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

ANTISPASMODICS. III.[2] TERTIARY AMINOALKYL ESTERS OF CYCLOPENTYL AND Δ^2-CYCLOPENTENYL SUBSTITUTED ACETIC ACIDS

ROBERT BRUCE MOFFETT,[3] CHARLOTTE ANNE HART,[4] AND JANICE NEIL

Received September 6, 1949

In Part I (2) of this series it was found that β-diethylaminoethyl esters of aliphatic acids substituted in the α-position by cyclopentyl or Δ^2-cyclopentenyl groups are active antispasmodics. In this paper the preparation and properties of more of these esters, as well as esters of other tertiary amino alcohols, are reported. The methods of preparation by way of the corresponding malonic esters and substituted acetic acids are similar to those described previously. In some cases where the malonic esters were difficult to prepare because of the steric hindrance of the groups involved, cyanoacetic esters were made instead. Monosubstituted cyanoacetic esters were made by the excellent method of Alexander and Cope (3), whereby an aldehyde or ketone is condensed with ethyl cyanoacetate and hydrogenated in one operation. The sodio derivatives of the monosubstituted cyanoacetates were alkylated with Δ^2-cyclopentenyl chloride to give the desired disubstituted cyanoacetates.

These cyanoacetic esters could be prepared in considerably better yields than the corresponding malonic esters, but this advantage was offset by the difficulty of hydrolysis and decarboxylation to the corresponding substituted acetic acids. Whereas the malonic esters usually yielded 85% to 95% of the desired acid, when hydrolyzed with 30% alcoholic potassium hydroxide in a bomb at 140–150° for three hours, the cyanoacetic esters gave only about 30% to 70% of the desired acid when heated with 50% alcoholic potassium hydroxide at 160–180° for forty hours. Most of the remaining material proved to be the corresponding substituted acetamides. More drastic conditions of hydrolysis led to decomposition.

The cyclopentyl-malonic and -cyanoacetic esters were prepared, with the exception of diethyl cyclopentyl-(2-methylallyl)malonate, by the hydrogenation of the corresponding Δ^2-cyclopentenyl-malonic or -cyanoacetic esters, under low pressure unless otherwise indicated. Diethyl cyclopentyl-(2-methylallyl) malonate was made by alkylating the sodio derivative of cyclopentylmalonic ester with 2-methylallyl chloride.

The esters of the tertiary amino alcohols were prepared by two methods. Method A is essentially that described previously (1, 2), whereby the sodium salt of the acid was allowed to react with a chloroalkylamine. Method B involves

[1] The functions of the George A. Breon and Company laboratories have been assumed by the Sterling-Winthrop Research Institute, Rensselaer, N. Y., and any requests for reprints should be addressed there. Other inquiries may be addressed to the first author.

[2] For Part II of this series see reference (1).

[3] Present address: The Upjohn Company, Kalamazoo, Michigan.

[4] Present address: Parke, Davis and Company, Detroit, Michigan.

the preparation of the acid chlorides, which were isolated in several instances, followed by their reaction with the amino alcohols. Either method usually gave good yields of the distilled free amino esters which were converted to their hydrochlorides in absolute ether by hydrogen chloride. In most cases, these hydrochlorides needed no further purification, but, nevertheless, some of them (noted in Table III) were recrystallized, usually from methyl isobutyl ketone. When low yields of hydrochlorides are reported in Table III, it is usually due either to the fact that some of the hydrochlorides were appreciably soluble in absolute ether containing an excess of hydrogen chloride, or failure to work up the filtrates from recrystallization.

Preliminary pharmacological screening in these laboratories indicates that these compounds all have some antispasmodic activity. However, only β-diethylaminoethyl Δ^2-cyclopentenyl-(1,2-dimethylpropyl)acetate hydrochloride and β-diethylaminoethyl cyclopentylisobutylacetate hydrochloride can be considered highly active. The series of + and − signs (Table III) indicate 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, hydrogen, and sulfur analyses are by Micro-Tech Laboratories, Skokie, Illinois.

EXPERIMENTAL

The specific examples given below illustrate the general methods used in this work. Any exceptions are listed in the footnotes of the tables.

Diethyl Δ^2-cyclopentenyl-(2-methylbutyl)malonate. To 23 g. (1 mole) of sodium, melted under 200 ml. of dry toluene in a 1-l. flask, was slowly added, with vigorous stirring (with a Hershberg wire stirrer), 226.3 g. (1 mole) of diethyl Δ^2-cyclopentenylmalonate. The mixture was refluxed until practically all the sodium had reacted, and then 181 g. (1.2 moles) of 2-methylbutyl bromide was added. After refluxing for thirteen hours, a 1-cc. sample titrated with 0.1 *N* acid required 0.9 cc. of the acid for neutralization. The reaction mixture was cooled and neutralized with acetic acid. Enough water was added to dissolve the salt, and the organic layer was separated. After removing the solvent, the product was distilled, first from a modified Claisen flask, and then through a twelve-inch fractionating column packed with 1/8-inch glass helices, giving 138 g. (46.6%) of nearly colorless liquid.

Ethyl (1,2-dimethylpropyl)cyanoacetate. A mixture of 56.6 g. (0.55 mole) of methyl isopropyl ketone, 6 ml. of glacial acetic acid, 3.9 g. of ammonium acetate, 75 ml. of 95% ethanol, and 2 g. of palladium on charcoal was hydrogenated at room temperature and 50 pounds pressure. The reduction was complete in about one hour. Five runs were combined, filtered, and the solvent was removed *in vacuo* on a steam-bath. The residue was taken up in ether, washed with water, sodium bicarbonate solution, and saturated salt solution, and dried over sodium sulfate. After removal of the solvent, the product was distilled twice from a Claisen flask and then through an efficient fractionating column, giving 143 g. (31.3%) of nearly colorless liquid, b.p. 60° (0.12 mm.); n_D^{25} 1.4322, d_4^{25} 0.9552.

Anal. Calc'd for $C_{10}H_{17}NO_2$: M_D, 49.80; N, 7.65.
Found: M_D, 49.78; N, 7.67.

Ethyl Δ^2-cyclopentenyl-(1-methylbutyl)cyanoacetate. To 18.4 g. (0.8 mole) of sodium, melted under 180 ml. of dry toluene in a 1-l. flask, was slowly added (with vigorous stirring) 124 g. (0.8 mole) of ethyl (1-methylbutyl)cyanoacetate (3). When practically all the sodium

had reacted, 123 g. (1.2 moles) of Δ^2-cyclopentenyl chloride was added. Salt separated and the reaction mixture became acidic almost immediately. Water was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layer was washed with saturated salt solution and the solvent was removed *in vacuo*. The product was distilled, first from a Claisen flask and then through an efficient column, giving 125 g. (62.6%) of nearly colorless liquid.

Ethyl cyclopentyl-(1-methylbutyl)cyanoacetate. A solution of 62.4 g. (0.25 mole) of ethyl Δ^2-cyclopentenyl-(1-methylbutyl)cyanoacetate in 100 ml. of ethanol was hydrogenated with 0.2 g. of platinum oxide catalyst at room temperature and 50 pounds pressure. In about one hour the reduction was complete. The catalyst was removed by filtration, and the solvent was distilled off *in vacuo*. The product was distilled from a Claisen flask, giving 62 g. (98.6%) of colorless liquid.

Diethyl cyclopentyl-(2-thienylmethyl)malonate. A solution of 40 g. (0.125 mole) of diethyl Δ^2-cyclopentenyl-(2-thienylmethyl)malonate in 100 ml. of ethanol was hydrogenated with about 6 g. of Raney nickel catalyst in a bomb at 1800 pounds pressure. The temperature was slowly raised during twelve hours to 100°. After filtration, the solvent was removed *in vacuo*, and the residue was distilled through a six-inch fractionating column packed with 1/8-inch glass helices. A colorless liquid, weighting 31 g. (77%), was obtained.

Anal. Calc'd for $C_{17}H_{24}O_4S$: C, 63.00; H, 7.45.
Found: C, 63.39; H, 7.49.

Cyclopentyl-(2-methylbutyl)acetic acid. A mixture of 40 g. of diethyl cyclopentyl-(2-methylbutyl)malonate with a solution of 40 g. of potassium hydroxide in 100 ml. of 95% ethanol was heated for three hours in a bomb immersed in an oil-bath at 140–160°. The contents were diluted with water, extracted with ether, and the aqueous solution was acidified with hydrochloric acid. The acid was taken up in ether, washed thoroughly with water, and dried over sodium sulfate. After removing the solvent, the product was heated to 180° and then distilled from a Claisen flask, giving 25 g. (94%) of colorless liquid.

Cyclopentyl-(1-methylbutyl)acetic acid and amide. A mixture of 40 g. of ethyl cyclopentyl-(1-meth lbutyl)cyanoacetate with a solution of 70 g. of potassium hydroxide in 115 ml. of 90% ethanol was heated in a bomb immersed in an oil-bath at 170–180° for 46 hours. On diluting the contents of the bomb with water, a crystalline precipitate separated which was collected, washed with water, and dried; weight, 11 g. (35%). This proved to be cyclopentyl-(1-methylbutyl)acetamide. A sample recrystallized from petroleum hexane melted at 94–109°.

Anal. Calc'd for $C_{12}H_{24}NO_2$: N, 7.10. Found: N, 7.04.

The basic aqueous filtrate was extracted with ether and then acidified with hydrochloric acid. It was worked up as described above and the acid was distilled from a Claisen flask, giving about 11 g. (35%) of colorless liquid.

Hydrolysis and decarboxylation of ethyl Δ^2-cyclopentenyl-sec-butylcyanoacetate. Forty grams of this cyanoacetate was hydrolyzed under conditions similar to those described above for the preparation of cyclopentyl-(2-methylbutyl)acetic acid. The acidic fraction was heated to 175° and then distilled from a Claisen flask, giving 5.5 g. of a viscous oil, b.p. 150° (0.56 mm.); n_D^{25} 1.4830. This compound gave correct neutral equivalent and nitrogen analysis for Δ^2-cyclopentenyl-*sec*-butylcyanoacetic acid.

Anal. Calc'd for $C_{12}H_{17}NO_2$: N.E., 207.26; N, 6.76.
Found: N.E., 208.05; N, 6.78.

The neutral fraction was distilled from a Claisen flask, giving 15.7 g. of crystalline solid, b.p. 120° (0.1 mm.), which, after recrystallization from benzene, gave 12.3 g., m.p. 114–115°. This proved to be Δ^2-cyclopentenyl-*sec*-butylacetamide.

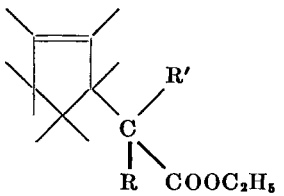
Anal. Calc'd for $C_{11}H_{19}NO$: N, 7.73. Found: N, 7.79.

This amide could not be hydrolyzed by refluxing for eight hours with 50% potassium hydroxide solution, but it was hydrolyzed to the corresponding acid (Table II) by heating with alcoholic potassium hydroxide in a bomb under conditions similar to those described above for the preparation of cyclopentyl-(1-methylbutyl)acetic acid.

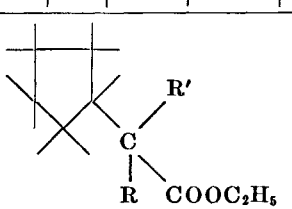
Δ^2-Cyclopentenylisopropylacetamide. This amide was isolated from the neutral fraction

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
H—[a]	—CN	41.6	70	0.09	1.4623	1.0435	$C_{10}H_{13}NO_2$	47.13	47.23	7.82	7.73
$CH_3CH_2CH_2$—	—CN	65.7	73	.04	1.4620	0.9975	$C_{13}H_{19}NO_2$	60.99	60.99	6.33	6.27
$CH_3CH(CH_3)$—	—CN	71.6	70	.04	1.4660	1.0077	$C_{13}H_{19}NO_2$	60.99	60.80	6.33	6.13
$CH_3CH(CH_3)CH_2$—[b]	—$COOC_2H_5$	45.7	73	.02	1.4580	1.0157	$C_{16}H_{26}O_4$	76.75	75.81	—	—
$CH_3CH_2CH(CH_3)$—	—CN	66.	93	.26	1.4680	1.004	$C_{14}H_{21}NO_2$	65.61	65.41	5.95	5.80
$CH_3CH(CH_3)CH_2CH_2$—[c]	—$COOC_2H_5$	45.	99	.038	1.4580	1.0007	$C_{17}H_{28}O_4$	81.37	80.84	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	46.6	83	.03	1.4581	0.9970	$C_{17}H_{28}O_4$	81.37	81.14	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	62.6	95	.21	1.4678	.9893	$C_{15}H_{23}NO_2$	70.23	70.04	5.62	5.67
$CH_3CH(CH_3)CH(CH_3)$—	—CN	67.4	84	.07	1.4709	.9974	$C_{15}H_{23}NO_2$	70.23	69.86	5.62	5.70
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	49.6	90	.01	1.4616	.9966	$C_{18}H_{30}O_4$	86.00	85.56	—	—
CH_2=$CClCH_2$—	—$COOC_2H_5$	60.	121	.28	1.4793	1.1214	$C_{15}H_{21}ClO_4$	76.52	76.09	—	—
$C_6H_5OCH_2CH_2$—	—$COOC_2H_5$	39.	161	.37	1.5069	1.0923	$C_{20}H_{26}O_5$	93.26	94.12	—	—
SCH=CHCH=CCH$_2$—	—$COOC_2H_5$	70.7	138	.17	1.5136	1.1373	$C_{17}H_{22}O_4S$	86.20	85.27	[d]	—

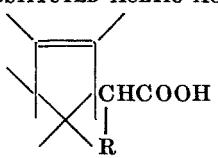


$CH_3CH(CH_3)$—	—CN	—	84	0.22	1.4578	0.9922	$C_{13}H_{21}NO_2$	61.46	61.39	6.27	6.37
$CH_3CH(CH_3)CH_2$—	—$COOC_2H_5$	98.[e]	96	.04	1.4536	1.0023	$C_{16}H_{28}O_4$	77.21	76.72	—	—
$CH_3CH_2CH(CH_3)$—	—CN	97.	96	.25	1.4603	0.9865	$C_{14}H_{23}NO_2$	66.08	65.93	5.90	5.98
$CH_2=C(CH_3)CH_2$—	—$COOC_2H_5$	63.	71	.01	1.4619	1.0170	$C_{16}H_{26}O_4$	76.75	76.32	—	—
$CH_3(CH_2)_3CH_2$—	—$COOC_2H_5$	86.3	98	.04	1.4525	0.9887	$C_{17}H_{30}O_4$	81.84	81.49	—	—
$CH_3CH(CH_3)CH_2CH_2$—[c]	—$COOC_2H_5$	100.	101	.04	1.4524	.9914	$C_{17}H_{30}O_4$	81.84	81.26	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	99.	109	.25	1.4527	.9874	$C_{17}H_{30}O_4$	81.84	81.39	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	98.6	95	.27	1.4606	.9762	$C_{15}H_{25}NO_2$	70.71	70.61	5.57	5.32
$CH_3CH(CH_3)CH(CH_3)$—	—CN	88.5	76	.01	1.4637	.9850	$C_{15}H_{25}NO_2$	70.71	70.38	5.57	5.51
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	94.7	95	.005	1.4571	.9884	$C_{18}H_{32}O_4$	86.47	86.11	—	—
SCH=CHCH=CCH$_2$—[f]	—$COOC_2H_5$	77.	112	.018	1.5068	1.1252	$C_{17}H_{24}O_4S$	86.67	85.8	—	—

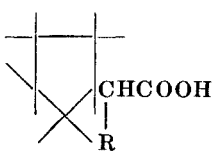
[a] Prepared by a method similar to the example in the Experimental part except that sodium ethoxide in ethanol was used in place of sodium and toluene. [b] Centolella, Nelson, and Kolloff, *J. Am. Chem. Soc.*, **65,** 2091 (1943). [c] Braun and Kurtz, *Ber.*, **70,** 1224 (1937). [d] *Anal.* Calc'd: S, 9.94. Found: S, 10.13. [e] The yield and physical constants are on material prepared by the hydrogenation of diethyl Δ^2-cyclopentenylisobutylmalonate in the usual way. The same compound was also prepared by the high pressure hydrogenation of diethyl cyclopentyl-(2-methyl allyl)malonate using Raney nickel catalyst. [f] For method of preparation, see Experimental part.

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
$CH_3CH(CH_3)$—[a, b]	60.	80	0.03	1.4680	0.9913	$C_{10}H_{16}O_2$	47.24	47.17	168.2	171.4
$CH_3CH(CH_3)CH_2$—[b]	75.	78	.07	1.4650	.9718	$C_{11}H_{18}O_2$	51.87	51.86	182.3	182.8
$CH_3CH_2CH(CH_3)$—	69.5	82	.013	1.4702	.9858	$C_{11}H_{18}O_2$	51.87	51.60	182.3	185.1
$CH_3CH(CH_3)CH_2CH_2$—	94.	101	.026	1.4653	.9626	$C_{12}H_{20}O_2$	56.50	56.40	196.3	196.5
$CH_3CH_2CH(CH_3)CH_2$—	87.6	123	1.0	1.4662	.9618	$C_{12}H_{20}O_2$	56.50	56.54	196.3	194.9
$CH_3(CH_2)_2CH(CH_3)$—	68.2	93	0.05	1.4710	.9733	$C_{12}H_{20}O_2$	56.50	56.38	196.3	197.6
$CH_3CH(CH_3)CH(CH_3)$—	58.5	87	.012	1.4729	.9816	$C_{12}H_{20}O_2$	56.50	56.08	196.3	196.0
$CH_3CH_2CH(C_2H_5)CH_2$—	97.5	98	.02	1.4687	.9620	$C_{13}H_{22}O_2$	61.13	60.91	210.3	207.7
SCH=CHCH=CCH$_2$—	83.4	130	.06	1.5449	1.1649	$C_{12}H_{14}O_2S$	60.33	60.34	222.3	224.9

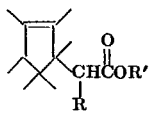


$CH_3CH(CH_3)$—	43.4	78	0.022	1.4582	0.9732	$C_{10}H_{18}O_2$	47.71	47.75	170.2	174.3
$CH_3CH(CH_3)CH_2$—	91.	79	.08	1.4549	.9525	$C_{11}H_{20}O_2$	52.34	52.48	184.3	184.6
$CH_3CH_2CH(CH_3)$—	46.6	89	.08	1.4618	.9693	$C_{11}H_{20}O_2$	52.34	52.26	184.3	186.0
$CH_2=C(CH_3)CH_2$—	55.	86	.04	1.4694	.9768	$C_{11}H_{18}O_2$	51.92	51.98	182.2	180.1
$CH_3(CH_2)_3CH_2$—	84.	96	.02	1.4569	.9481	$C_{12}H_{22}O_2$	56.97	56.95	198.3	197.1
$CH_3CH(CH_3)CH_2CH_2$—	89.	94	.055	1.4559	.9438	$C_{12}H_{22}O_2$	56.97	57.10	198.3	198.8
$CH_3CH_2CH(CH_3)CH_2$—	94.	114	.35	1.4570	.9483	$C_{12}H_{22}O_2$	56.97	57.09	198.3	196.4
$CH_3(CH_2)_2CH(CH_3)$—	35.	96	.07	1.4623	.9591	$C_{12}H_{22}O_2$	56.97	56.88	198.3	201.8
$CH_3CH(CH_3)CH(CH_3)$—	31.5	96	.062	1.4651	.9668	$C_{12}H_{22}O_2$	56.97	56.77	198.3	198.5
$CH_3CH_2CH(C_2H_5)CH_2$—	95.6	103	.028	1.4600	.9436	$C_{13}H_{24}O_2$	61.60	61.48	212.3	213.3
SCH=CHCH=CCH$_2$—	91.	135	.07	1.5330	1.1422	$C_{12}H_{16}O_2S$ [c]	60.80	60.94	224.3	224.6

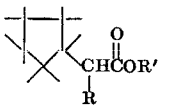
[a] Perkins and Cruz, *J. Am. Chem. Soc.*, **49**, 518 (1927). [b] For exceptions to general method of preparation, see Experimental part. [c] *Anal.* Calc'd: C, 64.25; H, 7.19. Found: C, 64.70, 64.96; H, 7.37, 7.22.

TABLE III

Esters of Amino Alcohols



R	R′	Method of Preparation	Free Base										Hydrochloride						Anti-spasmodic Activity
			Yield, %	B.p., °C.	mm.	n_D^{25}	d_4^{25}	Empirical Formula	Molecular Refractivity Calc'd	Molecular Refractivity Found	Analysis % Nitrogen Calc'd	Analysis % Nitrogen Found	Yield, %	M.p., °C.	Analysis N Calc'd	Analysis N Found	Analysis Cl Calc'd	Analysis Cl Found	
$CH_3CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	74.	106	0.025	1.4628	0.9344	$C_{16}H_{29}NO_2$	79.20	78.80	5.44	5.24	93.	93–98	–	–	11.67	11.77	++
$CH_3CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	–	93	.06	1.4595	.9245	$C_{17}H_{31}NO_2$	83.82	83.30	–	–	–	106–109	4.41	4.54	11.15	11.32	+
$CH_3CH_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	80.	106	.027	1.4642	.9334	$C_{17}H_{31}NO_2$	83.82	83.23	4.98	4.83	92.	101–103	–	–	11.15	11.10	±
$CH_3(CH_2)_3CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	70.	112	.04	1.4617	.9230	$C_{18}H_{33}NO_2$	88.44	87.96	–	–	84.	93.5–95	4.22	4.31	10.68	10.88	–
$CH_3CH(CH_3)CH_2CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	63.	100	.025	1.4618	.9209	$C_{18}H_{33}NO_2$	88.44	88.17	4.74	4.60	86.	99–100	–	–	10.68	10.67	±
$CH_3CH_2CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	90.5	110	.005	1.4612	.9208	$C_{18}H_{33}NO_2$	88.44	88.08	4.74	4.73	78.	99.5–101	–	–	10.68	10.72	–
$CH_3(CH_2)_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	25.1	106	.062	1.4638	.9279	$C_{18}H_{33}NO_2$	88.44	87.83	4.74	4.67	45.6[a]	99–103	–	–	10.68	10.85	–
$CH_3CH(CH_3)CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	49.4	118	.18	1.4673	.9392	$C_{18}H_{33}NO_2$	88.44	87.26	4.74	4.77	27.4[a]	120–123	–	–	10.68	10.48	+++
$SCH{=}CHCH{=}CCH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	86.	120	.015	1.5128	1.0483	$C_{18}H_{27}NO_2S$	93.27	92.13	4.36	4.30	94.	111–113	–	–	9.82	9.91	–
$CH_2(CH_2)_2CH{=}CHCH-$	$(CH_3)_2NCH_2CH_2-$	B	46.	110	.05	1.4948	1.0012	$C_{17}H_{27}NO_2$	81.15	80.77	–	–	94.[b]	129–133.5	4.46	4.48	11.30	11.00	–
$CH_2(CH_2)_2CH{=}CHCH-$	$(C_2H_5)_2NCH_2CH(CH_3)-$	B	30.	116	.03	1.4882	0.9786	$C_{20}H_{33}NO_2$	95.01	94.09	–	–	84.	118–120	3.94	4.10	9.96	9.97	±
$CH_2(CH_2)_2CH{=}CHCH-$	$(C_2H_5)_2NCH_2CH_2CH_2-$	B	86.	131	.07	1.4900	.9761	$C_{20}H_{33}NO_2$	95.01	94.63	–	–	95.	115–118	3.94	4.07	9.96	9.94	+
$CH_2(CH_2)_2CH{=}CHCH-$	$CH_2(CH_2)_4NCH_2CH_2-$	B	59.	125	.03	1.5070	1.0222	$C_{20}H_{31}NO_2$	92.81	92.42	–	–	94.	133–142	3.96	4.02	10.02	9.93	–
$CH_2(CH_2)_2CH{=}CHCH-$	$CH_2CH_2OCH_2CH_2NCH_2CH_2-$	B	28.	130	.018	1.5083	1.0655	$C_{19}H_{29}NO_3$	89.83	89.41	–	–	90.	144–145	3.94	3.96	9.96	9.96	–



R	R′	Method	Yield, %	B.p., °C.	Mm.	n_D^{25}	d_4^{25}	Formula	Calcd. C	Found C	Calcd. H	Found H	Yield, %	M.p., °C.	Calcd. N	Found N	Calcd. S	Found S	Activity[g]
$CH_3CH_2CH_2-$	$(CH_3)_2NCH_2CH_2-$	B	83.	73	0.05	1.4520	0.9267	$C_{14}H_{27}NO_2$	70.43	70.04	5.80	5.73	69.[a]	111–113	—	—	12.76	12.52	—
$CH_3CH(CH_3)-$	$(CH_3)_2NCH_2CH_2-$	B	—	68	.02	1.4542[c]	.9310[c]	$C_{14}H_{27}NO_2$	70.43	70.17	5.80	5.60	81.[a]	114–115	—	—	12.76	12.71	—
$CH_3CH(CH_3)-$	$(C_2H_5)NCH_2CH_2$	A	48.4	111	.28	1.4563	.9212	$C_{16}H_{31}NO_2$	79.67	79.50	5.20	5.15	80.5[a]	115–118	—	—	11.59	11.60	++
$CH_3CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	68.	113	.03	1.4527	.9119	$C_{17}H_{33}NO_2$	84.29	83.97	—	—	94.	118.5–119.5	4.38	4.51	11.08	11.22	+++
$CH_3CH(CH_3)CH_2-$	$(CH_3)_2NCH_2CH_2$	B	51.	90	.03	1.4519	.9204	$C_{15}H_{29}NO_2$	75.05	74.84	5.49	5.52	82.	111–114.5	—	—	12.15	12.10	±
$CH_3CH(CH_3)CH_2-$	$CH_2(CH_2)_4NCH_2CH_2-$	B	85.	106	.02	1.4717	.9600	$C_{18}H_{33}NO_2$	86.71	86.13	4.74	4.57	82.	177.5–180	—	—	10.68	10.67	++
$CH_3CH(CH_3)CH_2-$	$HOCH_2CH_2N(C_2H_5)CH_2CH_2-$	B	43.	106	.012	1.4653	.9706	$C_{17}H_{33}NO_3$	85.81	85.26	4.68	4.75	—	59–62	—	—	10.56	10.83	+
$CH_3CH(CH_3)CH_2-$	$CH_2CH_2CH=CHCHN(C_2H_5)CH_2CH_2-$	B	53.3	114	.008	1.4760	.9548	$C_{20}H_{35}NO_2$	95.48	94.97	4.36	4.22	[f]	—	—	—	—	—	—
$CH_3CH_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	73.0	110	.14	1.4591	.9198	$C_{17}H_{33}NO_2$	84.29	84.24	4.94	4.85	79.5[a]	115–116	—	—	11.09	11.28	—
$CH_3CH_2CH(CH_3)-$	$(CH_3)_2NCH_2CH_2-$	B	89.	76	.02	1.4565[c]	.9402[c]	$C_{16}H_{29}NO_2$	75.05	73.90	5.49	5.60	84.[a]	105–109	—	—	12.15	12.01	+
$CH_2=C(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	92.	108	.19	1.4629	.9276	$C_{17}H_{31}NO_2$	83.82	83.54	—	—	48.2[d]	99–105	4.41	4.37	11.15	11.28	++
$CH_3(CH_2)_8CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	85.	106	.02	1.4561	.9118	$C_{18}H_{35}NO_2$	88.91	88.71	—	—	91.	103.5–105	4.20	4.33	10.62	10.76	—
$CH_3CH(CH_3)CH_2CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	85.	83	.025	1.4550	.9100	$C_{18}H_{35}NO_2$	88.91	88.69	4.71	4.61	94.	117–118.5	—	—	10.62	10.52	±
$CH_3CH_2CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	80.	97	.02	1.4552	.9110	$C_{18}H_{35}NO_2$	88.91	88.63	4.71	4.53	80.	116–117	—	—	10.62	10.65	±
$CH_3(CH_2)_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	66.1	124	.35	1.4594	.9161	$C_{18}H_{35}NO_2$	88.91	88.80	4.71	4.66	58.2[a]	99–103	—	—	10.62	10.80	+
$CH_3CH(CH_3)CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	67.5	108	.06	1.4601	.9272	$C_{18}H_{35}NO_2$	88.91	87.90	4.71	4.69	61.3[a]	141–146	—	—	10.62	10.51	+
$CH_3CH_2CH(C_2H_5)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	B	79.	95	.005	1.4568[c]	.9176[c]	$C_{19}H_{37}NO_2$	93.53	92.44	4.50	4.35	55.[e]	111.5–113	—	—	10.19	10.11	+
$SCH=CHCH=CCH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	94.	113	.015	1.5051	1.0353	$C_{18}H_{29}NO_2S$	93.74	92.68	4.33	4.52	85.	130–133	—	—	9.85	9.85	—

[a] *Recrystallized from methyl isobutyl ketone.* [b] *Yield and analysis on material from absolute ether. Melting point taken on sample recrystallized from ethyl acetate plus absolute ether.* [c] Determined by Miss Elizabeth Beard in these laboratories. [d] Recrystallized from methyl ethyl ketone. [e] Recrystallized from ethyl acetate. [f] The hydrochloride of this amine separated as an oil from absolute ether and has not been obtained crystalline. [g] Tested on isolated intestinal muscle, stimulated by acetylcholine (1:5,000,000). The activities are estimated for dilution of 1:8,000,000 of the compounds being tested.

after the hydrolysis of ethyl Δ^2-cyclopentenylisopropylcyanoacetate. Yield, 50%; m.p. 118–121°.

Anal. Calc'd for $C_{10}H_{17}NO$: N, 8.38. Found: N, 8.26.

A sample of this amide was hydrolyzed as described above to the corresponding acid (Table II).

Cyclopentylisopropylacetamide. In a similar way this amide was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentylisopropylcyanoacetate. Yield, 33%, m.p. 142–143°.

Anal. Calc'd for $C_{10}H_{19}NO$: N, 8.27. Found: N, 8.14.

Cyclopentyl-sec-butylacetamide. Likewise, this amide was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentyl-*sec*-butylcyanoacetate. Yield, 30.6%; m.p. 131–132°.

Anal. Calc'd for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.47.

Cyclopentyl-(1,2-dimethylpropyl)acetamide. Similarly, this was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentyl-(1,2-dimethylpropyl)cyanoacetate. Yield, 33.5%; m.p. 87–93°.

Anal. Calc'd for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.17.

Method A. β-Diethylaminoethyl cyclopentyl-(2-methylbutyl)acetate and hydrochloride. A solution of 20.6 g. (0.104 mole) of cyclopentyl-(2-methylbutyl)acetic acid in 40 ml. of isopropanol was neutralized to phenolphthalein with alcoholic sodium ethoxide, and then a solution of 13.6 g. (0.104 mole) of β-diethylaminoethyl chloride in 40 ml. of isopropanol was added. After standing for several days (or refluxing several hours), the solution was filtered from salt and the solvent removed. The basic ester was taken up in ether, washed with water, and extracted with cold dilute hydrochloric acid. The acid solution was washed with ether, made basic with sodium carbonate, and the amine was taken up in ether and dried over sodium sulfate. After removing the ether, the basic ester was distilled from a Claisen flask, giving 24.4 g. (80%) of liquid.

The hydrochloride was prepared from 23 g. of this amine by passing hydrogen chloride gas into its solution in absolute ether. The precipitate crystallized and was collected, thoroughly washed with absolute ether, and dried in a vacuum desiccator. Yield, 20.7 g. (80%).

Method B. Cyclopentyl-(n-propyl)acetyl chloride. A solution of 255 g. (1.5 moles) of cyclopentyl-(*n*-propyl)acetic acid (2) in 185 ml. (2.5 moles) of thionyl chloride was allowed to stand at room temperature overnight and then refluxed on a steam-bath for one hour. After removal of the excess thionyl chloride *in vacuo*, the acid chloride was distilled from a Claisen flask, b.p. 108° (17 mm.); n_D^{25} 1.4620.

Anal. Calc'd for $C_{10}H_{17}ClO$: Cl, 18.79. Found: Cl, 18.38.

β-Dimethylaminoethyl cyclopentyl-(n-propyl)acetate and hydrochloride. To a solution of 18.8 g. (0.1 mole) of the above acid chloride in 50 ml. of dry benzene was added 17.2 g. (0.2 mole) of β-dimethylaminoethanol. The mixture became hot and crystals separated. After standing overnight (or refluxing for an hour), the mixture was diluted with ice-water, made strongly acidic with hydrochloric acid, and extracted with ether. The aqueous solution was made basic with cold dilute sodium hydroxide and extracted with ether. The ether solution was thoroughly washed with water and dried over sodium sulfate. After removing the ether, the free base was distilled from a Claisen flask, giving 20 g. (83%) of colorless liquid.

Hydrogen chloride was passed into a solution of 18.9 g. of this amine in absolute ether. The gelatinous precipitate was collected, washed with absolute ether, and dried; weight, 20 g. This was recrystallized from methyl isobutyl ketone and washed with absolute ether, giving 15 g. (69%) of a white hygroscopic powder.

Cyclopentylisobutylacetyl chloride. By a method similar to that described above, 814 g. (4.42 moles) of cyclopentylisobutylacetic acid was converted to its acid chloride. It was distilled from a Claisen flask, giving 866.2 g. (96.5%) of colorless liquid; n_D^{25} 1.4608, d_4^{25} 0.9913.

Anal. Calc'd for $C_{11}H_{29}ClO$: M_D, 55.69; Cl, 17.49.
Found: M_D, 55.91; Cl, 17.26.

Δ^2-Cyclopentenyl-Δ^2-cyclohexenylacetyl chloride. A solution of 41.2 g. (0.2 mole) of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid (2) and 35.7 g. (0.3 mole) of thionyl chloride in 100 ml. of dry benzene was refluxed for 2½ hours. The solvent was removed by distillation, more benzene was added and also removed. The residue was distilled *in vacuo*. Yield, 85%; b.p. 110° (0.3 mm.); n_D^{25}, 1.5180; d_4^{25}, 1.0974.

Anal. Calc'd for $C_{13}H_{17}ClO$: M_D, 61.79; Cl, 15.8.
Found: M_D, 62.05; Cl, 15.9.

β-[(Δ^2-Cyclopentenyl)ethylamino]ethanol.[5] One mole of Δ^2-cyclopentenyl chloride was added to a solution of 178 g. of ethylethanolamine in 300 ml. of ether. When the exothermic reaction had subsided, a hydrochloride crystallized rapidly and exothermically from the reaction mixture. After five days at room temperature, the mixture was shaken with 250 ml. of 20% sodium hydroxide. The ether layer was separated and combined with ether extracts of the alkaline solution. The ether solution was dried over potassium hydroxide pellets and distilled using a water-pump vacuum; no fractionation was attempted during the first distillation. The distillate was then distilled through a 12-inch column packed with glass helices to give 60 g. of product, b.p. 110–112° at 34 mm.; n_D^{25} 1.477.

Anal. Calc'd for $C_9H_{17}NO$: N, 9.02. Found: N, 9.11.

SUMMARY

1. The preparation and properties are reported for thirty-two new esters of tertiary amino alcohols with substituted acetic acids containing cyclopentyl or Δ^2-cyclopentenyl groups in the alpha position.

2. Twenty intermediate acetic acids are reported.

3. Many new malonic and cyanoacetic esters are described.

4. Preliminary tests of antispasmodic activity of the hydrochlorides of these basic esters indicate desirable properties for some of them.

KANSAS CITY, MISSOURI

REFERENCES

(1) MOFFETT, HART, AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1854 (1947).
(2) MOFFETT, HART, AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1849 (1947).
(3) ALEXANDER AND COPE, *J. Am. Chem. Soc.*, **66**, 886 (1944).

[5] Prepared by Dr. Louis H. Goodson, in these laboratories.