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.

KANSAS CITY, MISSOURI RECEIVED SEPTEMBER 28, 1946

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

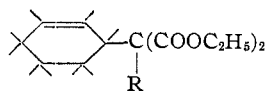
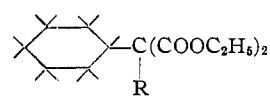
Antispasmodics. II. Cyclohexyl and Δ^2-Cyclohexenyl Substituted Diethylaminoethyl Esters[1]

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.

cyclohexylethylmalonate. The necessary substituted Δ^2-cyclohexenylmalonic esters were made by alkylating the sodio-derivative of diethyl Δ^2-cyclohexenylmalonate[4] with the corresponding alkyl halides. Likewise most of the substituted cyclohexylmalonic esters were made by alkylating diethyl cyclohexylmalonate. Diethyl cyclohexylethylmalonate, however, was prepared by hydrogenating diethyl Δ^2-cyclohexenylethylmalonate at low pressure with Adams catalyst.

The general process is illustrated in the experimental part by the preparation of diethylaminoethyl α-(Δ^2-cyclohexenyl)-γ-cyclohexylbutyrate hydrochloride. Although it is possible for many of these compounds to exist in several stereoisomeric forms, no attempt was made to separate them or to isolate more than one form. The substituted malonic esters[5] and acetic acids are listed with their physical properties in Table I and the diethylaminoethyl esters and their hydrochlorides are listed in Table II.

The pharmaceutical data concerning these compounds is to be published separately. The results of preliminary tests, however, are included here (Table II). All these compounds have some degree of antispasmodic action, none, however, equals diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate hydrochloride.[2]

(4) Buu-Hoï and Cagniant, *Bull. soc. chim.*, **9**, 99 (1942).

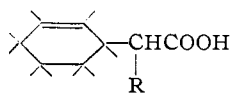
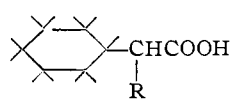
(5) Most of these malonic esters have been converted to the corresponding barbituric acids by the usual procedure. In all cases the nitrogen analyses gave satisfactory checks with the calculated values. These and other barbituric acids are to be reported in a future communication.

Experimental

Diethyl Δ^2-Cyclohexenylmalonate.—To a solution of 184 g. (8 moles) of sodium in 2.8 liters absolute ethanol was added 641 g. (4 moles) of diethylmalonate and then 968 g. (4 moles) of 1,2-dibromocyclohexane was slowly run in. After refluxing for six hours the mixture was practically neutral. Most of the alcohol was then removed by distillation and the residue was diluted with 1 liter of water. The layers were separated and the organic layer was distilled from a Claisen flask. The fraction distilling at 88–130° (0.1 mm.) was redistilled through an efficient column, giving 625 g. (65%) of a colorless liquid, b. p. 87° (0.11 mm.), $n^{25}D$ 1.4595; d^{25}_4 1.0443.

Diethyl Δ^2-Cyclohexenyl-(2-cyclohexylethyl)-malonate.—To a suspension of 4.6 g. (0.2 mole) of powdered sodium

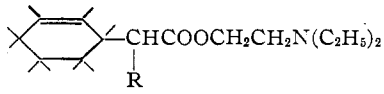
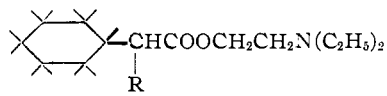
TABLE I (*Continued*)

Yield, %	B. p., °C. (mm.)	$n^{25}D$	d^{25}_4	Substituted acetic acids: Empirical formula	Molecular refractivity: Calcd.[a]	Molecular refractivity: Found	Neutral equivalent: Calcd.	Neutral equivalent: Found
								
..	.....	....	....	.....	...	...	...	...
83	76 (0.01)	1.4783	1.0141	$C_{10}H_{16}O_2$	47.26	46.98	168.2	168.4
76	100 (.03)	1.4777	0.99640	$C_{11}H_{18}O_2$	51.88	51.75	182.3	182.3
70	102 (.006)	1.4770	.98178	$C_{12}H_{20}O_2$	56.50	56.49	196.3	195.6
96.5	85 (.007)	1.4910	1.0136	$C_{11}H_{16}O_2$	51.41	51.48	180.2	183.2
81.5	140 (.17)	1.5185	1.0600	$C_{14}H_{20}O_2$	63.07	63.03	220.3	219.6
74	123 (.027)	....	....	$C_{14}H_{22}O_2$	...	...	222.3	225.9
91.9	113 (.01)	1.5000	1.0189	$C_{15}H_{24}O_2$	68.16	68.22	236.3	237.9
94.4	128 (.007)	1.4980	1.0055	$C_{16}H_{26}O_2$	72.78	72.99	250.4	251.2
94.5	138 (.04)	1.5394	1.0780	$C_{15}H_{18}O_2$	66.75	66.98	230.3	232.7
97.3	126 (.01)	1.5350	....	$C_{16}H_{20}O_2$	...	...	244.3	243.8
94.0	157 (.02)	....	....	$C_{17}H_{20}O_2$	...	...	256.3	260.1
62	111 (.03)	1.5140	1.1153	$C_{13}H_{16}O_3$	58.62	59.46	220.3	225.0
								
76.7[d]	107 (0.014)	1.4627	....	$C_{10}H_{18}O_2$	...	...	170.2	170.8
85[e,f]	98 (.02)	1.4649	0.96267	$C_{12}H_{22}O_2$	56.97	56.94	198.3	199.0
92.6	142 (.02)	1.4875	.9872	$C_{16}H_{28}O_2$	73.25	73.61	252.4	254.9
93[g]	126 (.005)	1.5251[h]	....	$C_{15}H_{20}O_2$	...	...	232.3	235.0
96	170 (.13)	....	....	$C_{17}H_{22}O_2$	...	...	258.3	255.3

[a] Molecular refractivity calculated from table in Gilman "Organic Chemistry, An Advanced Treatise," 1st ed., John Wiley and Sons, New York, N. Y., 1938, p. 1739. [b] Schulemann & Meisenburg, U. S. Patent 1,690,796. [c] On standing this ester crystallized. A sample was recrystallized from petroleum solvent (b. p. 69°), m. p. 80–90°. [d] Product was a solid melting at 52–55°. Leverne, Mikeska and Passoth, *J. Biol. Chem.*, **88**, 27 (1930). [e] Prepared by hydrogenation of α-(Δ^2-cyclohexenyl)-caproic acid. [f] Braun and Kurtz, *Ber.*, **70B**, 1224 (1937). [g] On standing the distilled product crystallized and a sample was recrystallized from petroleum solvent (b. p. 69°) m.p. 71–72°. Schwenk, Papa, Whitman and Ginsberg (*J. Org. Chem.*, **9**, 175 (1944)) prepared this acid by reducing α(Δ^1-cyclohexenyl)-cinnamic acid. [h] Index of fraction taken on super-cooled liquid. [i] On standing the distilled product crystallized and was recrystallized from petroleum solvent (b. p. 30–40°), m. p. 69.5–71.5°.

TABLE II

DIETHYLAMINOETHYL ESTERS

R =	Yield, %	Free base: B. p., °C. (mm.)	$n^{25}D$	d^{25}_4	Molecular refractivity: Calcd.[a]	Found
						
Ethyl	85	92 (0.04)	1.4672	0.94787	79.20	78.30
n-Propyl	72	94 (.025)	1.4674	.93998	83.82	83.14
n-Butyl	68	118 (.2)	1.4670	.93350	88.44	87.82
Allyl	..	.....	....	....	...	...
Δ^2-Cyclohexenyl	78	105 (.032)	1.4968	.98866	95.01	94.52
Cyclohexyl	..	.....	....	.....	...	...
Cyclohexylmethyl	..	.....	....	.....	...	...
2-Cyclohexylethyl	..	.....	....	.....	...	...
Benzyl	..	.....	....	.....	...	.
2-Phenylethyl	52	145 (.05)	1.5104	.....	...	...
α-Hydrindenyl	..	.....	....	.....	...	...
Furfuryl	..	.....	....	.....	...	...
						
Ethyl	86.5	98 (0.04)	1.4580	0.93021	79.67	79.03
n-Butyl	86	110 (.05)	1.4590	.92112	88.91	88.29
2-Cyclohexylethyl	..	.....	....	.....	...	...
Benzyl	..	.....	....	.....	...	...
α-Hydrindenyl	..	.....	....	.....	...	...

in 40 ml. of dry toluene was slowly added 48 g. (0.2 mole) of diethyl Δ^2-cyclohexenylmalonate. The mixture was refluxed until practically all the sodium had dissolved and then 48 g. (0.25 mole) of 2-cyclohexylethyl bromide was slowly added. After refluxing five hours the solution was nearly neutral. The mixture was cooled, sufficient water was added to dissolve the salt and the layers were separated. The organic layer was distilled from a Claisen flask, giving 45.7 g. (65.1%) of colorless liquid, b. p. 113° (0.02 mm.).

α-(Δ^2-Cyclohexenyl)-γ-cyclohexylbutyric Acid.—A solution of 35 g. (0.1 mole) of diethyl Δ^2-cyclohexenyl-(2-cyclohexylethyl)-malonate and 40 g. of potassium hydroxide in 100 ml. of ethanol was heated in a bomb at 140–160° for three hours. After cooling, the product was dissolved in 1 liter of water, extracted with ether and acidified with hydrochloric acid. The acid was taken up in ether, thoroughly washed with water and dried over sodium sulfate. After removal of the ether, the residue was heated at 180° until no more carbon dioxide was evolved and then distilled. A yield of 24.4 g. of material distilling at 132–150° (0.01 mm.) was obtained. This was dissolved in dilute sodium hydroxide, washed with ether, reacidified, taken up in ether, washed with water and dried over sodium sulfate. After removing the ether, the product was redistilled giving 23.4 g. (94.4%) of colorless liquid, b. p. 128° (0.007 mm.).

Diethyl Cyclohexylethylmalonate.—Three hundred and five grams (1.136 moles) of diethyl Δ^2-cyclohexenylethylmalonate was hydrogenated at room temperature and 50 lb. pressure in three portions. Each portion contained 50 ml. of ethanol and 0.2 g. of Adams platinum oxide catalyst. The combined product, after removal of the solvent and a small forerun, was distilled giving 243.4 g. (80%) of colorless liquid, b. p. 76° (0.02 mm.).

Diethylaminoethyl α-(Δ^2-Cyclohexenyl)-γ-cyclohexylbutyrate Hydrochloride.—A solution of 21.9 g. (0.0876 mole) of α-(Δ^2-cyclohexyl)-γ-cyclohexylbutyric acid in 15 ml. of isopropanol was brought to the neutral point with 25% methanolic sodium methoxide solution, and 11.9 g. (0.0876 mole) of diethylaminoethyl chloride was added. After refluxing for three hours, the solution was cooled, diluted with ether, and filtered from the precipitated salt. The crude base was converted to its hydrochloride by saturating the ether solution with hydrogen chloride. On decanting the ether and rubbing the amorphous hydrochloride with fresh dry ether it crystallized; yield 23.3 g. (69%), m. p. 99–107.5°.

Summary

1. The diethylaminoethyl esters were prepared from seventeen acids containing Δ^2-cyclohexenyl or cyclohexyl groups in the alpha position.

2. The intermediate acids were made from the corresponding malonic esters, many of which are herein reported for the first time.

3. All the diethylaminoethyl esters were found to have antispasmodic activity.

TABLE II (*Continued*)

Yield (from free base)	M. p., °C.	Hydrochloride: Empirical formula	Analyses, %: Cl, Calcd.	Cl, Found	N, Calcd.	N[i], Found	Pharmacology: Toxicity[b]	Antispasmodic activity[c]
93	89–91	$C_{16}H_{30}O_2NCl$	11.66	11.59	4.61	4.51		−
94	95.5–98	$C_{17}H_{32}O_2NCl$	11.15	11.02	4.41	4.30		+
85	103–104.5	$C_{18}H_{34}O_2NCl$	10.68	10.60	4.22	4.14	250–275[h]	+
54[d]	70–76	$C_{17}H_{30}O_2NCl$	11.23	11.00			80–90	+++
95	126–128.5	$C_{20}H_{34}O_2NCl$	9.96	9.90	3.94	3.93		−
56[d]	129.5–132.5	$C_{20}H_{36}O_2NCl$	9.91	9.97	3.91	3.85		−
89[d]	130–135	$C_{21}H_{38}O_2NCl$	9.53	9.53	3.77	3.62	135–145	++
69[d]	99–107.5	$C_{22}H_{40}O_2NCl$	9.19	9.14	3.63	3.45	125–135	−
68[d]	119–125	$C_{21}H_{32}O_2NCl$	9.69	9.63	3.83	3.70	60–70	−
90	109–113	$C_{22}H_{34}O_2NCl$	9.33	9.45	3.69	3.42		+
74[d]	87–98	$C_{23}H_{34}O_2NCl$	9.05	9.00	3.57	3.49	45–55	−
60[d]	82–98[e]	$C_{19}H_{30}O_3NCl$	9.97	10.12	3.94	3.27		++
80	94.5–97	$C_{16}H_{32}O_2NCl$	11.59	11.59	4.58	4.53		−
88	108–110	$C_{18}H_{36}O_2NCl$	10.62	10.58	4.20	4.12	225–250[h]	+
70[d]	120–130	$C_{22}H_{42}O_2NCl$	9.15	9.17	3.61	3.80		−
84[d]	137–140.5	$C_{21}H_{34}O_2NCl$	9.64	9.74	3.81	3.96		−
45[f,d]	122–127[g]	$C_{23}H_{36}O_2NCl$	9.00	8.92	3.58	3.44	60–70	++

[a] See (a) Table I. [b] Intravenous LD_{50}, in mg./kg. in rats. [c] Relative antispasmodic activity tested on isolated muscle, at a dilution of 1:3,000,000. [d] Calcd. from starting acid. [e] Recrystallized from isopropanol and ether. [f] Yield of unrecrystallized material. [g] Recrystallized from methyl isobutyl ketone. [h] Intraperitoneal LD_{50} in mg./kg. in mice. [i] Nitrogen analysis by Elizabeth Beard in this Laboratory.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Diamino Ketones. IV.[1] Addition and Cleavage with Grignard Reagents

BY NORMAN H. CROMWELL

Several years ago it was reported[2] from this Laboratory that α,β-dimorpholinobenzylacetone reacted with phenylmagnesium bromide to give a fair yield of the carbinol, 2,4-diphenyl-3,4-dimorpholinobutanol-2, and that the corresponding α,β-dimorpholinobenzylacetophenone reacted with methylmagnesium iodide to give the same carbinol, but in very low yields.

The present communication reports an extension of the investigation of the reactions of these more or less hindered carbonyl compounds with Grignard reagents. It was recognized in the earlier investigation[2] that lower molecular weight products were being formed in these reactions, resulting possibly from cleavage of the aliphatic chain of the diamino ketones. Since E. P. Kohler had reported cleavage reactions when 1,3-diketones[3] and epoxy ketones[4] were treated with Grignard reagents, it seemed important to attempt to relate the behavior of the diamino ketones to these compounds. Furthermore, since some of the diamino ketones which have been prepared in these studies have been found to possess mild avian antimalarial activity[5] it was important to search for ways to convert them into derivatives that might be expected to be more soluble and more active as antimalarials.

Ethylmagnesium bromide and methylmagne-

(1) Previous paper in this series: Cromwell and Hoeksema, THIS JOURNAL, **67**, 124 (1945).

(2) Cromwell, *ibid.*, **62**, 3470 (1940).

(3) Kohler and Erickson, *ibid.*, **53**, 2301 (1931).

(4) Kohler, Richtmyer and Hester, *ibid.*, **53**, 205 (1931).

(5) For the antimalarial activities of the various amino ketones and derivatives that have been reported in these several series of papers, see "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor, to be published soon.