[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY[1]]

ANTISPASMODICS. IV. TERTIARY AMINOALKYL ESTERS OF Δ^2-CYCLOHEXENYL SUBSTITUTED ACETIC ACIDS

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In Part II (1) of this series are reported a number of β-diethylaminoethyl esters of acetic acids substituted in the α-position by a Δ^2-cyclohexenyl group. In this work the series is extended and esters of other basic alcohols are included.

The methods used in these preparations are for the most part very similar to those already reported (1, 2, 3). These methods involved the synthesis of the necessary acids through malonic or cyanoacetic ester syntheses, and then their esterification by the appropriate tertiary amino alcohols. In the preparation of the malonic esters (Table I) the Δ^2-cyclohexenyl group was introduced first, while in the case of the cyanoacetic esters the alkyl group was introduced first. Unless otherwise stated, the hydrochlorides of the amino esters (Table III) were recrystallized from methyl isobutyl ketone.

Preliminary pharmacological screening in these laboratories, indicates that these compounds all have some degree of antispasmodic activity. However, only β-diethylaminoethyl Δ^2-cyclohexenylisoamylacetate hydrochloride can be considered very highly active. The series of + and − signs (Table III) indicates the relative activities, ++++ being highly active and −− being inactive at dilutions of 1:8,000,000. A ++++ rating is the equivalent of about 0.1 the activity of atropine sulfate.

We are indebted to Dr. Willard M. Hoehn, Director of these laboratories, for valuable help and guidance in this work. The nitrogen analyses are by Miss Elizabeth Beard in these laboratories, and the carbon and hydrogen analyses are by Micro-Tech Laboratories, Skokie, Illinois.

EXPERIMENTAL

Ethyl Δ^2-Cyclohexenyl-sec-butylcyanoacetate. To sodium ethoxide, prepared in a 1-l. flask from 36.8 g. (1.6 moles) of sodium and 600 ml. of absolute ethanol, was added 127 g. (0.75 mole) of ethyl *sec*-butylcyanoacetate (4), and then 194 g. (0.8 mole) of 1,2-dibromocyclohexane. After refluxing for 3½ hours, a 1-ml. sample used only 0.7 ml. of 0.1 *N* acid for neutralization. Most of the solvent was removed by distillation, water was added, and the layers were separated. The aqueous solution was extracted with ether which was added to the ester and washed with saturated salt solution. After removing the solvent, the product was distilled, first from a Claisen flask, and then through a 12-inch column packed with ⅛-inch glass helices, giving 110.2 g. (59%) of nearly colorless liquid.

Δ^2-Cyclohexenylisobutylacetonitrile.[3] During the preparation of ethyl Δ^2-cyclohexenylisobutylcyanoacetate, by a method essentially similar to that described above, a fraction

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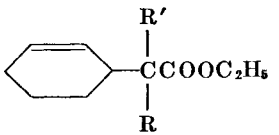
TABLE I

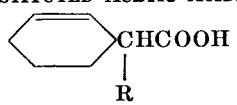
Malonic and Cyanoacetic Esters



R	R′	Yield, %	B.P., °C.	Mm.	n_D^{25}	d_4^{25}	Empirical formula	Molecular refractivity		Analysis, N	
								Calc'd	Found	Calc'd	Found
$CH_3CH(CH_3)$—	—$COOC_2H_5$	30.	83	0.022	1.4675	1.0265	$C_{16}H_{26}O_4$	76.74	76.40	—	—
$CH_3CH(CH_3)CH_2$—	—CN	20.	92	.05	1.4727	0.9913	$C_{15}H_{23}NO_2$	70.23	70.52	5.62	5.48
$CH_3CH_2CH(CH_3)$—	—CN	59.	94	.02	1.4750	1.0015	$C_{15}H_{23}NO_2$	70.23	69.88	5.62	5.42
$CH_3CH(CH_3)CH_2CH_2$—	—$COOC_2H_5$	48.5	97	.02	1.4643	0.9993	$C_{18}H_{30}O_4$	86.00	85.77	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	42.4	98	.018	1.4648	1.0071	$C_{18}H_{30}O_4$	86.00	85.64	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	55.	101	.05	1.4750	0.9882	$C_{16}H_{25}NO_2$	74.85	74.87	5.32	5.13
$CH_3CH(CH_3)CH(CH_3)$—	—CN	59.5	96	.045	1.4778	.9974	$C_{16}H_{25}NO_2$	74.85	74.73	5.32	5.29
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	47.5	106	.026	1.4684	.9984	$C_{19}H_{32}O_4$	90.63	90.35	—	—

TABLE II

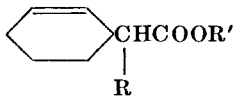
Substituted Acetic Acids



R	Yield, %	B.P., °C.	Mm.	n_D^{25}	d_4^{25}	Empirical formula	Molecular refractivity		Neutral equivalent	
							Calc'd	Found	Calc'd	Found
$CH_3CH(CH_3)$—	96.4	90	0.048	1.4783	0.9968	$C_{11}H_{18}O_2$	51.87	51.78	182.3	179.9
$CH_3CH(CH_3)CH_2$—	85.	110	.013	1.4754	.9810	$C_{12}H_{20}O_2$	56.50	56.37	196.3	198.1
$CH_3CH_2CH(CH_3)$—	68.8	92	.01	1.4800	.9912	$C_{12}H_{20}O_2$	56.50	56.25	196.3	197.9
$CH_3CH(CH_3)CH_2CH_2$—	100.	104	.07	1.4746	.9669	$C_{13}H_{22}O_2$	61.13	61.19	210.3	208.2
$CH_3CH_2CH(CH_3)CH_2$—	90.8	103	.03	1.4758	.9715	$C_{13}H_{22}O_2$	61.13	61.04	210.3	207.4
$CH_3(CH_2)_2CH(CH_3)$—	60.	106	.046	1.4790	.9778	$C_{13}H_{22}O_2$	61.13	60.99	210.3	213.8
$CH_3CH(CH_3)CH(CH_3)$—	15.4	108	.04	1.4806	—	$C_{13}H_{22}O_2$	—	—	210.3	206.6
$CH_3CH_2CH(C_2H_5)CH_2$—	97.6	111	.026	1.4775	.9660	$C_{14}H_{24}O_2$	65.76	65.67	224.3	224.1

TABLE III

Esters of Amino Alcohols



R	R'	FREE BASE											HYDROCHLORIDE				
		Method of Preparation[a]	Yield, %	B.p., °C.	MM.	n_D^{25}	d_4^{25}	Empirical Formula	Molecular Refractivity Calc'd	Molecular Refractivity Found	Analysis N Calc'd	Analysis N Found	Yield, %	M.p., °C.	Analysis Cl Calc'd	Analysis Cl Found	Antispasmodic Activity[f]
$CH_3CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	87.0	122	0.5	1.4700	0.9414	$C_{17}H_{31}NO_2$	83.86	83.41	4.98	4.98	88.	102–104	11.15	10.81	+
$CH_3CH(CH_3)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	43.9	108	.01	1.4669	.9305	$C_{18}H_{33}NO_2$	88.48	88.08	4.74	4.67	46.	116–118	10.68	10.31	+++
$CH_3CH_2CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	—	109	.04	1.4701	.9428	$C_{18}H_{33}NO_2$	88.48	87.46	4.74	4.83	24.	105–110	10.69	11.19	+
$CH_3CH(CH_3)CH_2CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	54.2	109	.029	1.4660	.9285	$C_{19}H_{35}NO_2$	93.06	92.41	4.52	4.44	56.4	101–105	10.25	10.32	++++
$CH_3CH(CH_3)CH_2CH_2$—	$(CH_3)_2NCH_2CH_2$—	B	89.	93	.015	1.4665[b]	.9373[b]	$C_{17}H_{31}NO_2$	83.82	83.23	4.98	4.75	46.4	114–115	11.12	10.93	−
$CH_3CH(CH_3)CH_2CH_2$—	$CH_2(CH_2)_4NCH_2$- CH_2—	B	76.6	130	.01	1.4832[b]	.9768[b]	$C_{20}H_{35}NO_2$	95.48	94.00	4.36	4.29	76.4	157–159	9.91	9.94	+
$CH_3CH_2CH(CH_3)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	46.2	110	.025	1.4664	.9324	$C_{19}H_{35}NO_2$	93.06	92.04	4.52	4.48	82.7	102–104	10.25	10.48	−
$CH_3(CH_2)_2CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	80.4	130	.5	1.4695	.9319	$C_{19}H_{35}NO_2$	93.06	92.70	4.52	4.32	74.1[c]	102–107	10.24	10.41	−
$CH_3CH(CH_3)CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	B	—	124	.15	1.4720[b]	.9454[b]	$C_{19}H_{35}NO_2$	93.06	91.66	4.52	4.46	73.3	128–132	10.25	10.16	+
$CH_3CH_2CH(C_2H_5)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	B	70.	114	.016	1.4690[b]	.9358[b]	$C_{20}H_{37}NO_2$	97.08	96.28	4.33	4.49	78.7[d]	100–102	9.85	10.08	+
$CH_3CH(CH_3)CH_2$—and C_6H_{11}[e]	$(C_2H_5)_2NCH_2CH_2$—	A	76.3	112	.07	1.4597	.9174	$C_{18}H_{35}NO_2$	88.95	88.84	4.71	4.51	89.	134–135	10.62	10.96	+

[a] Examples of Methods A and B are given in the foregoing article (3). [b] Determined by Miss Elizabeth Beard, in these laboratories. [c] This separated from absolute ether in crystalline form and was not recrystallized. [d] Recrystallized from ethyl acetate. [e] Cyclohexyl in place of Δ^2-cyclohexenyl. [f] Tested on isolated intestinal muscle, stimulated by acetylcholine (1:5,000,000). The activities are estimated for dilutions of 1:8,000,000 of the compounds being tested.

was isolated by distillation through an efficient column which proved to be this nitrile, b.p. 65° (0.06 mm.); n_D^{25} 1.4720, d_4^{25} 0.91075.

Anal. Calc'd for $C_{12}H_{19}N$: M_D, 54.79; N, 7.92.
Found: M_D, 54.51; N, 8.09.

This nitrile doubtless arose through hydrolysis and decarboxylation of the desired ester during the working up of the product.

The acetonitrile could be hydrolyzed under the usual conditions to give Δ^2-cyclohexenylisobutylacetic acid (Table II).

Cyclohexylisobutylacetic acid.[3] This was prepared in 55% yield by the low pressure hydrogenation of Δ^2-cyclohexenylisobutylacetic acid using Adams' catalyst; b.p. 98° (0.025 mm.); n_D^{25} 1.4651; d_4^{25} 0.9604.

Anal. Calc'd for $C_{12}H_{22}O_2$: M_D, 56.97; N.E., 198.3.
Found: M_D 57.09; N.E., 199.8.

Δ^2-Cyclohexenylisoamylacetyl chloride. A solution of 44 g. (0.21 mole) of Δ^2-cyclohexenylisoamylacetic acid in 36.3 ml. of thionyl chloride was warmed at 50° until the reaction was complete. The excess thionyl chloride was removed *in vacuo*, and the product was distilled, b.p. 85° (0.07 mm.), giving 45 g. (94%) of colorless liquid; n_D^{25} 1.4800, d_4^{25} 1.0017.

Anal. Calc'd for $C_{13}H_{21}ClO$: M_D, 64.35; Cl, 15.51.
Found: M_D, 64.88; Cl, 15.89.

SUMMARY

1. The preparation and properties are reported for eleven new esters of tertiary aminoalcohols, ten of which contain the Δ^2-cyclohexenyl group in the alpha position.

2. Many new substituted acetic acids and malonic and cyanoacetic esters were prepared as intermediates.

3. Preliminary tests for antispasmodic activity are reported for the hydrochlorides of these basic esters, and one of them appears to be highly active.

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(3) MOFFETT, HART, AND NEIL, *J. Org. Chem.*, **15**, preceding paper.
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[3] Prepared by Miss Charlotte Anne Hart in these laboratories.