Anal. Calcd. for $C_{32}H_{44}$: C, 89.71; H, 10.29. Found: C, 89.10; H, 10.63.

Nitration A.—The nitration of III was carried out in a chloroform solution as described above. A solid was obtained melting at 150–153°. After two crystallizations from ethanol–chloroform solution the melting point of the nitroderivative VI was 162–163°.

Anal. Calcd. for $C_{26}H_{38}N_2O_4$: C, 70.39; H, 7.55; N, 6.40. Found: C, 70.68; H, 7.37; N, 6.50.

Nitration B.—The hydrocarbon III was nitrated with a solution consisting of 2 vol. of 96% sulfuric acid and 1 vol. of 72% nitric acid. A tetranitroderivative was obtained melting at 251–252°, which was identical with compound V.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.69; H, 4.71; N, 12.31.

Acknowledgment.—We are indebted to Patricia Craig and Nelda Mold for the microanalyses.

Summary

Isopropyl-*p*-cymene and cyclohexyl-*p*-cymene reacted with 3-methylcyclohexene in the presence of hydrogen fluoride as a catalyst. Hydrogen transfer was the main reaction; the aromatic hydrocarbons acted as a hydrogen donor and methylcyclohexene as a hydrogen acceptor. The hydrogen transfer amounted to over 60 and 40%, respectively, based on methylcyclohexene charged.

The products obtained from the respective aromatic hydrocarbons through a hydrogen transfer were: 1,3,3,6-tetramethyl-5-isopropyl-1-(4-methyl-3-isopropylphenyl)-indan and 1,3,3,6-tetramethyl-5-cyclohexyl-1-(4-methyl-3-cyclohexylphenyl)-indan.

The structure of these compounds was proven by nitration and conversion to known nitro derivatives.

Part of the substituted *p*-cymene apparently reacted with methylcyclohexene to form the expected cycloalkylation product.

EVANSTON, ILLINOIS RECEIVED MARCH 22, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. I. Pyrrolidylalkyl Esters of Disubstituted Acetic Acids

BY H. G. KOLLOFF, JAMES H. HUNTER, E. H. WOODRUFF AND ROBERT BRUCE MOFFETT

In a search for new compounds which might have desirable spasmolytic activity, we have prepared a series of esters of β-(1-pyrrolidyl)-ethanol and γ-(1-pyrrolidyl)-propanol.

These esters were prepared by allowing the acid chloride of the requisite acid to react with the appropriate pyrrolidyl alkanol. β-(1-Pyrrolidyl)-ethanol has been reported[1] previously and γ-(1-pyrrolidyl)-propanol was made from pyrrolidine and trimethylene chlorohydrin. The acids used in making these esters were prepared by the methods indicated in Table I. In a few instances new intermediate malonic acids were isolated.

The free basic esters were isolated, characterized, and converted to their hydrochloride salts; when the hydrochlorides proved very difficult to crystallize the acid citrate salts were prepared instead. Some of these basic esters were further characterized by converting them to quaternary salts with various alkyl halides.

Preliminary pharmacological assays by Dr. Milton J. Vander Brook of our Department of Pharmacology indicate that the salts of β-(1-pyrrolidyl)-ethyl esters of phenyl-Δ^2-cyclopentenyl-, phenyl-Δ^2-cyclohexenyl-, phenylcyclopentyl-, phenylcyclohexyl-, cyclopentyl-*n*-propyl-, cyclopentyl-*n*-butyl- and Δ^2-cyclopentenyl-Δ^2-cyclohexenyl-acetic acids, all have antispasmodic activity, of the order of one-eighth or better than that of atropine sulfate, when tested on isolated rabbit intestine stimulated with acetylcholine chloride. The corresponding γ-(1-pyrrolidyl)-propyl esters were less active. Further pharmacological investigation of these compounds is in progress, and the results will be published elsewhere.

(1) v. Braun, Braunsdorf and Räth, *Ber.*, **55**, 1666 (1922).

Experimental[2,3]

γ-(1-Pyrrolidyl)-propanol.—To a hot solution of 507 g. of sodium hydroxide in 457 ml. of water was added 605 g. (8.5 moles) of pyrrolidine with stirring. To this was slowly added 1 kg. (10.6 moles) of trimethylene chlorohydrin. When the temperature had risen to 100° the mixture was allowed to cool to approximately 70°. After stirring for one-half hour and standing overnight the mixture was saturated with sodium hydroxide and extracted with benzene. After removing the solvent the product was distilled; b. p. 98° (18 mm.), $n^{25}D$ 1.4707.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.43.

Diethyl Phenyl-Δ^2-cyclohexenylmalonate.—To a solution of 48.4 g. (2.1 moles) of sodium in 800 ml. of absolute alcohol was added 236.3 g. (1 mole) of diethyl phenylmalonate,[4] and then 254 g. (1.05 moles) of 1,2-dibromocyclohexane was slowly added with stirring at reflux temperature. After heating under reflux for six hours the reaction mixture was acidified with acetic acid and most of the solvent was removed by distillation. Water was added, the organic layer was separated, and distilled first from a Claisen flask and then through a 6-inch column packed with 1/8-inch glass helices. A yield of 174 g. (55%) of nearly colorless liquid, b. p. 126° (0.07 mm.), was obtained; $n^{25}D$ 1.5169; d^{25}_4 1.0933.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.64. Found: C, 71.67; H, 7.64.

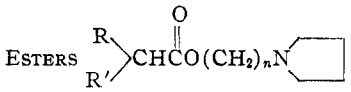
Phenyl-Δ^2-cyclohexenylacetic Acid.—A solution of 68 g. (0.215 mole) of diethyl phenyl-Δ^2-cyclohexenylmalonate and 75 g. of potassium hydroxide in 350 ml. of 95% ethanol was heated under reflux for six hours. Water was added

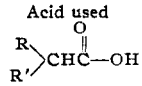
(2) Analyses by Mr. Harold Emerson and Staff of our Microanalytical Laboratory.

(3) Melting points are uncorrected.

(4) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 288.

TABLE I

PYRROLIDYL ALKANOL ESTERS 

Acid used 	n	Free base: Yield from acid, %	B. p., °C.	Mm.	$n^{25}D$	Empirical formula	Nitrogen analyses, % Calcd.	Found
PYRROLIDYL ALKANOL ESTERS								
Diphenylacetic	2	62.3	168	0.08	....	$C_{20}H_{23}NO_2$	..	..
Diphenylacetic	3	78.7	148	.01	1.5492[a]	$C_{21}H_{25}NO_2$	4.33	4.36
Phenyl-Δ^2-cyclohexenylacetic[b]	2	86.3	137	.07	1.5295	$C_{20}H_{27}NO_2$	4.47	4.61
Phenyl-Δ^2-cyclohexenylacetic[b]	3	80.5	139	.07	1.5260	$C_{21}H_{29}NO_2$	4.28	4.41
Phenylcyclohexylacetic[c]	2	87.4	125	.06	1.5204	$C_{20}H_{29}NO_2$	4.44	4.46
Phenylcyclohexylacetic[c]	3	81.8	145	.06	1.5177	$C_{21}H_{31}NO_2$	4.25	4.16
Phenyl-Δ^2-cyclopentenylacetic[d,e]	2	65.5	140	.04	....	$C_{19}H_{25}NO_2$	4.68	4.68[f]
Phenyl-Δ^2-cyclopentenylacetic[d,e]	3	86.8[g]	129	.04	1.5220	$C_{20}H_{27}NO_2$	4.47	4.61
Phenylcyclopentylacetic[h]	2	70.0	135	.04	....	$C_{19}H_{27}NO_2$	4.64	4.50[i]
Phenylcyclopentylacetic[h,j]	3	93.4[g]	125	.03	1.5146	$C_{20}H_{29}NO_2$	4.44	4.45
Phenylphenoxyacetic[k]	2	42.5	174	.125	....	$C_{20}H_{23}NO_3$	..	..
Δ^2-Cyclopentenyl-Δ^2-cyclohexenylacetic[l]	2	59.4	110	.01	1.5064	$C_{19}H_{29}NO_2$	4.62	4.77
Δ^2-Cyclopentenyl-Δ^2-cyclohexenylacetic[l]	3	66.8	124	.01	1.5043	$C_{20}H_{31}NO_2$	4.41	4.36
Δ^2-Cyclopentenyl-*n*-propylacetic[d]	2	77.4	100	.03	1.4761	$C_{16}H_{27}NO_2$	5.28	5.40
Δ^2-Cyclopentenyl-*n*-propylacetic[d]	3	89.6	120	.05	1.4758	$C_{17}H_{29}NO_2$	5.01	5.10
Cyclopentyl-*n*-propylacetic[l,m]	2	61.0	95	.01	1.4686	$C_{16}H_{29}NO_2$	5.24	5.56
Cyclopentyl-*n*-propylacetic[l,m]	3	82.4	101	.01	1.4690	$C_{17}H_{31}NO_2$	4.98	5.11
Δ^2-Cyclopentenyl-*n*-butylacetic[d]	2	65.8	100	.02	1.4752	$C_{17}H_{29}NO_2$	5.01	5.03
Δ^2-Cyclopentenyl-*n*-butylacetic[d]	3	83.2	99	.005	1.4750	$C_{18}H_{31}NO_2$	4.77	5.06
Cyclopentyl-*n*-butylacetic[l,n]	2	66.1	104	.01	1.4683	$C_{17}H_{31}NO_2$	4.98	5.00
Cyclopentyl-*n*-butylacetic[l,n]	3	77.2	104	.009	1.4688	$C_{18}H_{33}NO_2$	4.74	4.87

[a] d^{25}_4 1.0756. [b] This acid and the corresonding malonic ester were mentioned as intermediates by Miescher and Hoffmann (*Helv. Chim. Acta*, **24**, 458 (1941)) but presumably were not isolated, since no physical constants are given. We have prepared and characterized them as described in the experiment part. [c] This acid has been prepared previously by partial hydrogenation of diphenylacetic acid, benzilic acid or their esters (Miescher and Hoffmann, *ibid.*, and Smith, Alderman and Nadig, THIS JOURNAL, **67**, 272 (1945)) and by alkylation of benzyl cyanide with cyclohexyl bromide followed by hydrolysis (Venus-Danilova and Bol'ahukin, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 2823 (1937); *C. A.*, **32**, 2925 (1938)). In this work we prepared it by the hydrogenation of phenyl Δ^2-cyclohexenylacetic acid as described in the experimental part. [d] Horclois, *Chemie and Industrie*, Special No., 357-363 (April 1934). [e] Phenyl-Δ^2-cyclopentenylacetic acid was obtained in a crystalline state from hexane, m. p. 71–73°. [f] Calcd.: C, 76.22; H, 8.42. Found: C, 76.55; H, 8.37. [g] Yield based on purified acid chloride. [h] This acid has been previously prepared (Vasiliu, Dumitrascu and Vulcan, *Soc. Chim. Romania Sect. ramâne Stiinte, Bul. chim. pura apl.*, [2] **3A**, 54–60 (1941–1942); *C. A.*, **38**, 5493 (1944)) by the alkylation of benzyl cyanide with cyclopentyl bromide, followed by hydrolysis. In this work we have prepared it by the hydrogenation of phenyl-Δ^2-cyclopentenylacetic acid by a procedure similar to that described in the experimental part for phenylcyclohexylacetic acid. We also prepared it similarly using Raney nickel in place of platinum oxide. It was distilled (b. p. 105° (0.04 mm.)) and recrystallized from hexane, m. p. 99–101°; yield 91%. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.65; H, 7.90. Found: C, 76.73; H, 7.96. [i] Calcd.: C, 75.71; H, 9.03. Found: C, 74.35, 76.48; H, 8.69, 8.64. [j] The acid chloride of this acid was isolated and distilled, yield 90.5%, b. p. 74° (0.1 mm.), $n^{25}D$ 1.5308. [k] Meyer and Boner, *Ann.*, **220**, 51 (1883). [l] Moffett, Hart and Hoehn, THIS JOURNAL, **69**, 1849 (1947). [m] In the preparation of this acid from the corresponding malonic ester the intermediate malonic acid was isolated and a sample recrystallized from ether–hexane, m. p. 163–166° (dec.). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.55; H, 8.29. [n] In the preparation of this acid from the corresponding malonic ester the intermeidate malonic acid was isolated and a sample recrystallized from ether–hexane, m. p. 158.5–160° (dec.). *Anal.* Calcd. for $C_{12}H_{20}O_4$: C, 63.15; H, 8.83. Found: C, 63.15; H, 8.72.

from time to time to dissolve the solid which separated. After removing most of the alcohol by distillation the product was dissolved in water, extracted with ether, and the aqueous layer acidified. The resulting oily acid soon crystallized giving 48.1 g. of the crude substituted acetic acid, m. p. 116–120°. A sample recrystallized from ethyl acetate melted at 120–122°.

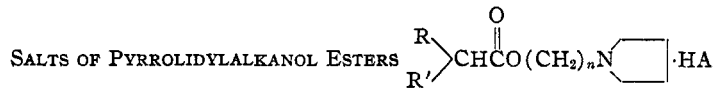
Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.70; H, 7.46; neutral equivalent, 216.3. Found: C, 77.50, 77.89; H, 7.38, 7.44; neutral equivalent, 216.7.

Phenylcyclohexylacetic Acid.—A solution of 41.3 g. (0.19 mole) of phenyl Δ^2-cyclohexenylacetic acid in 125 ml. of 95% alcohol was hydrogenated in the presence of 0.2 g. of platinum oxide catalyst at approximately 3 atmospheres and room temperature. The catalyst was removed by filtration, and concentration and cooling of the solution gave crystals which after recrystallizing from ethanol gave 23.6 g. (56.5%) of acid, m. p. 146.5–147.5°.

Pyrrolidyl Alkanol Esters.—The following is the general procedure used to prepare the esters listed in Table I. A solution of 0.05 mole of the acid in a large excess of thionyl chloride was warmed on a steam-bath until the reaction was complete. The excess thionyl chloride was distilled under diminished pressure; about 25 ml. of dry benzene was added to the residue, and the solvent removed *in vacuo* in order to remove the last trace of thionyl chloride. In some cases the acid chloride was prepared in larger quan-

TABLE II

SALTS OF PYRROLIDYLALKANOL ESTERS



R	R′	n	Amine salts: Kind of salt	Yield,[a] %	M. p., °C.	Solvent[b]	Empirical formula	Analyses, % Calcd.	Found
Phenyl	Phenyl	2	HCl	75.6	126.5–127.5	EtOAc	$C_{20}H_{24}ClNO_2$	Cl, 10.25	10.11[c]
Phenyl	Phenyl	3	HCl	73.2	142.5–143.5	AcEt	$C_{21}H_{26}ClNO_2$	Cl, 9.85	9.75
Phenyl	Δ²-Cyclohexenyl	2	HCl	87.4	132–134	AcEt–EtOAc	$C_{20}H_{28}ClNO_2$	Cl, 10.13	10.08
Phenyl	Δ²-Cyclohexenyl	2	CH_3Br	87.3	127–129	AcEt–EtOAc	$C_{21}H_{30}BrNO_2$	Br, 19.57	19.49
Phenyl	Δ²-Cyclohexenyl	2	CH_3CH_2I	65.4	136–138	MeOH–EtOAc	$C_{22}H_{32}INO_2$	I, 27.04	27.01
Phenyl	Δ²-Cyclohexenyl	3	HCl	80.0	129–133	EtOAc	$C_{21}H_{30}ClNO_2$	Cl, 9.74	9.83
Phenyl	Cyclohexyl	2	HCl	88.0	129–130	EtOAc	$C_{20}H_{30}ClNO_2$	Cl, 10.08	9.95
Phenyl	Cyclohexyl	3	HCl	88.8	123–124.5	EtOAc	$C_{21}H_{32}ClNO_2$	Cl, 9.69	9.60
Phenyl	Δ²-Cyclopentenyl	2	HCl	80.0	106.5–107	EtOAc	$C_{19}H_{26}ClNO_2$	Cl, 10.56	10.36[d]
Phenyl	Δ²-Cyclopentenyl	2	Citric acid[e]	92.0	96–97	MeOH–EtOAc	$C_{26}H_{33}NO_9$	N, 2.85	2.86
Phenyl	Δ²-Cyclopentenyl	2	CH_3Br[e]		103.5–105.5	AcEt–EtOAc	$C_{20}H_{28}BrNO_2$	Br, 20.27	19.77
Phenyl	Δ²-Cyclopentenyl	2	CH_3CH_2Br[e]		129–131	MeOH–EtOAc	$C_{21}H_{30}BrNO_2$	Br, 19.57	19.76
Phenyl	Δ²-Cyclopentenyl	2	CH_3I[e]		112.5–114.5	MeOH–EtOAc	$C_{20}H_{28}INO_2$	I, 28.79	28.34
Phenyl	Δ²-Cyclopentenyl	2	CH_3CH_2I[e]		127.5–129	MeOH–EtOAc	$C_{21}H_{30}INO_2$	C, 55.38	54.95
								H, 6.64	6.55
Phenyl	Δ²-Cyclopentenyl	2	$CH_2{=}CHCH_2Br$[e]		117–119	MeOH–EtOAc	$C_{22}H_{30}BrNO_2$	Br, 19.05	18.25
Phenyl	Δ²-Cyclopentenyl	3	HCl	85.0	117–120	EtOAc	$C_{20}H_{28}ClNO_2$	Cl, 10.13	10.04
Phenyl	Cyclopentyl	2	HCl	75.0	101–102	EtOAc	$C_{19}H_{28}ClNO_2$	Cl, 10.50	10.61[g]
Phenyl	Cyclopentyl	3	HCl	91.8	130–131.5	EtOAc	$C_{20}H_{30}ClNO_2$	Cl, 10.08	10.04
Phenyl	Phenoxy	2	HCl	51.5	117.5–118	EtOAc	$C_{20}H_{24}ClNO_3$	Cl, 9.80	9.56
									10.02[g]
Δ²-Cyclopentenyl	Δ²-Cyclohexenyl	2	HCl	79.0	105.5–106.5	EtOAc	$C_{19}H_{26}ClNO_2$	Cl, 10.43	10.45
Δ²-Cyclopentenyl	Δ²-Cyclohexenyl	3	Citric acid	93.5	120.5–122	EtOH–EtOAc	$C_{26}H_{33}NO_9$	N, 2.75	2.78
Δ²-Cyclopentenyl	*n*-Propyl	2	HCl	76.0	67–71	EtOAc–Et_2O	$C_{16}H_{26}ClNO_2$	Cl, 11.74	11.65
Δ²-Cyclopentenyl	*n*-Propyl	3	HCl	..	83–85	EtOAc–Et_2O	$C_{17}H_{28}ClNO_2$	Cl, 11.23	11.02
Cyclopentyl	*n*-Propyl	2	HCl	71.8	102–104	EtOAc–Et_2O	$C_{16}H_{28}ClNO_2$	Cl, 11.67	11.60
Cyclopentyl	*n*-Propyl	3	HCl	65.0	115.5–116.5	EtOAc–Et_2O	$C_{17}H_{30}ClNO_2$	Cl, 11.16	11.20
Δ²-Cyclopentenyl	*n*-Butyl	2	Citric acid	92.2	88–89	EtOH–EtOAc	$C_{23}H_{31}NO_9$	N, 2.99	2.99
Δ²-Cyclopentenyl	*n*-Butyl	3	HCl	53.0	76–78	EtOAc–Et_2O	$C_{18}H_{32}ClNO_2$	Cl, 10.75	10.69
Δ²-Cyclopentenyl	*n*-Butyl	3	Citric acid	70.0	117–118	EtOH–EtOAc	$C_{24}H_{39}NO_9$	N, 2.89	2.96
Cyclopentyl	*n*-Butyl	2	HCl	85.7	88–90	EtOAc–Et_2O	$C_{17}H_{32}ClNO_2$	Cl, 11.16	11.15
Cyclopentyl	*n*-Butyl	3	HCl	90.0	98.5–102	EtOAc–Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.77

[a] This yield is the amount of pure recrystallized salt that was obtained from the free base. If the filtrates are reworked the yields are usually nearly quantitative. [b] The abbreviations used are as follows: EtOAc, ethyl acetate; AcEt, methyl ethyl ketone; MeOH, methanol; EtOH, absolute ethanol; Et_2O, absolute ether. [c] Calcd.: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.73; H, 6.72; N, 4.35. [d] Calcd.: C, 67.94; H, 7.80; N, 4.18. Found: C, 68.06; H, 7.42; N, 4.50. [e] Prepared in this Laboratory by Mrs. Margery Rabbers. [f] Calcd.: C, 67.54; H, 8.35; N, 4.14. Found: C, 67.12; H, 8.12; N, 4.36. [g] Calcd.: C, 66.23; H, 6.70; N, 3.87. Found: C, 66.08; H, 6.82; N, 3.85.

tities and distilled. The acid chloride was dissolved in 25 ml. of dry benzene and a benzene solution of 0.06 mole of the appropriate pyrrolidyl alkanol added. The reaction took place immediately and usually generated enough heat to reflux the solvent. In a short time the product separated as an oil or crystalline solid. After standing overnight or heating for a short time on a steam-bath under reflux the mixture was diluted with ether and ice-water containing a few drops of hydrochloric acid. The aqueous layer was separated, washed with a fresh portion of ether, and made basic with cold sodium hydroxide. The oily amino ester was taken up in ether, washed thoroughly with water, and dried over sodium sulfate. After removal of the solvent the product was distilled under reduced pressure. The free bases were colorless or light yellow oils.

Salts of Pyrrolidylalkanol Esters (Table II).—The hydrochlorides were prepared by adding a slight excess of an isopropanol solution of hydrogen chloride to a dilute ether solution of the free base. In most cases the hydrochlorides crystallized either immediately or on standing, and were recrystallized from the solvent mentioned in Table II. In some cases it was necessary to remove the solvent completely *in vacuo*, leaving an oily residue which usually crystallized and could be recrystallized from an appropriate solvent. The acid citrate salts were obtained by adding a saturated absolute ethanolic solution of a slight excess of citric acid to a solution of the free base in ethyl acetate.

Quaternary Salts of the Basic Esters.—These salts were prepared by warming a mixture of the free base with the appropriate alkyl halide either with or without ether as a solvent. The crystalline salts were washed with absolute ether and recrystallized from the solvent indicated in Table II.

Summary

Twenty-one new esters of β-(1-pyrrolidyl)-ethanol and γ-(1-pyrrolidyl)-propanol have been prepared, characterized and converted to the salts.

Preliminary pharmacological assays indicate that several of these salts have high antispasmodic activity.

KALAMAZOO, MICHIGAN RECEIVED JUNE 21, 1948