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Aminoacyl Derivatives of 9-Aminofluorene

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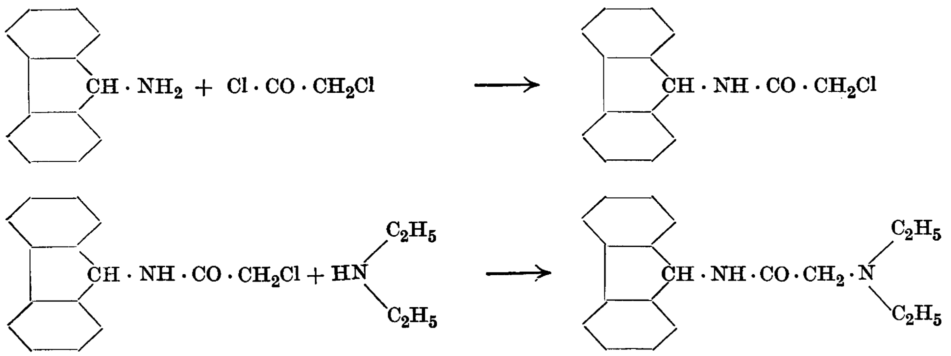
Some time ago we synthesised in this laboratory a series of aminoacyl-substituted phenothiazine derivatives[1]. As they possessed rather interesting pharmacological properties, we thought it worth while preparing similar compounds containing other condensed ring systems. Derivatives of fluorene have proved to possess interesting features, especially as antispasmodics[2], and we have now prepared several aminoacyl derivatives of 9-aminofluorene, analogous to the phenothiazine compounds.

Haloacylhalides react easily with 9-aminofluorene to form haloacylaminofluorenes. The reaction can be carried out using either sodium acetate[3] or pyridine as condensing agent, the latter method giving a somewhat higher yield. The haloacylamines are then treated with excess of the appropriate amine, which gives the desired aminoacyl compounds. The procedure may be examplified by the following reactions:



The compounds have been subjected to preliminary pharmacological tests (S. Wiedling). They all showed a high local anesthetic power, 1—12 times the activity of Xylocaine when tested on rabbit cornea. However, the time of onset was much longer, and they all exhibited an irritant action. When tests were carried out on isolated guinea pig ileum, the compounds showed a very weak antihistaminic and antispasmodic effect.

EXPERIMENTAL

Halogenoacylaminofluorenes

9-(Chloroacetylamino)-fluorene. 9-Aminofluorene hydrochloride[4] (11.0 g) was suspended in water (125 ml) and made alkaline with sodium hydroxide. The precipitated base was extracted with ether (2 × 100 ml), the ether solution dried over solid NaOH and filtered. Pyridine (4.0 ml) was then added to the ether solution and chloroacetyl chloride (6.8 g) was added drop by drop with stirring and cooling with ice water. A white precipitate was formed, which was collected and washed with dilute acetic acid. After drying in air the crude product (11.0 g) was recrystallised twice from ethanol. M. p. 238–239°.

$C_{15}H_{12}ClNO$ (257.7)	Calc.	C	69.9	H	4.70	N	5.44
	Found	»	70.0	»	4.81	»	5.35

9-(β-Chloropropionylamino)-fluorene. From 9-aminofluorene hydrochloride (6.7 g) and β-chloropropionyl chloride (3.8 g) in the same way as described above. M. p. 202–203.5° (dec.) after recrystallisation of the crude product (7.2 g) from acetone.

$C_{16}H_{14}ClNO$ (271.7)	Calc.	C	70.7	H	5.19	Cl	13.1
	Found	»	70.8	»	5.36	»	13.1

9-(α,β-Dibromopropionylamino)-fluorene. From 9-aminofluorene hydrochloride (4.3 g) and α,β-dibromopropionyl chloride (4.8 g). M. p. 227–228° after recrystallisation of the crude product (5.5 g) from light petroleum-ethanol (1 : 2).

$C_{16}H_{13}Br_2NO$ (395.1)	Calc.	C	48.6	H	3.31	Br	40.4
	Found	»	49.0	»	3.21	»	40.0

9-(α-Bromopropionylamino)-fluorene. 9-Aminofluorene (18.1 g) was mixed with glacial acetic acid (85 ml) and α-bromopropionyl bromide (23.0 g) was added. An aqueous solution of sodium acetate (33 g in 140 ml) was then added in portions with stirring. The mixture was stirred for half an hour and the resulting precipitate was collected and dried in air. The crude product (21.0 g) was recrystallised twice from ethanol. M. p. 243–244°.

$C_{16}H_{14}BrNO$ (316.2)	Calc.	C	60.8	H	4.46	N	4.43
	Found	»	60.5	»	4.44	»	4.40

9-(α-Bromobuturylamino)-fluorene. This compound was prepared from 9-aminofluorene (15.8 g) and α-bromobuturyl bromide (22.0 g). The crude product (21.0 g) was recrystallised from ethanol. M. p. 226–227°.

$C_{17}H_{16}BrNO$ (330.2)	Calc.	C	61.8	H	4.89	Br	24.2	N	4.24
	Found	»	61.3	»	4.91	»	23.9	»	4.15

Aminoacylfluorenes

These compounds were all prepared in the same manner. The halogenoacyl derivative (1 mol) was heated under reflux in benzene or toluene with the appropriate amine (usually 2.6 mol). The hydrobromide or hydrochloride of the amine was separated and the filtrate extracted with *N* hydrochloric acid. The acid extract was made alkaline with sodium hydroxide and the precipitated base, which usually soon solidified, collected and recrystallised.

9-(Diethylaminoacetylamino)-fluorene. 9-(Chloroacetylamino)-fluorene (3.0 g) and diethylamine (2.2 g) were heated under reflux in toluene (50 ml) for five hours. The reaction mixture was treated according to the general procedure outlined above. The resulting product (3.3 g) was crystallised from light petroleum. M. p. 92.5—93.5°.

$C_{19}H_{22}N_2O$ (294.4)	Calc.	C	77.5	H	7.53
	Found	»	77.6	»	7.48

9-(Dimethylaminoacetylamino)-fluorene. 9-(Chloroacetylamino)-fluorene (2.0 g) was heated with dimethylamine (1.4 g) in benzene (30 ml) in a sealed vessel at 100° over night. After extracting the solution with hydrochloric acid the slightly soluble hydrochloride of the aminoacylfluorene was separated, suspended in water, and the suspension made alkaline. A further quantity of base was obtained in the same manner from the filtrate, and the combined products (together 2.0 g) recrystallised twice from 50 % ethanol. M. p. 135—136°.

$C_{17}H_{18}N_2O$ (266.3)	Calc.	C	76.7	H	6.81	N	10.5
	Found	»	76.9	»	6.92	»	10.7

9-(β-Hydroxyethyl-ethylaminoacetylamino)-fluorene. From 9-(chloroacetylamino)-fluorene (2.0 g) and ethylaminoethanol (2.7 g) by boiling in benzene (25 ml) for six hours. The crude base (2.3 g) was crystallised from light petroleum-acetone (10 : 1). M. p. 96.5—97.5°.

$C_{19}H_{22}N_2O_2$ (310.4)	Calc.	C	73.5	H	7.15
	Found	»	73.6	»	7.19

9-(Piperidinoacetylamino)-fluorene. From 9-(chloroacetylamino)-fluorene (1.5 g) and piperidine (1.33 g) by boiling in benzene (25 ml) for six hours. The base (1.75 g) was recrystallised from 50 % ethanol. M. p. 139.5—140.5°.

$C_{20}H_{22}N_2O$ (306.4)	Calc.	C	78.4	H	7.24	N	9.15
	Found	»	78.3	»	7.36	»	9.31

9-(Morpholinoacetylamino)-fluorene. 9-(Chloroacetylamino)-fluorene (1.5 g) and morpholine (1.3 g) were boiled in benzene (25 ml) for six hours. The crude base (1.7 g) was crystallised from light petroleum. M. p. 162.5—163.5°.

$C_{19}H_{20}N_2O_2$ (308.4)	Calc.	C	74.0	H	6.54	N	9.09
	Found	»	73.8	»	6.63	»	9.07

9-(α-Diethylaminopropionylamino)-fluorene. 9-(α-Bromopropionylamino)-fluorene (2.4 g) and diethylamine (1.5 g) were heated in toluene (40 ml) in a sealed vessel over night at 110°. The base obtained was an oil which was extracted with ether and a saturated ethereal solution of oxalic acid added until no more precipitate was formed. The oxalate (1.5 g) was purified by dissolving in acetone and precipitating with light petroleum when it melted at 174—176° (dec.). The analysis indicated that three moles of oxalic acid were bound to two moles of the base. The percentage of oxalic acid could also be determined directly. A sample of the salt was decomposed with alkali, the base removed by extraction and the water solution acidified and titrated with permanganate.

$2 \cdot C_{20}H_{24}N_2O \cdot 3(COOH)_2$ (887.0)	Calc.	C 62.3	H 6.14	N 6.32	$(COOH)_2$ 30.5
	Found	» 62.3	» 6.13	» 6.35	» 30.6

9-(α-Piperidinopropionylamino)-fluorene. 9-(α-Bromopropionylamino)-fluorene (1.1 g) and piperidine (0.8 g) were boiled in toluene for six hours. The base (1.1 g) was recrystallised from 50 % ethanol. M. p. 102.5—103.5°.

$C_{21}H_{24}N_2O$ (320.4)	Calc.	C 78.7	H 7.55	N 8.75
	Found	» 78.6	» 7.48	» 8.65

9-(α-Diethylaminobuturylamino)-fluorene. From 9-(α-bromobuturylamino)-fluorene (1.5 g) and diethylamine (0.9 g) by boiling in toluene (25 ml) for six hours. The crude base (0.6 g) was recrystallised from light petroleum. M. p. 115—116°.

$C_{21}H_{26}N_2O$ (322.4)	Calc.	C 78.2	H 8.13
	Found	» 78.4	» 8.15

SUMMARY

The synthesis of five halogenoacyl and eight aminoacyl derivatives of 9-aminofluorene is described.

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