivalent amount of sulfuric acid. The filtrate was treated with an excess of silver carbonate to remove the chloride ion and excess silver ion was removed as sulfide. Since decolorizing carbon had been added before each filtration the solution was colorless at this point. Most of the solvent was removed by evaporation under reduced pressure at 50°. Absolute ethanol was added and the material crystallized; yield 0.8 g., m. p. 195° (dec., unreliable). Pure material was obtained on further crystallization from water-ethanol, m. p. 195–197° (dec., unreliable) $[\alpha]^{21}D$ +6.7° (*c*, 2.3, water), $[\alpha]^{22}D$ 0° (initial) → −32° (twenty-four hours) → slowly diminishes (*c* 2.3, 2.5% hydrochloric acid).

Anal. Calcd. for $C_7H_{15}O_6N$: C, 40.18; H, 7.22; N, 6.71. Found: C, 40.04; H, 7.25; N, 6.81.

Hydrolysis of pentaacetyl-N-methyl-L-glucosaminic acid effected in the above-described manner, produced N-methyl-L-glucosaminic acid; m. p. 215–220° (dec., unreliable), $[\alpha]^{25}D$ −5.3° (*c* 3.7, water).

Acknowledgment.—Preliminary experiments on the synthesis of pentaacetyl-N-methyl-D-glucosamine were carried out by Mr. J. M. Berkebile. The assistance of Mr. W. S. Gee is acknowledged. This work was supported in part from funds of The Ohio State University Research Foundation administered by the Graduate School and in part by the Bristol Laboratories, Inc. (Project 224 of The Ohio State University Research Foundation).

Summary

1. The hydrochlorides of N-methyl-L-glucosaminic acid and its nitrile are described.

2. Laboratory details are recorded for the preparation of N-methyl-L-glucosamine hydrochloride from the corresponding acid and for the preparation of its enantiomorph (pentaacetyl derivative) from D-glucosamine—reactions previously cited by Folkers and co-workers.

3. Pentaacetyl-N-methyl-α-L-glucosamine and pentaacetyl-N-methyl-α-D,L-glucosamine have been synthesized.

4. N-Methyl-L-glucosamine is described.

5. N-Methyl-L-mannosaminic acid has been isolated, through its acetylated nitrile, from the cyanohydrin reaction on L-arabinosyl-N-methylamine.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY]

Antispasmodics. I. Cyclopentyl and Δ^2-Cyclopentenyl Substituted Diethylaminoethyl Esters[1]

BY ROBERT BRUCE MOFFETT, CHARLOTTE ANNE HART AND WILLARD M. HOEHN

A search of the literature reveals that very few diethylaminoethyl esters of acids containing the cyclopentyl or Δ^2-cyclopentenyl groups have been prepared. Miescher and Hoffmann[2] mention a few in two patents, but no pharmacological data are given. We have therefore prepared a series of such esters in which the cyclopentyl or Δ^2-cyclopentenyl group is substituted in the alpha position.

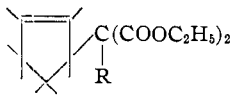
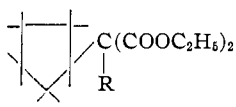
These esters were prepared by refluxing the sodium salt of the corresponding acid with diethylaminoethyl chloride. In most cases the basic ester was distilled under reduced pressure and then converted to the hydrochloride. These diethylaminoethyl esters and their hydrochlorides are listed in Table II with their physical constants. The method of preparation is illustrated in the experimental part by diethylaminoethyl α-(Δ^2-cyclopentenyl)-β-phenylpropionate, and its hydrochloride.

The necessary acids were prepared from the corresponding malonic esters. Considerable difficulty was encountered in the hydrolysis of some of the disubstituted malonic esters, but it was

(1) Presented before the 110th meeting of the Am. Chem. Soc. at Chicago, Ill., September 1946.

(2) Miescher and Hoffmann, U. S. Patents 2,265,184 and 2,265,185 (1941).

TABLE I

R	Malonic esters[6] Yield, %	B. p., °C. mm.		$n^{25}D$	d^{25}_4	Molecular refractivity Calcd.[a]	Found
							
2-Methylallyl	50.6[b]	81	0.025	1.4690	1.0275	76.28	76.00
Δ^2-Cyclohexenyl	53.2	124	.15	1.4900	1.0640	83.32	83.26
Cyclohexyl	21.8	111	.10	1.4795	1.0460	83.79	83.67
Cyclohexylmethyl	56.7	102	.01	1.4774	1.0316	88.41	88.38
2-Cyclohexylethyl	63.0	135	.08	1.4755	1.0182	93.01	93.13
Benzyl	66.6	146	.25	1.5082	1.0820	87.00	87.21
Phenylethyl	10.9	121	.02	1.5022	1.0600	91.62	92.00
α-Hydrindenyl	64.7	170	.45	1.5235	1.1059	94.65	94.04
1-Acenaphthenyl[e]	57.5[f]	170	.06	1.5698[f]	1.1494[f]	104.9	107.9
Furfuryl	52.0	116	.18	1.4857	1.1018	79.87	79.79
							
n-Propyl	99.0[h]	77	0.15	1.4495	1.0024	72.60	72.43
n-Butyl	99.0[i]	81	.02	1.4494	0.99367	77.21	76.82
Allyl	64[j]	80	.14	1.4589	1.0172	72.13	72.11
Δ^2-Cyclopentenyl	66	113	.29	1.4770	1.0553	79.17	78.97
Δ^2-Cyclohexenyl	28	112	.075	1.4907	1.0919	83.8	81.8
Cyclohexyl	..	...	...	....	....	...	...
Cyclohexylmethyl	86.5[m]	111	0.034	1.4845	1.0431	89.17	87.07
2-Cyclohexylethyl	70	115	.01	1.4710	1.0105	93.50	93.64
Benzyl	99[n]	115	.03	1.5018	1.0702	87.47	87.76
Furfuryl	96.5[p]	107	.07	1.4790	1.0925	80.34	80.03

found that by carrying out the hydrolyses in 30% alcoholic potassium hydroxide at 140–150° in a bomb and decarboxylating the crude malonic acids, excellent yields of the acids could be obtained. These acids are listed in Table I with their physical constants and the method for preparing them is illustrated in the experimental part by α-(Δ^2-cyclopentenyl)-β-phenylpropionic acid.

The substituted Δ^2-cyclopentenylmalonic esters were made (with the exception of diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate discussed below, and diethylcyclopentyl-Δ^2-cyclopentenylmalonate prepared as described for the other cyclopentylmalonic esters) by the action of the appropriate alkyl halide on the sodio derivative of diethyl Δ^2-cyclopentenylmalonate.[3] The method used is illustrated by that described in the experimental part for diethyl Δ^2-cyclopentenylbenzylmalonate except that in most cases only a 20–30% excess of alkyl halide was used instead of a 50% excess. The lower molecular weight esters were distilled through an efficient column and the higher molecular weight esters were distilled from a Claisen flask. In some cases the forerun was removed through the column which was then replaced by a simple Claisen head for the distillation of the product.

Diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate was prepared by the reaction of 1,2-dibromocyclohexane on sodio-Δ^2-cyclopentenylmalonic ester in the presence of an excess of sodium ethoxide. This is a modification of the reaction described by Miescher and Hoffmann[4] for diethyl phenyl-Δ^2-cyclohexenylmalonate.

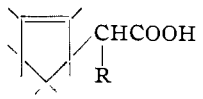
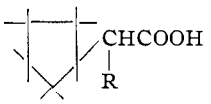
Diethyl cyclopentylmalonate is well known[5] but it has always previously been prepared from a cyclopentyl halide and sodio-malonic ester. Due to the ready availability of dicyclopentadiene from which Δ^2-cyclopentenyl chloride can easily be made,[3] we have found it to be more economical to make diethyl Δ^2-cyclopentenylmalonate first and then hydrogenate it with Adams platinum oxide catalyst at low pressure to diethyl cyclopentylmalonate. Most of the substituted cyclopentylmalonic esters were prepared by alkylating diethyl cyclopentylmalonate with the appropriate alkyl halide in a manner similar to that described in the experimental part for diethyl Δ^2-cyclopentenylbenzylmalonate. In several cases (indicated in Table I) already substituted Δ^2-cyclo-

(3) (a) Noller and Adams, THIS JOURNAL, **48**, 2444 (1926); (b) Perkins and Cruz, *ibid.*, **49**, 518 (1927); (c) Wagner-Jauregg and Arnold, *Ann.*, **529**, 274 (1937); (d) Horclois, *Chimie & industrie*, Special No. 357–63 (April, 1934).

(4) Miescher and Hoffmann, *Helv. Chim. Acta*, **24**, 458 (1941).

(5) Yerwey, *Ber.*, **29**, 1996 (1896); Yohe and Adams, THIS JOURNAL, **50**, 1503 (1928); Shoule, Keltch and Swanson, *ibid.*, **52**, 2440 (1930).

TABLE I (*Continued*)

Yield, %	B. p., °C. (mm.)		$n^{25}D$	d^{25}_4	Empirical formula	Molecular refractivity Calcd.[a]	Found	Neutral equivalent Calcd.	Found
					Substituted acetic acids 				
56[c]	143	7	1.4802	1.0002	$C_{11}H_{16}O_2$	51.41	51.21	180.3	191.6
95	101	0.01	1.5120	1.0600	$C_{13}H_{18}O_2$	58.45	58.40	206.3	208.9
17.3[d]	135	.1	1.4970	1.0345	$C_{15}H_{24}O_2$	58.92	58.92	208.3	211.8
87	109	.04	1.4912	1.0115	$C_{14}H_{22}O_2$	63.54	63.68	222.3	223.1
85.0	141	.05	1.4910	1.0017	$C_{15}H_{24}O_2$	68.16	68.32	236.3	243.4
89.3	134	.04	1.5348	1.0778	$C_{14}H_{16}O_2$	62.13	62.47	216.3	213.6
85	123	.01	1.5300	1.0649	$C_{15}H_{18}O_2$	66.75	66.81	230.3	234.2
94.5	159	.05	1.5558	....	$C_{18}H_{18}O_2$	...	...	242.3	242.6
34.6[g]	185	.006	....	....	$C_{19}H_{18}O_2$	...	...	278.3	281.0
47.6	110	.07	1.5090	1.1239	$C_{12}H_{14}O_3$	55.00	54.78	206.2	208.2
									
80	62	0.002	1.4559	0.9668	$C_{10}H_{16}O_2$	47.73	47.84	170.2	171.5
86	88	.09	1.4555	.9549	$C_{11}H_{20}O_2$	52.35	52.41	184.3	183.8
64.4	80	.13	1.4673	.9898	$C_{10}H_{16}O_2$	47.26	47.40	168.2	168.2
58	100	.082	1.4944	....	$C_{12}H_{16}O_2$	...	...	194.3	202.6
24	130	.15	1.4995	1.0476	$C_{13}H_{20}O_2$	57.82	58.43	208.3	209.3
81[k]	120	.026	1.4870	1.0184[l]	$C_{13}H_{22}O_2$	59.40	59.31	210.3	209.7
98.4	113	.057	1.4978	1.0194	$C_{14}H_{24}O_2$	64.01	64.47	224.3	229.1
96	122	.04	1.4819	0.9833	$C_{15}H_{26}O_2$	68.6	69.1	238.4	242.0
100[o]	122	.02	....	....	$C_{14}H_{18}O_2$	...	...	218.3	221.0[o]
69.4	105	.025	1.4962	1.1010	$C_{12}H_{16}O_3$	55.47	55.27	208.2	208.2

[a] Molecular refractivity calculated from table in Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, 1st ed., 1938, p. 1739. No allowance was made for conjugation, etc. [b] Centolella, Nelson and Kolloff, THIS JOURNAL, **65**, 2091 (1943). [c] Malonic ester hydrolyzed by the use of potassium hydroxide in diethyleneglycol. [d] Malonic ester hydrolyzed by refluxing with 20% aqueous sodium hydroxide. [e] Ring numbered as in *C. A.*, 1944. [f] Values obtained on supercooled liquid. On standing it crystallized and was recrystallized from petroleum solvent (b. p. 69°), m. p. 63–65°. [g] Yield based on recrystallized solid (from acetone), m. p. 125–152°. This is probably a mixture of stereoisomers. [h] Prepared by the hydrogenation of diethyl Δ^2-cyclopentenylallylmalonate. [i] Prepared by the hydrogenation of diethyl Δ^2-cyclopentenyl-*n*-butylmalonate. [j] Shonle, U. S. Patent 1,998,101. [k] Prepared by the low pressure hydrogenation of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid with platinum oxide catalyst. Distillation gave a liquid which crystallized on standihg, m. p. 60.5–63.5°. [l] Value obtained on supercooled liquid at 27°. [m] Prepared by the high pressure hydrogenation of diethyl Δ^2-cyclopentenylbenzylmalonate (see experimental part). [n] Prepared by the low pressure hydrogenation of diethyl Δ^2-cyclopentenylbenzylmalonate. [o] Yield based on distilled product which crystallized in the receiver, m. p. 73–76° (neut. equiv. taken on this material). A sample was recrystallized from petroleum solvent (b. p. 69°), m. p. 75–76.5°. [p] Prepared by the hydrogenation of diethyl Δ^2-cyclopentenylfurfurylmalonate.

pentenylmalonic esters were reduced by a method similar to that described for diethyl cyclopentylmalonate. Similarly diethyl cyclopentyl-(cyclohexylmethyl)-malonate was prepared from diethyl Δ^2-cyclopentenylbenzylmalonate by hydrogenation under high pressure. Diethyl cyclopentyl-Δ^2-cyclohexenylmalonate was prepared from diethyl cyclopentylmalonate, 1,2-dibromocyclohexane and sodium ethoxide by a procedure similar to that described for diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate. All these malonic esters are listed in Table I together with their physical constants.[6]

(6) Most of these malonic esters have been converted to the corresponding barbituric acids by the usual procedure. In all cases the nitrogen analyses gave satisfactory checks with the calculated values. These and other barbituric acids are to be reported in a future communication.

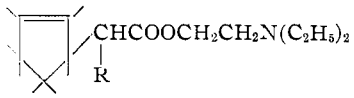
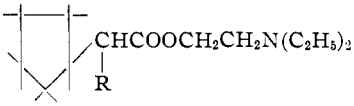
Although many of the compounds herein described may exist in several stereoisomeric forms, no attempt was made to separate them or isolate more than one form. The pharmaceutical data concerned with these compounds are to be published separately; however, the results of preliminary tests are included here (Table II). All these compounds have some degree of antispasmodic action and a few of them have activity of a high order. Diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate hydrochloride appears to have very desirable pharmacological activity.

Experimental

Diethyl Δ^2-Cyclopentenylbenzylmalonate.—To a suspension of 32.2 g. (1.4 moles) of sodium powdered under 275 ml. of dry toluene in a 1 liter three-necked flask was added slowly with vigorous stirring 317 g. (1.4 moles) of

TABLE II

DIETHYLAMINOETHYL ESTERS

R	Yield, %	B. p., °C. (mm.)	Free base $n^{25}D$	d^{25}_4	Molecular refractivity Calcd.[a]	Found
						
Ethyl	79	87	0.06	1.4610	0.93996	74.58	73.96
n-Propyl	75	97	.008	1.4603	.93354	79.20	78.67
n-Butyl	94	116	.03	1.4608	.92899	83.82	83.09
Allyl	..	...	..	....	.....	...	...
2-Methylallyl	54	120	.30	1.4713[f]	.9437	83.35	83.24
Δ^2-Cyclopentenyl	66	110	.15	1.4874	.98890	87.13	84.81
Δ^2-Cyclohexenyl	94	116	.02	1.4912	.....	...	...
Cyclohexyl	51	150	.38	1.4812	.978	90.9	89.4
Cyclohexylmethyl	..	...	..	....	.....	...	...
2-Cyclohexylethyl	..	...	..	....	.....	...	...
Benzyl	79	148	.09	1.5069	1.0024	94.07	93.63
2-Phenylethyl	..	...	..	....	.....	...	...
α-Hydrindenyl	62	180	.93	....	.....	...	...
1-Acenaphthenyl	..	...	..	....	.....	...	...
Furfuryl	..	...	..	....	.....	...	...
						
Ethyl	60.5	88	0.015	1.4540	0.92561	75.05	74.72
n-Propyl	..	...	..	....	.....	...	...
n-Butyl	52	101	.02	1.4548	.91657	84.29	83.87
Allyl	..	...	..	....	.....	...	...
Δ^2-Cyclopentenyl	63.5	105	.06	1.4811	.98042	87.60	85.18
Δ^2-Cyclohexenyl	56	115	.48	1.4858	.....	...	...
Cyclohexyl	87	107	.01	1.4759	.96048	91.33	90.87
Cyclohexylmethyl	63	135	.04	1.4837	.96700	95.95	95.66
2-Cyclohexylethyl	..	...	..	....	.....	...	...
Benzyl	..	...	..	....	.....	...	...
Furfuryl	..	...	..	....	.....	...	...

diethyl Δ^2-cyclopentenylmalonate.[3] The mixture was refluxed gently until practically all the sodium had reacted and then 266 g. (2.1 moles, 50% excess) of benzyl chloride was added at such a rate that the solvent refluxed gently. After the addition was complete the refluxing and stirring were continued and 1-cc. samples were removed from time to time. These were titrated with 0.1 *N* acid and when only a few drops of acid were required or when no change in the basicity occurred during one-half hour the reaction was assumed to be complete. After cooling, enough water was added to dissolve the salt, and the organic layer was separated. After removing most of the solvent and unchanged benzyl chloride, a low boiling forerun (probably largely unchanged Δ^2-cyclopentenylmalonic ester) was removed through an efficient column. The column was then replaced by a Claisen head and the product distilled at 146–150° (0.25 mm.), giving 295 g. (66.6%) of a colorless liquid.

Diethyl Δ^2-Cyclopentenyl-Δ^2-cyclohexenylmalonate.—To a solution of 74 g. (3.2 moles) of sodium in 1.2 liters of absolute ethanol was added 271.2 g. (1.2 moles) of diethyl Δ^2-cyclopentenylmalonate. Most of the alcohol was then distilled off and toluene was added and distilled off until the boiling point reached about 110°. Enough more dry toluene was added to bring the volume to about 800 ml. and then 387.2 g. (1.6 moles) of 1,2-dibromocyclohexane was added slowly. After refluxing for two hours the mixture was cooled, 600 ml. of water was added and the layers were separated. The solvent was removed and the product was distilled through an efficient column giving 202 g. (53.2%) of ester, b. p. 124° (0.15 mm.).

Diethyl Cyclopentylmalonate.—A solution of 113.1 g. (0.5 mole) of diethyl Δ^2-cyclopentenylmalonate in 50 ml. of ethanol was treated with 0.1 g. of Adams platinum oxide catalyst and reduced with hydrogen at about 50 lb. pressure. The reduction was complete in about forty minutes and after removing the catalyst by filtration five runs were combined and the product was distilled giving 568.6 g. (99%) of ester, b. p. 70° (0.18 mm.), $n^{25}D$ 1.4428.

Diethyl Cyclopentyl-(cyclohexylmethyl)-malonate.—A solution of 47.5 g. (0.15 mole) of diethyl Δ^2-cyclopentenylbenzylmalonate made up to 100 ml. with ethanol was reduced in a high pressure bomb in the presence of 0.2 g. of Adams platinum oxide catalyst and a hydrogen pressure of about 1800 lb. At room temperature 0.15 mole of hydrogen was absorbed and then the reaction stopped until the temperature was raised to about 210°. At this temperature approximately 0.45 mole of hydrogen was absorbed during four and one-half hours. The solution was filtered from the catalyst, the solvent was removed, and the product was distilled giving 42 g. (86.5%) of clear colorless liquid, b. p. 111° (0.034 mm.).

TABLE II (*Continued*)

Hydrochloride							Pharmacology	
			Analysis, %					
			Chlorine		Nitrogen			
Yield, %	M. p., °C.	Empirical formula	Cl, calcd.	Cl, found	N, calcd.	N, found[n]	Toxicity[b]	Antispasmodic activity[c]
98	92–98	$C_{15}H_{28}O_2NCl$	12.23	12.18	4.83	4.72		−
90	85–87.5	$C_{16}H_{30}O_2NCl$	11.67	11.65				++++
12	99–101[d]	$C_{17}H_{32}O_2NCl$	11.16	10.90	4.41	4.63	200–250[m]	++
84[e]	63–70	$C_{16}H_{28}O_2NCl$	11.79	11.89	4.64	4.65	120–130	−
63	81–84	$C_{17}H_{31}O_2NCl$	11.15	11.28			70–80	−
52	105–107.5[g]	$C_{16}H_{30}O_2NCl$	10.81	10.89	4.27	4.32		−
96	113–114.5	$C_{19}H_{32}O_2NCl$	10.37	10.42	4.10	3.83	75–85	++++
65	126–128	$C_{19}H_{34}O_2NCl$	10.30	10.36	4.07	4.26	80–90	+
57[e]	114–120	$C_{20}H_{36}O_2NCl$	9.92	10.00	3.91	3.85		−
76[e]	80–86	$C_{21}H_{38}O_2NCl$	9.53	9.66				−
..	104–106	$C_{20}H_{30}O_2NCl$	10.09	9.98	3.98	4.08	105–110	−
40[e]	105.5–111[h]	$C_{21}H_{32}O_2NCl$	9.69	9.82	3.82	3.57	38	+
50	113–122[i]	$C_{22}H_{32}O_2NCl$	9.38	9.21	3.71	3.66	50–60	−
10[e]	97–99[j]	$C_{25}H_{32}O_2NCl$	8.56	8.22	3.38	3.61		+
64[k,e]	69–78[l]	$C_{16}H_{23}O_3NCl$	10.37	10.15				++
85	116–118	$C_{15}H_{30}O_2NCl$	12.15	11.90	4.80	5.04		−
79[e]	104.5–106.5	$C_{16}H_{32}O_2NCl$	11.60	11.59	4.58	4.39	90–100	++++
58	107–108[d]	$C_{17}H_{34}O_2NCl$	11.08	10.91	4.38	4.44	400–425[m]	+++
72[e]	74–88.5	$C_{18}H_{30}O_2NCl$	11.67	11.69	4.61	4.87		−
85.4	112–114	$C_{18}H_{32}O_2NCl$	10.75	10.71	4.25	4.34		−
83	112–115	$C_{19}H_{34}O_2NCl$	10.30	10.41	4.07	3.96		−
93	134–136	$C_{19}H_{36}O_2NCl$	10.25	10.21	4.05	3.99		+
83	114–117	$C_{20}H_{38}L_2NCl$	9.85	9.80	3.89	4.10	220–230[m]	+
85[e]	113–114	$C_{21}H_{40}O_2NCl$	9.48	9.58	3.75	3.61		+
75[e]	120.5–123.5	$C_{20}H_{32}O_2NCl$	10.02	9.99	3.96	4.05		−
67[e]	81–88[l]	$C_{16}H_{30}O_3NCl$	10.31	10.42	4.07	3.93		++

[a] See Table I. [b] Intravenous LD_{50} in mg./kg. in rats. [c] Relative antispasmodic activity tested on isolated muscle at a dilution of 1:8,000,000. [d] Recrystallized from methyl-*i*-butyl-ketone. [e] Calcd. from acid. [f] Taken at 23°. [g] Recrystallized from ethyl alcohol and ether. [h] Recrystallized from toluene. [i] Recrystallized from methyl *n*-amyl ketone. [j] Recrystallized from benzene. [k] Yield on unrecrystallized material. [l] Recrystallized from isopropanol and ether. [m] Intraperitoneal LD_{50} in mg./kg. in mice. [n] Nitrogen analyses by Elizabeth Beard in this Laboratory.

α-(Δ²-Cyclopentenyl)-β-phenylpropionic Acid.—To a solution of 40 g. of potassium hydroxide in 100 ml. of ethanol was added 40 g. of diethyl Δ²-cyclopentenylbenzylmalonate, and the resulting solution was heated in a bomb in an oil-bath at 140–160° for three hours. After cooling, the product was dissolved in about 1 liter of water and washed with ether. The aqueous solution was acidified with hydrochloric acid giving an oil which was taken up in ether, washed thoroughly[7] with water, and dried over sodium sulfate. After removing the ether by distillation the residue was heated in an oil-bath at 180° until no more carbon dioxide was evolved. The acid was then distilled giving 25.5 g. of nearly pure acid which gave a slightly cloudy solution in dilute sodium hydroxide. Its solution in sodium hydroxide was therefore washed with ether and acidified. The oily acid was again taken up in ether, washed thoroughly with water, dried and distilled giving 24.4 g. (91%) of colorless liquid, b. p. 134° (0.04 mm.).

Diethylaminoethyl α-(Δ²-Cyclopentenyl)-β-phenylpropionate.—A solution of 11.6 g. (0.054 mole) of α-(Δ²-cyclopentenyl)-β-phenylpropionic acid in 10 ml. of isopropanol was brought to the neutral point with 25% methanolic sodium methoxide solution, and 7.3 g. (0.054 mole) of diethylaminoethyl chloride[8] was added. The solution was refluxed for three hours, cooled, diluted with ether and filtered from the precipitated salt. After removal of the solvent the amine ester was distilled giving 13.4 g. (79%) of a nearly colorless oil, b. p. 148° (0.09 mm.).

Hydrochloride.—This amine was dissolved in absolute ether and saturated with hydrogen chloride gas. The white crystalline precipitate was collected, washed with ether and dried, m. p. 104–106°.

(7) There is indication that unless all traces of mineral acid are removed the product may lactonize during heating by addition of the carboxyl group to the double bond.[3]

(8) This chloride was prepared by the procedure used by Gilman and Shirley (THIS JOURNAL, **66**, 888 (1944)) for γ-diethylaminopropylchloride.

Summary

1. The diethylaminoethyl esters were made from twenty-five acids with Δ^2-cyclopentenyl or cyclopentyl groups in the alpha position.

2. The intermediate acids were made from the corresponding malonic esters. Many of these malonic esters and acids are hitherto unreported.

3. All the diethylaminoethyl esters were found to have antispasmodic activity, the diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate having desirable activity.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY]

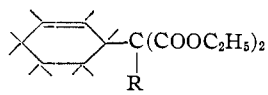
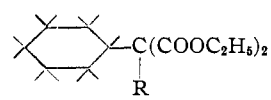
Antispasmodics. II. Cyclohexyl and Δ^2-Cyclohexenyl Substituted Diethylaminoethyl Esters[1]

BY ROBERT BRUCE MOFFETT, CHARLOTTE ANNE HART AND WILLARD M. HOEHN

In the first article of this series[2] we described a series of diethylaminoethyl esters having cyclopentyl or Δ^2-cyclopentenyl groups in the alpha position. Of this series, diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate hydrochloride proved to be a promising antispasmodic. We have therefore prepared another series of diethylaminoethyl esters of acids containing Δ^2-cyclohexenyl and cyclohexyl groups in the alpha position. Miescher and Hoffmann[3] have prepared a few diethylaminoethyl esters of this type but the ones included herein have not been previously reported.

The esters and intermediate acids were prepared by a process similar to that previously described,[2] except that α-cyclohexylcaproic acid was prepared by the hydrogenation of α-(Δ^2-cyclohexenyl)-caproic acid by a process similar to that described in the experimental part for diethyl

TABLE I

R =	Yield, %	B. p., °C. (mm.)	$n^{25}D$	d^{25}_4	Molecular refractivity Calcd.[a]	Found
						
H	65.0[g]	87 (0.11)	1.4595	1.0443	62.89	62.96
Ethyl	69.5[b]	94 (.12)	1.4644	1.0332	72.13	71.72
n-Propyl	63.5	95 (.04)	1.4633	1.0180	76.75	76.44
n-Butyl	59	95 (.09)	1.4638	1.0071	81.37	81.18
Allyl	61[b]	83 (.055)	1.4735	1.0307	76.28	76.37
Δ^2-Cyclohexenyl	54	130 (.22)	1.4942	1.0657	87.94	87.56
Cyclohexyl	10.6	132 (.11)	1.4858	1.0472	88.41	88.36
Cyclohexylmethyl	65	116 (.03)	1.4828	1.0331	93.03	92.98
2-Cyclohexylethyl	65.1	113 (.02)	1.4820	1.0229	97.65	97.89
Benzyl	71.7	152 (.02)	1.5128	1.0766	91.62	92.21
2-Phenylethyl	16.3	132 (.015)	1.5035	1.0610	96.24	96.04
α-Hydrindenyl	65.4[c]	157 (.04)	....	....	...	...
Furfuryl	69	124 (.05)	1.4911	1.1035	84.49	84.10
						
Ethyl	80	76 (.02)	1.4545	1.0140	72.60	72.27
n-Butyl	..	.....	....	....	...	...
2-Cyclohexylethyl	56.3	143 (.07)	1.4740	1.0092	98.12	98.18
Benzyl	61.6	132 (.04)	1.5031	1.0627	92.09	92.48
α-Hydrindenyl	65.6[i]	156 (.03)	....	....	...	...

(1) Presented before the 110th meeting of the Am. Chem. Soc. at Chicago, Ill., September 1946.

(2) Moffett, Hart and Hoehn, THIS JOURNAL, **68**, 1849 (1946).

(3) Miescher and Hoffmann, *Helv. Chim. Acta*, **24**, 458 (1941); U. S. Patents 2,265,184 and 2,265,185.