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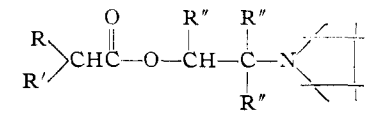
Antispasmodics. III. Pyrrolidylethyl Esters of Disubstituted Acetic Acids

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

In a previous communication[1] we have reported various esters of pyrrolidylethanol and pyrrolidylpropanol. Since the pyrrolidyl ethyl esters were found to have greater antispasmodic activity than the corresponding propyl esters, we have now prepared a series of pyrrolidylethyl esters in which methyl groups are substituted on one or both of the ethyl carbon atoms.



R'' = H or CH_3

The method used to prepare these esters and their hydrochlorides or acid citrates was similar to that previously described.[1] The general procedure is given in the experimental part. The free bases and their salts are listed in Table I.

TABLE I

ESTERS OF N-(2-HYDROXYALKYL)-PYRROLIDINES AND THEIR HYDROCHLORIDES (OR ACID CITRATES)

Acid	Free bases: Yield, %[a]	B. p., °C.	Mm.	$n^{25}D$	Empirical formula	Nitrogen, % Calcd.	Found[b]	Hydrochlorides or acid citrates: Yield,[c] %	M. p.,[d] °C.	Crystallizing solvent	Analyses, Calcd.	Found[b]	Anti-spasmodic activity[e]
N-(2-Hydroxypropyl)-pyrrolidine Esters													
Diphenylacetic	83[f]	119	0.01	1.5455[g]	$C_{21}H_{25}NO_2$	4.33	4.45	68.7	166–167	MeEtCO	9.85	9.72	<0.01
Phenyl-Δ^2-cyclohexenylacetic	67.5[f]	120	.03	1.5219	$C_{21}H_{29}NO_2$	4.28	4.33	59.8	177–186	Me iso-BuCO + iso-PrOH (trace)	9.74	9.48	.02
Phenyl-Δ^2-cyclopentenylacetic[h]	86.0	119	.05	1.5175	$C_{20}H_{27}NO_2$	4.47	4.61	34.9	184–187	iso-PrOH + MeEtCO	10.13	10.04	< .01
Phenylcyclopentylacetic	87.0	112	.03	1.5103	$C_{20}H_{29}NO_2$	4.44	4.42	73.7	120–125	MeEtCO	10.08	10.02	< .01
Δ^2-Cyclohexenyl-Δ^2-cyclopentenylacetic	48.6[f]	125	.03	1.5008	$C_{20}H_{31}NO_2$	4.41	4.47	31.2	147–158	MeEtCO	10.02	10.00	< .01
α-(Δ^2-Cyclopentenyl)-valeric	70.5[f]	105	.025	1.4719	$C_{17}H_{29}NO_2$	5.01	4.87	79.6	97–99	EtOAc + Et_2O	11.23	11.16	< .01
α-Cyclopentylcaproic	61.0[f]	100	.01	1.4649	$C_{18}H_{33}NO_2$	4.74	4.89	84.7	103–108	EtOAc + Et_2O	10.68	10.58	< .01
α-Cyclopentylvaleric	54.6[f]	87	.008	1.4648	$C_{17}H_{31}NO_2$	4.98	5.24	71.6	107–109	EtOAc + Et_2O	11.16	11.28	< .01
N-(1-Hydroxy-2-propyl)-pyrrolidine Esters													
Diphenylacetic	83.5[f]	146	.01	1.5493[i]	$C_{21}H_{25}NO_2$	4.33	4.26	65.2	117.5–120	EtOAc + Et_2O	9.85	9.81	< .01
Phenyl-Δ^2-cyclohexenylacetic[i]	73.3	147	.03	1.2578	$C_{21}H_{29}NO_2$	4.28	4.24	89.0	116–120	EtOAc	9.74	9.64	.20–.25
Phenyl-Δ^2-cyclopentenylacetic[h]	89.2	148	.15	1.5230	$C_{20}H_{27}NO_2$	4.47	4.44	85.0	123–127	EtOAc	10.13	10.31	.25
Phenylcyclopentylacetic	93.6[f]	118	.012	1.5157	$C_{20}H_{29}NO_2$	4.44	4.45	85.7	105–111	EtOAc + Et_2O	10.08	9.54	.25
Δ^2-Cyclohexenyl-Δ^2-cyclopentenylacetic	53.0[f]	114	.01	1.5065	$C_{20}H_{31}NO_2$	4.41	4.46	95.3[m]	127–129	EtOH + EtOAc	2.75	2.74[m]	.07–.1
α-Cyclopentylcaproic	62.9[f]	100	.03	1.4700	$C_{18}H_{33}NO_2$	4.74	4.69	83.9	77–81	EtOAc + Et_2O	10.68	10.56	.1
α-Cyclopentylvaleric[k]	...	90	.012	1.4708	$C_{17}H_{31}NO_2$	4.98	4.89	100[m]	131–132	EtOH + EtOAc	2.96	3.01[m]	.07
N-(1-Hydroxy-2-methyl-2-propyl)-pyrrolidine Esters													
Phenyl-Δ^2-cyclohexenylacetic[i]	87.2	147	.028	1.5259	$C_{22}H_{31}NO_2$	4.10	4.21	74.6[m]	112–114	EtOH + EtOAc	2.63	2.70[m]	.07
Phenyl-Δ^2-cyclopentenylacetic[h]	80.3	128	.015	1.5220	$C_{21}H_{29}NO_2$	4.28	4.25	84.5[m]	103–107	EtOH + EtOAc	2.70	2.73[m]	.07
Δ^2-Cyclohexenyl-Δ^2-cyclopentenylacetic[k]	44.7	124	.008	1.5070	$C_{21}H_{33}NO_2$	4.23	4.15	64.0	117–119	EtOAc	9.64	9.44	.03
α-Cyclopentylvaleric[k]	61.0	107	.05	1.4775	$C_{18}H_{33}NO_2$	4.74	4.73	87.8[m]	103–103.5	EtOH + EtOAc	2.87	2.94[m]	.01
N-(3-Hydroxy-2-butyl)-pyrrolidine Esters													
Phenyl-Δ^2-cyclohexenylacetic[i]	79.7	132	.012	1.5230	$C_{22}H_{31}NO_2$	4.10	4.28	93.6[m]	90–102	EtOH + EtOAc	2.62	2.61[m]	.02
Phenyl-Δ^2-cyclopentenylacetic[h]	78.7	120	.01	1.5183	$C_{21}H_{29}NO_2$	4.28	4.26	100[m]	80–106	EtOH + EtOAc	2.70	2.71[m]	.03
Δ^2-Cyclohexenyl-Δ^2-cyclopentenylacetic[k]	59.8	144	.04	1.5030	$C_{21}H_{33}NO_2$	4.23	4.33	63.3[m]	97–103	EtOH + EtOAc	2.66	2.65[m]	.01
α-Cyclopentylvaleric[k]	71.8	90	.03	1.4696	$C_{18}H_{33}NO_2$	4.74	4.69	57.1	106.5–111	EtOAc + Et_2O	10.68	10.45	.01
N-(2-Hydroxyethyl)-pyrrolidine Ester													
α-Phenylisocaproic[i]	92.7	130	.15	1.5001	$C_{18}H_{27}NO_2$	4.84	4.77	90.4	99.5–100.5	EtOAc	10.88	10.85	< .01

[a] Unless otherwise indicated the yield is based on the acid chloride. [b] Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratories. [c] The yield is based on the distilled free base and would in most cases be essentially

(1) Kolloff, Hunter, Woodruff and Moffett, THIS JOURNAL, 70, 3862 (1948).

quantitative except that the filtrates from the crystallizations were not reworked. [d] Melting points are uncorrected. [e] Tested by the method of Magnus [*Arch. ges. Physiol.* (*Pflügers*), **102**, 123 (1904); **103**, 515 (1904)] against acetylcholine chloride spasm. The results are expressed as a fraction of the activity of atropine sulfate. [f] In this preparation the intermediate acid chloride was not isolated. The yield is based on the acid. [g] d^{25}_4 1.0650. [h] Phenyl-Δ^2-cyclopentenylacetyl chloride [Horclois, *Chemie and Industrie*, Special No. 357–363 (April, 1934)] was obtained in crystalline, form; freezing point about 11°. [i] The intermediate acid chloride is reported in second paper of this series [THIS JOURNAL, **71**, 3988 (1949)]. [j] d^{25}_4 1.0756. [k] The intermediate acid chloride was reported by Moffett, Hart and Neil, in press [l] Hydrochlorides were analyzed for chlorine, acid citrates for nitrogen. [m] Acid citrate salt.

The intermediate pyrrolidylalkanols have been reported recently from this Laboratory,[2] and the intermediate acids are in general those found to give the most active antispasmodics when esterified with pyrrolidylethanol.[1]

It will be noted that these esters contain one or more asymmetric carbon atoms, but no attempt was made to separate either diastereoisomers or optically active forms.

Preliminary pharmacological assays have been carried out by Dr. Milton J. Vander Brook of our Department of Pharmacology and the results are indicated in Table I. It appears that substitution of a methyl group on the carbon atom next to the nitrogen has little effect on the antispasmodic activity, whereas substitution of a methyl group on the carbon atom adjacent to the oxygen greatly decreases the activity.

Experimental

Pyrrolidyl-alkyl Esters.—To a solution of 0.05 mole of the appropriate acid chloride in 10 ml. of dry benzene was added a solution of 0.06 mole of the pyrrolidylalkanol in 15 ml. of dry benzene. After the initial reaction had subsided the mixture was refluxed on a steam-bath for one-half to four hours. The longer times of refluxing were used when the initial reaction appeared sluggish. The reaction mixture was diluted with ice water, acidified with hydrochloric acid, and extracted twice with ether. The aqueous solution was made basic with cold sodium hydroxide solution, and the oil which separated was taken up in ether. The ether solution of the free base was washed twice with water and dried over anhydrous sodium sulfate. After removal of the ether the product was distilled from a Claisen flask giving a nearly colorless liquid with the properties listed in Table I.

Salts of the Pyrrolidylalkyl Esters.—Hydrogen chloride gas was bubbled into an absolute ether solution of the free base until the solution tested strongly acidic. In most cases the hydrochlorides crystallized either immediately or on standing and scratching. In a few cases crystallization was obtained by removing the solvent *in vacuo* and scratching the oily residue. The crude crystals were recrystallized from the solvents indicated in Table I. When the hydrochlorides proved very difficult to crystallize the acid citrates were prepared by adding a slight molar excess of citric acid in a minimum amount of hot absolute ethyl alcohol to a solution of the free base in ethyl acetate. The acid citrates separated on standing and needed no further purification. The properties of all these salts are listed in Table I.

Phenylcyclopentylacetyl Chloride.—A solution of 102.1 g. (0.5 mole) of phenylcyclopentylacetic acid[1] and 75 ml. of thionyl chloride in 75 ml. of dry benzene was warmed on a steam-bath for one-half hour and allowed to stand overnight. After removal of the solvent, the acid chloride was distilled through a short column (packed with glass helices) giving 101 g. (90.8%) of a light yellow liquid, b. p. 145° (12 mm.), $n^{25}D$ 1.5312.

Anal. Calcd. for $C_{13}H_{15}ClO$: Cl, 15.92. Found: Cl, 15.34.

Summary

1. Twenty-four new pyrrolidylethyl esters of disubstituted acetic acids are described in which methyl groups are substituted on the ethyl link.

2. Preliminary pharmacological assays indicate that some of these compounds have high antispasmodic activity.

(2) Moffett, *J. Org. Chem.*, **14**, 862 (1949).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

Bromination of Trifluoromethylbenzenes

BY E. T. MCBEE, R. A. SANFORD[1] AND P. J. GRAHAM

A study of the bromination of trifluoromethyl and bis-(trifluoromethyl) derivatives of benzene and chlorobenzene was conducted to produce intermediates for use in the synthesis of fluorine-containing styrenes. The catalytic bromination of trifluoromethylbenzene[2] in the presence of iron at 60° gave a low yield of bromo-(trifluoromethyl)-benzene since a substantial proportion of the trifluoromethylbenzene was converted to benzoic acid. A search for other halogen carriers, applicable in brominations, led to the use of antimony(V) chloride. Although the activity of this halogen carrier diminished rapidly because of its reduction to antimony(III) salts, continuous introduction of chlorine into the reaction mixture maintained a sufficient concentration of antimony(V) chloride for satisfactory bromination. The application of this technique proved particularly advantageous since the yield of bromo-(trifluoromethyl)-benzene, for example, was greater than that expected from the stoichiometric relationship: $C_6H_5CF_3 + Br_2 \rightarrow C_6H_4(CF_3)Br + HBr$. In some instances, as high as 94% of the bromine added was converted to the desired organic bromo compound. Bromine chloride, which is known to be a powerful brominating

(1) Abstracted from doctoral theses of R. A. Sanford and P. J. Graham. Presented before the Division of Organic Chemistry at the 113th meeting of the American Chemical Society, Chicago, Illinois.

(2) J. H. Simons and E. O. Ramler, THIS JOURNAL, **65**, 389 (1943).