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Note

The Effect of Alkyl Substitution in Drugs—VI *ortho*-Ethyl Substituted *N*,*N*-Diethylamino-acetanilides

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Many compounds of the ω-dialkylaminoacetanilide type have been synthesized since the discovery of lidocaine, but apparently not the 2,6-diethyl homologue. We have now synthesized this compound from commercially available* 2,6-diethylaniline. We also included the known 2-ethyl compound in our investigation, as only scanty information about its properties is available in the literature.[2–4]

The hydrochlorides of both compounds were tested for surface anaesthesia on the rabbit cornea by von Frey's[5] method, for infiltration anaesthesia on the guinea-pig back according to Bülbring[6] and for conduction anaesthesia on the rat tail according to Herr,[7] while the spasmolytic activity and the acute toxicity were also determined. The local anaesthetic activity of the ethyl-substituted compounds was about the same as or slighly less than that of lidocaine, but of longer duration. However, although both derivatives showed less acute toxicity than the parent substance, they caused tissue irritation in concentrations needed for local anaesthetic effect.

Both compounds, like lidocaine, have only slight spasmolytic activity.

Methods and Results

Chloroaceto-2,6-diethylanilide. 2,6-Diethylaniline (75 g, 0·5 mole) was dissolved in glacial acetic acid (425 g), cooled down to

* Farbenfabriken Bayer A. G., Leverkusen.

10° and treated with chloroacetyl chloride (62 g, 0·55 mole). Rapid addition of sodium acetate (165 g, 1·2 mole) in water (690 ml) caused the anilide to precipitate. After half an hour's stirring, the material was collected on a Büchner funnel and dried; m.p. 125–128°, yield 70 per cent.

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 63·86; H, 7·09. Found: C, 63·7; H, 7·1.

Diethylaminoaceto-2,6-diethylanilide. A solution of the chloroanilide (75 g, 0·33 mole) and of diethylamine (63 g, 0·86 mole) in dry benzene (180 ml) was refluxed for 5 h. A. precipitate of diethylamine hydrochloride was filtered off. The filtrate was concentrated and the residue dissolved in 125 ml of 3N hydrochloric acid. Some insoluble material was filtered off and discarded and the solution extracted with ether. Enough concentrated ammonia solution was added to make the solution markedly alkaline and to precipitate the base. Extraction with ether and subsequent evaporation yielded 77 g (88 per cent) of the desired substance; m.p. after crystallization from ligroin 88–89·5°.

Anal. Calcd. for $C_{16}H_{26}N_2O$: C, 73·28; H, 9·92; N, 10·69. Found: C, 73·1; H, 10·0; N, 10·3.

M.P. of the hydrochloride (from ethanol–ether) 150–152·5°.

The 2-ethyl compound was prepared in an analogous way. The hydrochloride had a m.p. of 138–140·5° (lit. m.p., 138–140°).

In the *pharmacological* experiments, the hydrochlorides of the above substances were used.

Comparison of toxicity, local anaesthetic and irritating effect of lidocaine and two ethyl-substituted derivatives

	LD_{50} mice, mg/kg		Local anaesthetic effect (lidocaine = 1)			Irritating effect (lidocaine = 1)
	s.c.	i.p.	Rabbit eye	Guinea pig	Rat tail	
Lidocaine	425–450	200	1	1	1	1
2-Ethyl analogue	850–900	500	< 1[a]	< 1[a]	0·2[a]	4
2,6-Diethyl analogue	475–500	250	1[a]	< 1	0·4[a]	7

[a] Effect lasting longer (about 2 times) than after lidocaine.

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