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HETEROCYCLIC AMINOACRYLATE ESTERS OF POTENTIAL BIOLOGICAL ACTIVITY

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ABSTRACT

This work describes the synthesis of N-substituted piperidyl 2-benzoxazole acrylates (la-d); 2-benzothiazole acrylates (2a-d); 2-furyl acrylates (3a-d) and 2-thiophene acrylates (4a-d). The esters of 3-quinuclidyl (le, 2e, 3e, 4e) and N, N-dimethylaminoethyl - (1f, 2f, 3f, 4f) and of N, N-diethylaminoethyl - (1g, 2g, 3g, 4g) of the respective acids have been also synthesized.

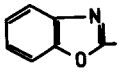
The psychotopathic properties of the prepared compounds will be published elsewhere.

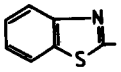
INTRODUCTION

Substituted piperidinols form an important class of psychotopathic agents (Abood *et al*, 1958, 1959, Biel *et al.*, 1955, 1961; Cannon, 1960; Kadin and Cannon, 1962).

This work reports the synthesis of a number of acrylate esters of substituted piperidinols and of other amino-alcohols (1-4).

The acids employed were 2-benzoxazole-, 2-benzothiazole-, 2-furyl-, and 2-thienylacrylic acids.

(1)  CH=CH–COOR

(2)  CH=CH–COOR

(3)  CH=CH–COOR

(4)  CH=CH–COOR

R =

a: N-methyl - 4 - piperidyl
b: N-ethyl - 4 piperidyl
c: N-methyl - 3 piperidyl
d: N-ethyl - 3 piperidyl
e: - 3 - quinuclidinyl
f: 2 - N, N - dimethylaminoethyl
g: 2-N, N-dithylaminoethyl

Table 1

Compound	Procedure	Yield %	m.p°c	b.p°c	Molecular formula	Elemental analysis %						CO ester i.r. absorption cm $^{-1}$
						Calculated			Found			
						C	H	N	C	H	N	
Ia	b	32	82 Pet. ether (60-80)		$C_{16}H_{18}N_2O_3$	67.11	6.34	9.78	67.43	6.30	9.66	1736
Ib	b	30	100 Pet. ether (40-60)		$C_{17}H_{20}N_2O_3$	67.98	6.71	9.33	67.73	6.59	9.26	1740
Ic	b c	23 32	93 93 n. heptane		$C_{16}H_{18}N_2O_3$	67.11	6.34	9.78	66.94	6.25	9.63	1735
Id	c a	57 42	80 80 Pet. ether		$C_{17}H_{20}N_2O_3$	67.98	6.71	9.33	68.09	6.76	9.24	1736
Ie	c	40	112 Pet. ether (40-60)		$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39	68.62	5.97	9.31	1740
If	b	25	77 Pet. ether		$C_{14}H_{16}N_2O_3$	64.60	6.2	10.76	64.42	6.27	10.52	1740
Ig	a	42	50 n. hexane		$C_{16}H_{20}N_20_3$	66.64	6.99	9.72	66.55	7.04	9.61	1736
2a	b	33	99 isopropanol		$C_{16}H_{18}N_2O_2S$	63.55	6.0	9.26	63.6	5.7	9.02	1740

Table 1 (Contd.)

Compound	Procedure	Yield %	m.p°c	b.p°c	Molecular formula	Elemental analysis %						CO ester i.r. absorption cm^{-1}
						Calculated			Found			
						C	H	N	C	H	N	
2b	b	34	89 ether		$C_{17}H_{20}N_2O_2S$	64.53	6.37	8.58	64.7	6.36	9.02	1736
2c	a	54	216 isopropanol		$C_{16}H_{19}ClN_2O_2S$	56.66	5.35	8.27	56.51	5.66	8.49	1740
2d	b	38	67 Pet. ether 60-80		$C_{17}H_{20}N_2O_2S$	64.53	6.37	8.85	64.2	6.7	8.93	1740
2e	c	50	121 n. heptane		$C_{17}H_{18}N_2O_2S$	64.94	5.77	8.91	64.78	5.7	8.84	1736
2f	a	30	69 n. hexane		$C_{14}H_{16}N_2O_2S$	60.84	5.84	10.14	60.61	6.06	10.31	1735
2g	a	50	37 n. hexane		$C_{16}H_{20}N_2O_2S$	63.13	6.62	9.2	63.32	6.54	9.42	1736
3a	d	55	57	137/0.1 ethanol (mm)	$C_{13}H_{17}NO_3$	66.36	7.28	5.96	66.31	7.31	6.11	1712
3b	d	50		162/0.5 (mm)	$C_{14}H_{19}NO_3$	67.44	7.68	5.62	67.34	7.85	5.76	1710
3c	d	40		152/0.5 (mm)	$C_{13}H_{17}NO_3$	66.36	7.28	5.96	66.43	7.36	6.11	1710

Table 1 (Contd.)

Compound	Procedure	Yield %	m.p°c	b.p°c	Molecular formula	Elemental analysis %						CO ester i.r. absorption cm^{-1}
						Calculated			Found			
						C	H	N	C	H	N	
3d	d	56		158/0.5 (mm)	$C_{14}H_{19}N\ O_3$	67.44	7.68	5.62	67.42	7.7	5.57	1710
3e	d	40		187/0.5 (mm)	$C_{14}H_{17}N\ O_3$	67.72	7.3	5.64	67.76	7.06	5.66	1710
4a	d	76		176/1.5 (mm)	$C_{13}H_{17}N\ O_2S$	62.12	6.82	5.57	62.04	6.91	5.5	1730
4b	d	62		167/1.0 (mm)	$C_{14}H_{19}N\ O_2S$	63.36	7.22	5.28	63.22	7.34	5.21	1736
4c	d	71		153/1.0 (mm)	$C_{13}H_{17}N\ O_2S$	62.12	6.82	5.57	62.03	6.73	5.63	1735
4d	d	58		160/1.0 (mm)	$C_{14}H_{19}N\ O_2S$	63.36	7.22	5.28	63.42	7.09	5.31	1735
4e	d	47		178/1.0 (mm)	$C_{14}H_{17}N\ O_2S$	63.85	6.5	5.32	63.67	6.42	5.23	1730

Esterification was accomplished using four different methods, namely, condensation of the acid with the respective alkyl chloride in 2-propanol; reaction of the respective acid with aminoalcohol in the presence of ethyle chloroformate; transesterification with sodium methoxide as a catalyst and condensation of the respective acrylic acid chloride with the aminoalcohol in dry benzene.

The synthesized acrylate esters were characterized by micro-analytical data, ir and nmr spectral measurements. Constants of these compounds are given in Table (1).

EXPERIMENTAL

The following illustrates the general procedures:

a) N-Methyl-3-piperdly-2-benzoxazole acrylate (lc):

A mixture of 2-benzoxazole acrylic acid (2.0 g; 0.011 mole), 3-chloro-N-methylpiperidine (2.0 g; 0.015 mole) and 50 ml of 2-propanol was heated under reflux for 30 h. It was allowed to attain room temperature, filtered off and the solvent removed under reduced pressure. The residue was dissolved in 50 ml of 10% HCl, extracted three times with ether and the acidic layer made alkaline by the addition of 40 ml of ice-cold 20% NaOH. The precipitated product was, again, extracted with a 1:2 mixture of methylenechloride-ether, and, the organic layer dried over anhydrous sodium sulphate. Evaporation of the organic layer gave 1.0 g (32% yield) of lc.

b) N-Ethyl-4-piperidyl-2-benzoxazole acrylate (lb)

To a cooled solution of 2-benzoxazole acrylic acid (3.8 g; 0.02 mole) in 30 ml of methylene chloride was added, portionwise, with stirring (2.0g, 0.02 mole) of triethylamine. To the resulting clear solution, 2.4 g, (0.022 mole) of ethyl chloroformate was added, dropwise, with stirring during which time the temperature was maintained between 0-5°. The reaction mixture was kept at this temperature for 30 min. A solution of N-ethyl-piperidinol (2.58 g; 0.02 mole) in 60 ml of methylene chloride was then added with continuous cooling. After the addition was completed, the reaction mixture was allowed to stand at room temperature for two hours and the product was isolated as described under procedure(a).

c) 3-Quinuclidinyl-2-benzothiazole acrylate (2e):

A mixture of methyl-2-benzothiazol acrylate (2.5 g; 0.011 mole), and 3-quinuclidinol (1.6 g; 0.0125 mole) in 140 ml of n-heptane was placed in a reaction flask fitted with a Dean-Stark moisture separating tube which allows azeotropic separation of methanol. Solid sodium methoxide (0.2 g; 0.004 mole) was added and the flask heated at

waterbath temperature until no more methanol distilled off. The reaction mixture was filtered off, the solvent evaporated and the product worked up as described under procedure (a). Recrystallization from n-heptane furnished compound (2e)-(1.7 g. 50%), m.p. 121°C.

d) N-Methyl-4-piperidyl-2-furan acrylate (3a):

To a mixture of 2-furylacrylic acid (7.0 g; 0.05 mole) and dimethylformamide (0.5 g) in 50 ml of dry benzene was added, portionwise, with stirring (11.9 g; 0.1 mole) of thionyl chloride. The reaction mixture was then heated at reflux temperature for 5.0 h and the solvent was then removed under reduced pressure. To the crude acid chloride dissolved in 50 ml of dry benzene, 11.5 g; (0.1 mole) of N-methyl-4- piperidinol was added, dropwise, with stirring. The reaction mixture was heated reflux for 5.0 h, cooled and filtered off.

The benzene layer was washed with water, dried over anhydrous sodium sulphate and evaporated. The product was distilled under reduced pressure. The product (6.5 g; 55% yield), distilled at 137°C (0.1 mm). Recrystalization from ethanol furnished crystals m.p. 57°C.

Physical constants, recrystallization solvents, and percentage yields of the prepared compounds la-g; 2a-g; 3a-e and 4a-e are presented in Table (1).

The pharmacological data of the tested compounds will appear elsewhere.

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المركبات الحلقية غير المتجانسة لاسترات الأكريل الأمينية ذوات النشاط البيولوجي المتوقع

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يشمل هذا البحث نتيجة تفاعلات أحماض بنزأوكسازول ـ ٢ ـ أكريليك ، بنزوثيازول ـ ٢ ـ أكريليك ، فيوران ـ ٢ ـ أكريليك ، ثيوفين ـ ٢ ـ أكريليك أو مشتقاتها مع الببريدينول أو مشتقاته ، ثنائي ميثيل وثنائي ايثيل ايثانول أمين لتحضير استرات هذه الأحماض للكحولات المذكورة .

والغرض من تحضير هذه الاسترات اختبار فعاليتها البيولوجية على الجهاز العصبي .