[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

ANTISPASMODICS. IV. TERTIARYAMINO ALKYL ESTERS OF DISUBSTITUTED ACETIC ACID

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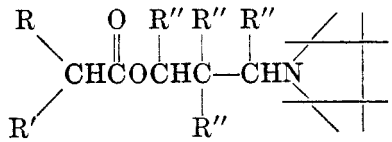
In previous work (1, 2) it was found that pyrrolidylethyl esters have higher antispasmodic activity than the pyrrolidylpropyl esters. To test further this generalization and to determine whether it would extend to branched chain compounds, we have now prepared a series of pyrrolidylpropyl esters in which methyl groups are substituted on the propyl link (Formula I).

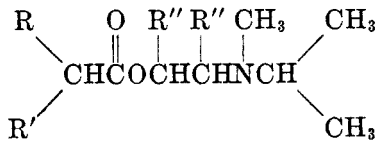


I R″ = H or CH_3

The low activity of these compounds (Table II) has confirmed this generalization.

Included in this paper are a few pyrrolidylbutyl and pyrrolidylethoxyethyl esters. These also have low activity.

A number of N-isopropyl-N-methylaminoalkyl esters (Formula II) have been prepared.



II R = H or CH_3

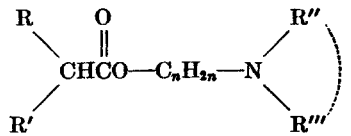
Their activity (Table II) seems to be in general a little greater than that of the isomeric diethylaminoalkyl esters.

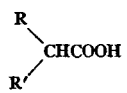
These esters were prepared from the corresponding acid chlorides and tertiary-amino alcohols by the method previously described (1, 2). The preparation of the requisite pyrrolidyl alcohols (3) and N-isopropyl-N-methylamino-ethanol and -isopropanol (4) have been recently reported. 2-(N-Isopropyl-N-methyl-amino)propanol was prepared[1] by the reductive alkylation of 2-aminopropanol with acetone in the presence of platinum and hydrogen, followed by methylation with formaldehyde and formic acid.

[1] Prepared by Mr. Gordon F. Kurtz in these laboratories.

TABLE I

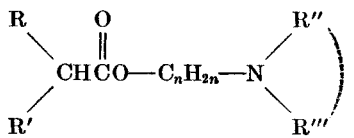
FREE BASES

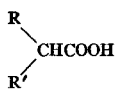
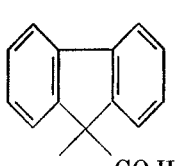


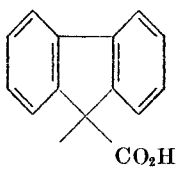
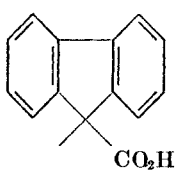
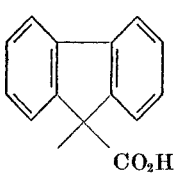
NO.	ACID USED 	AMINO ALCOHOL USED HOC_nN_{2n}—N	YIELD, %[a]	B.P. °C.	B.P. mm.	n_D^{25}	EMPIRICAL FORMULA	NITROGEN, % Calc'd	NITROGEN, % Found[b]
1	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH(CH_3)CH_2CH_2$—$NCH_2CH_2CH_2CH_2$	83.8	140	0.016	1.5205	$C_{22}H_{31}NO_2$	4.10	4.19
2	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH(CH_3)CH_2CH_2$—$NCH_2CH_2CH_2CH_2$	81.3	135	.22	1.4671	$C_{18}H_{33}NO_2$	4.74	4.82
3	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3)CH_2$—$NCH_2CH_2CH_2CH_2$	97.0	128	.01	1.5223	$C_{22}H_{31}NO_2$	4.10	4.08
4	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH(CH_3)CH_2$—$NCH_2CH_2CH_2CH_2$	96.1	100	.013	1.4681	$C_{18}H_{33}NO_2$	4.74	4.72
5	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH(CH_3)$—$NCH_2CH_2CH_2CH_2$	92.3	146	.024	1.5213	$C_{21}H_{29}NO_2$	4.28	4.38
6	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2CH(CH_3)$—$NCH_2CH_2CH_2CH_2$	96.2	115	.027	1.4717	$C_{18}H_{33}NO_2$	4.74	4.75
7	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2C(CH_3)_2CH_2$—$NCH_2CH_2CH_2CH_2$[c,d]	85.5	130	.007	1.5187	$C_{23}H_{33}NO_2$	3.94	3.92
8	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2C(CH_3)_2CH_2$—$NCH_2CH_2CH_2CH_2$	90.6	131	.11	1.4677	$C_{19}H_{35}NO_2$	4.53	4.57

9	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	86.0	138	.17	1.5192	$C_{21}H_{29}NO_2$	4.28	4.26
10	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	87.7	162	.38	1.5241	$C_{22}H_{31}NO_2$	4.10	4.21
11	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	95.4	130	.07	1.4698	$C_{18}H_{33}NO_2$	4.74	4.83
12	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}O{-}CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	87.2	152	.03	1.5188	$C_{21}H_{29}NO_3$	4.08	4.07
13	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2{-}O{-}CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	75.1	130	.04	1.4691	$C_{18}H_{33}NO_3$	4.49	4.50
14	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.2	112	.015	1.5091	$C_{19}H_{27}NO_2$	4.65	4.69
15	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.2	145	.15	1.5017	$C_{19}H_{29}NO_2$	4.62	4.84
16	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.4	123	.01	1.5140	$C_{20}H_{29}NO_2$	4.44	4.46
17	$CH_2CH_2CH_2CH{=}CHCHCH(CH_2CH_2CH{=}CHCH)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	51.1	125	.03	1.4918	$C_{19}H_{31}NO_2$	4.59	4.58
18	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	77.2	98	.03	1.4547	$C_{16}H_{31}NO_2$	5.20	5.26
19	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH(CH_3)CH_2{-}N(CH_3)CH(CH_3)_2$[c, e]	63.8	122	.01	1.5080	$C_{21}H_{31}NO_2$	4.25	4.52
20	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3){-}N(CH_3)CH(CH_3)_2$	85.6	116	.01	1.5082	$C_{20}H_{29}NO_2$	4.44	4.47

TABLE I—*Continued*

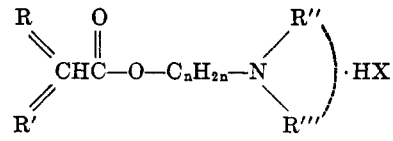
FREE BASES 

NO.	ACID USED 	AMINO ALCOHOL USED HOC_nN_{2n}—N 	YIELD, %[a]	B.P. °C.	B.P. mm.	n_D^{25}	EMPIRICAL FORMULA	NITROGEN, % Calc'd	NITROGEN, % Found[b]
21	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3)—N(CH_3)CH(CH_3)_2$	78.4	129	.02	1.5131	$C_{21}H_{31}NO_2$	4.25	4.17
22	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH(CH_3)—N(CH_3)CH(CH_3)_2$	79.2	85	.01	1.4578	$C_{17}H_{33}NO_2$	4.94	4.99
23	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	55.0[f]	130	.04	—	$C_{19}H_{27}NO_2$	—	—
24	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	75.9[f]	130	.04	—	$C_{19}H_{29}NO_2$	—	—
25	$C_6H_5OCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	52.0[f]	175	.07	—	$C_{20}H_{25}NO_3$	—	—
26		$HOCH_2CH_2—NCH_2CH_2CH_2CH_2$[g]	—	—	—	—	—	—	—

27		$HOCH_2CH_2CH_2-N\langle CH_2CH_2CH_2CH_2$ [a]	—	—	—	—	—	—	—
28		$HOCH(CH_3)CH_2-N\langle CH_2CH_2CH_2CH_2$ [a]	—	—	—	—	—	—	—
29		$HOCH_2CH(CH_3)-N\langle CH_2CH_2CH_2CH_2$ [a]	—	—	—	—	—	—	—

[a] Yield based on acid chloride. [b] Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratory. [c] No crystalline salt was obtained from this free base, but it was dissolved in dilute hydrochloric acid and tested pharmacologically (Table II, footnote [e]). [d] Antispasmodic activity, 0.05. [e] Antispasmodic activity, 0.013. [f] Yield based on acid used. The acid chloride was not isolated in this run. [g] The free base was not isolated. See Table II for salt.

TABLE II

SALTS  ·HX

NO.[a]	SALT FORMING ACID	YIELD, %[b]	M.P., °C.[c]	CRYSTALLIZING SOLVENT	EMPIRICAL FORMULA	ANALYSES, %		ANTISPASMODIC ACTIVITY[e]
						Calc'd	Found[d]	
1	HCl	74.0	153–154.5	MeEtCO	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.23	0.01
2	HCl	87.5	125–127	EtOAc	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.78	.01
3	HCl	71.8	119–123	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.31	.01
4	HCl	78.2	88–89	EtOAc + Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.72	.01
5	HCl	83.8	133–136	MeEtCO	$C_{21}H_{30}ClNO_2$	Cl, 9.74	9.73	.03
6	HCl	68.4	78–80	EtOAc + Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.64	.01
8	HCl	90.2	134–135.5	EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.02	10.00	.01
9	HCl	84.6	101–103	EtOAc	$C_{21}H_{30}ClNO_2$	Cl, 9.74	9.52	.01
10	HCl	65.4	97–99	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.47	.01
11	Citric acid	92.0	93.5–94.5	EtOH + EtOAc	$C_{24}H_{41}NO_9$	N, 2.87	2.89	.01
12	Citric acid	79.3	87–90	MeEtCO	$C_{27}H_{37}NO_{10}$	N, 2.62	2.65	.01
13	Citric acid	92.2	77–79	EtOAc	$C_{24}H_{41}NO_{10}$	N, 2.78	2.85	.01
14	HCl	64.0	93–98	EtOAc + Et_2O	$C_{19}H_{28}ClNO_2$	Cl, 10.49	10.44	.15
15	HCl	75.3	105–106.5	EtOAc + EtO_2	$C_{19}H_{30}ClNO_2$	Cl, 10.43	10.48	.33
16	HCl	65.3	121–124	EtOAc	$C_{20}H_{30}ClNO_2$	Cl, 10.08	10.21	.33
17	HCl	66.5	90–97	EtOAc + Et_2O	$C_{19}H_{32}ClNO_2$	Cl, 10.37	10.32	.12
18	HCl	77.6	74–80	EtOAc + Et_2O	$C_{16}H_{32}ClNO_2$	Cl, 11.59	11.70	.10
20	Citric acid	76.9	83–90	EtOH + EtOAc + Et_2O	$C_{16}H_{37}NO_9$	N, 2.76	2.92	.17
21	Citric acid	71.3	85–95	EtOH + EtOAc + Et_2O	$C_{27}H_{39}NO_9$	N, 2.69	2.84	.30
22	Citric acid	87.4	81–84	EtOH + EtOAc + Et_2O	$C_{23}H_{41}NO_9$	N, 2.95	2.91	.10
23	HCl	94.5	146–147	EtOAc + Et_2O	$C_{19}H_{28}ClNO_2$	Cl, 10.49	10.58[f]	.14
24	HCl	78.6	128–129	EtOAc	$C_{19}H_{30}ClNO_2$	Cl, 10.43	10.61[g]	.12
25	HCl	72.8	114–115	EtOAc	$C_{20}H_{26}ClNO_3$	Cl, 9.74	9.88[h]	.01
26	HCl	62.9[i]	109–114[j]	Me_2CO	$C_{20}H_{22}ClNO_2$	N, 4.07 Cl, 10.31	4.05 10.38	.02

TABLE II (*Continued*)

NO.[a]	SALT FORMING ACID	YIELD %[b]	M.P., °C.[c]	CRYSTALLIZING SOLVENT	EMPIRICAL FORMULA	ANALYSES, %		ANTISPASMODIC ACTIVITY
						Calc'd	Found[d]	
27	Citric acid	27.2[i]	108–112[k]	EtOH	$C_{27}H_{31}NO_9$	N, 2.73	2.77	.01
28	HCl	58.1[i]	217–220	EtOH	$C_{21}H_{24}ClNO_2$	N, 3.92 Cl, 9.91	3.92 9.82	.01
29	HCl	45.3[i]	157–162	Me_2CO	$C_{21}H_{24}ClNO_2$	N, 3.92 Cl, 9.91	4.11 9.81	.01

[a] Numbers correspond to the numbers of the free bases in Table I. [b] The yield is based on the distilled free base and would in most cases be essentially quantitative except that the filtrates from the crystallizations were usually not reworked. [c] Melting points are uncorrected. [d] Table I footnote [b]. [e] Preliminary testing was done by Dr. Milton J. Vander Brook of our Department of Pharmacology by the method of Magnus [Arch. ges. Physiol. (Pflügers), **102**, 123 (1904); Arch. ges. Physiol. (Pflügers), **103**, 515 (1904)] and the results are expressed as a fraction of the activity of atropine sulfate when tested on muscle stimulated with acetylcholine chloride. [f] Calc'd: C, 67.54; H, 8.35; N, 4.14. Found: C, 67.46; H, 8.21; N, 4.07. [g] Calc'd: C, 67.14; H, 8.90. Found: C, 67.20; H, 8.68. [h] Calc'd: C, 66.01; H, 7.20; N, 3.88. Found: C, 65.12; H, 7.28; N, 4.01. [i] Yield based on the acid chloride used in the preparation. [j] A sample of this hydrochloride heated at 100° under a vacuum of 0.01 mm., sintered and then again crystallized, m.p. 131–136°. *Anal.* Found: N, 4.35; Cl, 10.30. [k] After sintering at about 93–96°.

EXPERIMENTAL

2-(N-Isopropylamino)propanol.[1] This was prepared in 85% yield from acetone and 2-aminopropanol by the procedure described by Hancock and Cope (5) for 2-isopropylaminoethanol. B.p. 71° (15 mm.).

2-(N-Isopropyl-N-methylamino)propanol.[1] This was prepared in 65% yield from the above amine by the procedure described by Icke, Wisegarner, and Alles (6) for β-phenylethyldimethylamine. B.p. 81° (35 mm.), n_D^{25} 1.4371.

Anal. Calc'd for $C_7H_{17}NO$: N, 10.68. Found: N, 10.71.

SUMMARY

Twenty-nine new tertiary amino alkyl esters of disubstituted acetic acids have been prepared and their antispasmodic activity is reported.

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REFERENCES

(1) KOLLOFF, HUNTER, WOODRUFF, AND MOFFETT, *J. Am. Chem. Soc.*, **70**, 3862 (1948).
(2) KOLLOFF, HUNTER, AND MOFFETT, *J. Am. Chem. Soc.*, **72**, 1650 (1950).
(3) MOFFETT, *J. Org. Chem.*, **14**, 862 (1949).
(4) WRIGHT, LINCOLN, AND HUNTER, *J. Am. Chem. Soc.*, **72**, in press.
(5) HANCOCK AND COPE, *Org. Syntheses*, **26**, 38 (1946).
(6) ICKE, WISEGARNER, AND ALLES, *Org. Syntheses*, **25**, 89 (1945).