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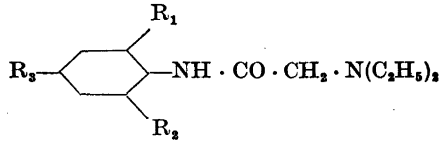
Studies on Local Anesthetics XII *

NILS LÖFGREN, BENGT LUNDQVIST† and SVEN LINDSTRÖM

Institute of Organic Chemistry and Biochemistry, University of Stockholm, Stockholm, Sweden, and School of Pharmacy, University of Lausanne, Lausanne, Switzerland

The N-(diethylaminoacetyl) derivatives of 2- and 4-fluoroaniline, 2-fluoro-4-toluidine, 4-fluoro-2-toluidine, 6-fluoro-2-toluidine and 4-fluoro-2,6-xylidine have been synthesized and tested for their local anesthetic action on the rabbit cornea. In comparison with xylocaine the compounds were found to have a lower activity and contrary to xylocaine they exercised an irritant action.

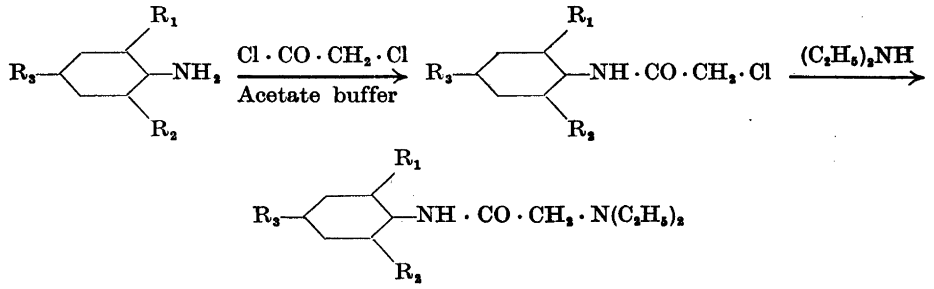
Six xylocaine analogues (I—VI), each with a fluorine atom in the benzene nucleus and which belong to the formula



	R_1	R_2	R_3
I:	F	H	H
II:	H	H	F
III:	F	H	CH_3
IV:	CH_3	H	F
V:	F	CH_3	H
VI:	CH_3	CH_3	F

have been synthesized and studied on their local anesthetic action.

The syntheses of the compounds were carried out according to the following scheme:



* For paper XI of this series see Löfgren and Tegnér [1].

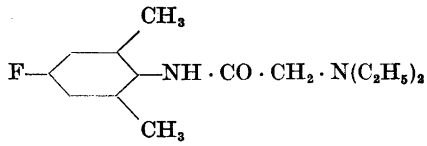
The necessary fluoroarylamines, $R_1R_2R_3{\equiv}C_6H_2.NH_2$, were produced by catalytical hydrogenation (Raney nickel) of the corresponding nitro derivatives. One of these nitro derivatives, 4-nitro-3,5-dimethyl-fluorobenzene, has not been prepared previously. It was made in the following manner: 3,5-Dimethylaniline was converted into 3,5-dimethylfluorobenzene by the Schiemann reaction. The fluoro derivative was then cautiously nitrated yielding a crystalline mixture which should consist of the two possible isomers, *viz.* 2-nitro- and 4-nitro-3,5-dimethylfluorobenzene. This mixture was subjected to a systematic fractional crystallization from methanol. In this way two substances, A and B, were obtained. They had about the same melting point value, but their crystalline forms differed distinctly. Further recrystallizations from a solvent mixture di-*n*-butyl ether — light petroleum 1:2 (v/v) did not alter the melting points. Product A, m.p. 56—57°, consisted of octahedral crystals, product B, m. p. 57—58°, of thin needles. A mixture of equal parts of A and B melted between 31° and 43°. The elementary analyses proved that each product corresponded to the composition of a mononitro-dimethylfluorobenzene. The yield of A was 46 % and that of B 14 %. By heating A with KOH in methanolic solution the fluorine atom was replaced by the methoxy group. The yield of anisole was high (78 %, calc. on recrystallized material). It should consist of either 2-nitro-3,5-dimethylanisole or the corresponding 4-nitro derivative. The melting point (51—52°) agreed with that reported [2,3] for 4-nitro-3,5-dimethylanisole. This compound was synthesized by way of nitration of 3,5-dimethylphenol and subsequent methylation of the 4-nitro derivative (Rowe *et al.*[2]). The mixed melting point showed no depression. If our anisole had consisted of the 2-nitro isomer (recorded [2,3] m. p. 45—46°), admixture with the 4-nitro isomer would have produced a large depression (*cf.* Wilds and Djerassi [3]). — Thus nitro derivative A was proved to be 4-nitro-3,5-dimethylfluorobenzene and consequently nitro derivative B was presumed to consist of 2-nitro-3,5-dimethylfluorobenzene.

The compounds I—VI were tested for their local anesthetic action on the rabbit cornea and compared with xylocaine *. In these tests the compounds gave durations of anesthesia which were inferior to that of xylocaine. Whith the exception of III which had about half the duration of that of xylocaine the other compounds gave durations equal to approximately one tenth of the xylocaine value. Further it was found that, contrary to xylocaine, all the compounds were irritating to the cornea.

Toxicity measurements, carried out with compounds V and VI by injections in white mice, gave LD_{50} values 0.88 g/kg and 0.60 g/kg, respectively. The corresponding value for xylocaine [4] is 0.34 g/kg.

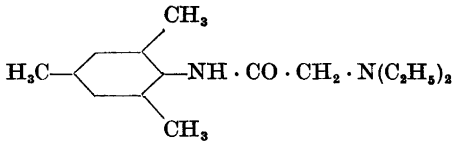
* For this purpose solutions containing 2 % of *base* and 0.9 % of NaCl were prepared by dissolving the base and NaCl in water under the addition of hydrochloric acid so that a pH value of 6.0 was obtained. The solutions were then compared on the cornea, using Wiedling's technique [4].

Since xylocaine is the non-fluorinated derivative of VI



VI

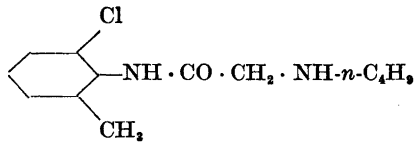
it might, perhaps, seem somewhat confusing that VI, in comparison with xylocaine, has such a low activity. If in VI, the fluorine atom is replaced by a methyl group, the resultant compound,



LL 31

known under the name of LL 31 (Löfgren [5], Löfgren and Lundqvist [6]), will have about the same effect on the cornea as has xylocaine (Wiedling [7]). In xylocaine there is a marked *ortho*-effect (Löfgren [8], Fischer and Löfgren [9]), the *ortho*-methyl groups being believed to interact with the electron pair of the amide nitrogen (Löfgren [8], *cf.* also Branch and Calvin [10]). This *ortho*-effect in xylocaine might be responsible for the outstanding physicochemical and physiological properties as compared with those of its nuclear isomers. In the LL 31 molecule there is also an *ortho*-effect (Löfgren [8]) though it very probably is less pronounced than that in xylocaine (*cf.* measurements of exaltations and ionization constants of xylocaine and related compounds[8]). The σ values of p-CH_3 and m-CH_3 are both negative whereas the corresponding values for fluorine are positive (*cf.* Hammet [11]). Thus in the vicinal grouping of LL 31 and VI, the electron pair of the nitrogen as well as the binding electrons in the two methyl groups are oppositely influenced, and therefore the strengths of the *ortho*-effects in the two molecules should be different and different from the *ortho*-effect in xylocaine. If, however, the *ortho*-effect in VI is weakened or strengthened relative to that of xylocaine, it becomes a question which can only be solved by further experiments.

A local anesthetic which differs from xylocaine in having a *n*-butylamino group instead of the diethylamino group and a chlorine atom instead of one of the two methyl groups is hostacain



Hostacain

which appeared some years ago on the market. According to Edlund and Wiedling [12] the compound is an irritant and has a duration on the rabbit cornea which is about one fifth of that of xylocaine. Replacement of the chlorine atom in hostacain by a methyl group leads to a compound, α-*n*-butylamino-2,6-dimethylacetanilide, which is an isomer of xylocaine and which was synthesized previously by Löfgren and Fischer [13]. The compound was found by Goldberg [14] to be a strong irritant and to exercise the same duration

as that of xylocaine on the rabbit cornea. Thus hostacain must have a shorter duration on the cornea than that of the xylocaine isomer and apparently chlorine, like fluorine (*cf.* above), cannot replace one of the *o*-situated methyl groups without causing a considerable decrease in the duration.

EXPERIMENTAL *

o-Fluoroaniline. The amine has previously been prepared by reduction of *o*-fluoronitrobenzene with iron and sulphuric acid [15] or with stannous chloride and hydrochloric acid [16].

Here the nitro compound — prepared according to Bennet *et al.*[17] by the Schiemann reaction — was hydrogenated in the presence of Raney nickel. Thus a solution of 21 g (0.14 mole) of *o*-fluoronitrobenzene in 100 ml of tetrahydrofuran and 2 g of moist catalyst were shaken with hydrogen at a pressure of about 2 atm. and a temperature of 50°. After about four hours no more hydrogen was consumed. The cooled solution was filtered from the catalyst and after removal of the solvent the residue was taken up in ether. The ethereal solution was exhaustively extracted with 1 N hydrochloric acid. To the combined aqueous extracts was added concentrated ammonia and the liberated base again taken up in ether. After drying the solution (Na_2SO_4), the solvent was driven off and the residue distilled *in vacuo*. The *o*-fluoroaniline was collected as an oil boiling at 55—56°/12 mm. Yield 7.3 g (0.066 mole), *i. e.* 44 %.

p-Fluoroaniline. *p*-Fluoronitrobenzene was prepared by nitration of fluorobenzene as described by Bradlow and VanderWerf.[18] This nitro compound was then hydrogenated catalytically under the same experimental conditions as given in the preparation of *o*-fluoroaniline (*cf.* above) with the only difference that absolute ethanol was used instead of tetrahydrofuran. The *p*-fluoroaniline was obtained as a colourless oil boiling at 84—85°/19 mm. The yield was 84 %. — The amine has previously been prepared by reducing the nitro derivative in various ways.[15,16,18,19]

α-Chloro-2-fluoroacetanilide and α-chloro-4-fluoroacetanilide. The compounds were synthesized by reaction between *o*-fluoroaniline or *p*-fluoroaniline and chloroacetyl chloride in an aqueous acetate buffer according to the general directions given by Löfgren [5,8] for this type of reaction.

α-Chloro-2-fluoroacetanilide: Thin, colourless needles from toluene; m. p. 89—90°; yield 68 %. (Found: C 51.1; H 3.83. Calc. for C_8H_7ClFNO (187.7): C 51.2; H 3.76).

α-Chloro-4-fluoroacetanilide: Colourless plates from 95 % ethanol; m. p. 129—130°; yield 85 %. (Found: C 51.4; H 3.94. Calc.: C 51.2; H 3.76).

α-Diethylamino-2-fluoroacetanilide (I) and α-diethylamino-4-fluoroacetanilide (II). A mixture of 12.0 g (0.0640 mole) of α-chloro-2-fluoroacetanilide or α-chloro-4-fluoroacetanilide, 12.2 g (0.167 mole) of diethylamine and 30 ml of dry benzene was refluxed for five hours. To the cool mixture were added 30 ml of dry ether and the solution was then filtered from the precipitated diethylammonium chloride. The filtrate was exhaustively extracted with 3 N hydrochloric acid and the combined extracts were made alkaline with concentrated ammonia. The liberated base was taken up in ether and after drying the solution (Na_2SO_4) the ether and some excess of diethylamine were evaporated. The residue was distilled under reduced pressure.

α-Diethylamino-2-fluoroacetanilide (I): Colourless oil of b. p. 104—105°/0.4 mm; $n_D^{20} = 1.5127$; yield 11.2 g (0.0499 mole), *i.e.* 78 %. (Found: C 64.2; H 7.72; Equiv.wt. 224. Calc. for $C_{12}H_{17}FN_2O$ (224.3): C 64.3; H 7.64; Equiv. wt. 224). — *Hydrochloride:* Colourless crystals from dioxan; m. p. 123—124°. (Found: C 55.1; H 7.10. Calc. for $C_{12}H_{18}ClFN_2O$ (260.7): C 55.3; H 6.96). — *Perchlorate:* Colourless, thin needles from absolute ethanol; m. p. 185—186°. (Found: C 44.4; H 5.63. Calc. for $C_{12}H_{18}ClFN_2O_5$ (324.7): C 44.4; H 5.59).

* M. p.'s corrected; b. p.'s uncorrected. The determination of equivalent weights on the synthesized bases was made by titrating them in 30 % ethanol with 0.1 N HCl; mixed indicator, methylene blue-methyl red.

α-Diethylamino-4-fluoroacetanilide (II): Colourless oil of b.p. 117—118°/0.3 mm; $n_D^{20} = 1.5163$; yield 12.3 g (0.0550 mole) *i. e.* 86 %. (Found: C 64.3; H 7.77; Equiv. wt. 224. Calc.: C 64.3; H 7.64; Equiv. wt. 224) — *Perchlorate:* Colourless crystals from absolute ethanol; m. p. 155—157°. (Found: C 44.5; H 5.65. Calc.: C 44.4; H 5.59).

2-Fluoro-4-methylaniline, 4-fluoro-2-methylaniline and 6-fluoro-2-methylaniline. First 3-fluoro-4-nitrotoluene, 5-fluoro-2-nitrotoluene and 3-fluoro-2-nitrotoluene were produced by nitration of 3-fluorotoluene, the procedure given by Schiemann [20] being followed. The nitro compounds were then reduced catalytically as described above in the preparation of *p*-fluoroaniline. Of the three anilines only 4-fluoro-2-methylaniline has been prepared previously (Schiemann [20]) and by reduction of the corresponding nitro derivative with tin and hydrochloric acid.

2-Fluoro-4-methylaniline: Colourless oil of b. p. 80—81°/14 mm; $n_D^{20} = 1.5355$; yield 66 %. (Found: N 11.0. Calc. for C_7H_8FN (125.1): N 11.2). — *Hydrochloride:* Colourless. thin needles from 95 % ethanol; m. p. > 300°; sublimation p. ~ 175°. (Found: Cl 22.1. Calc. for C_7H_9ClFN (161.6): Cl 21.9).

4-Fluoro-2-methylaniline: Colourless oil boiling at 94°/16 mm (the same b. p. as reported by Schiemann [20]); yield 75 %.

6-Fluoro-2methylaniline: Colourless oil of b. p. 88—89°/13 mm; yield 64 %. (Found: N 11.3. Calc.: N 11.2). — *Hydrochloride:* Colourless leaflets from 98 % ethanol; m. p. > 300°; sublimation p. ~ 170°. (Found: Cl 22.1. Calc.: Cl 21.9).

α-Chloro-2-fluoro-4-methylacetanilide, α-chloro-4-fluoro-2-methylacetanilide and α-chloro-6-fluoro-2-methylacetanilide. These anilides were all prepared by reaction between chloroacetyl chloride and the appropriate aniline according to the acetate buffer method given by Löfgren [5,8].

α-Chloro-2-fluoro-4-methylacetanilide: Colourless needles from 95 % ethanol; m. p. 132—133° yield 86 %. (Found: C 53.8; H 4.67. Calc. for C_9H_9ClFNO (201.6): C 53.6; H 4.50).

α-Chloro-4-fluoro-2-methylacetanilide: Colourless crystals from 95 % ethanol; m. p. 122—123°; yield 81 %. (Found: C 53.7; H 4.60. Calc.: C 53.6; H 4.50).

α-Chloro-6-fluoro-2-methylacetanilide: Colourless, thin needles from 95 % ethanol; m. p. 116—117°; yield 80 %. (Found: C 53.7; H 4.63. Calc.: C 53.6; H 4.50).

α-Diethylamino-2-fluoro-4-methylacetanilide (III), α-diethylamino-4-fluoro-2-methylacetanilide (IV) and α-diethylamino-6-fluoro-2-methylacetanilide (V). These bases were all synthesized from the corresponding α-chloro derivatives (see above) and diethylamine, applying the experimental conditions as described in the synthesis of α-diethylamino--2-fluoroacetanilide.

α-Diethylamino-2-fluoro-4-methylacetanilide (III): Colourless oil of b. p. 116—117°/0.4 mm; $n_D^{20} = 1.5133$; yield 81 %. (Found: C 65.5; H 8.06; Equiv. wt. 238. Calc. for $C_{13}H_{19}FN_2O$ (238.3): C 65.5; H 8.04; Equiv. wt. 238). — *Perchlorate:* Colourless, thin needles from absolute ethanol; m. p. 141—142°. (Found: C 46.1; H 6.11. Calc. for $C_{13}H_{20}ClFN_2O_5$ (338.8): C 46.1; H 5.95).

α-Diethylamino-4-fluoro-2-methylacetanilide (IV): Colourless oil of b. p. 134—135°/0.6 mm; $n_D^{20} = 1.5135$; yield 79 %. (Found: C 65.7; H 8.21; Equiv. wt. 239. Calc.: C 65.5; H 8.04; Equiv. wt. 238). — *Perchlorate:* Colourless needles from 95 % ethanol; m. p. 135—137°. (Found: C 46.2; H 6.14. Calc.: 46.1; H 5.95).

α-Diethylamino-6-fluoro-2-methylacetanilide (V): Colourless oil of b. p. 113—115°/0.2 mm; $n_D^{20} = 1.5155$; yield 72 %. (Found: C 65.5; H 8.07; Equiv. wt. 238. Calc.: C 65.5; H 8.04; Equiv. wt. 238). — *Perchlorate:* Colourless, thin needles from 95 % ethanol; m. p. 135—136°. (Found: C 46.2; H 6.16. Calc.: C 46.1; H 5.95).

3,5-Dimethylfluorobenzene. The compound was synthesized from 3,5-dimethylaniline by the Schiemann reaction.

The intermediate, 3,5-dimethylbenzenediazonium fluoborate, was made by adding fluoboric acid to the diazotised amine, the experimental conditions being the same as described by Roe [21] in the preparation of *m*-nitrobenzenediazonium fluoborate. Yield 91 %; decomposition p. 86°.

The salt was decomposed by following Roe's directions [21] for the production of *m*-fluorotoluene from *m*-toluenediazonium fluoborate. The desired 3,5-dimethylfluorobenzene was obtained as a colourless oil of b. p. 145°; $n_D^{25} = 1.4737$; yield 53 % (overall from amine). (Found: C 76.9; H 7.22. Calc. for C_8H_9F (124.2): C 77.4; H 7.31).

2-Nitro- and 4-nitro-3,5-dimethylfluorobenzene. In a 500 ml round-bottomed flask, provided with a mechanical stirrer, a dropping funnel and a thermometer, were placed 48.4 g (0.390 mole) of 3,5-dimethylfluorobenzene and 78 g of acetic anhydride. The flask was placed in an ice bath, and the mixture was cooled below 10°. Under stirring a solution of 36.9 g (0.586 mole) of fuming nitric acid ($d = 1.51$) in 23 g of glacial acetic acid and 23 g of acetic anhydride was added over a period of forty minutes, the temperature being kept between 15° and 20°.

When the addition of the nitric acid was complete, the reaction mixture was removed from the ice bath and allowed to stand at room temperature for two hours. The flask was then placed in a water bath and under shaking the mixture was kept at a temperature of 50° for ten minutes. The cooled reactants were poured slowly into 950 ml of ice-water and well stirred. Sodium chloride, 47 g, was added and the aqueous layer was decanted and extracted with 300 ml of ether. The ethereal extract was added to the residual nitro product, and the ethereal solution thus obtained was washed with 35 ml portions of a 10 % sodium hydroxide solution until the water extract was distinctly alkaline. The ether was then distilled off. At the end of this distillation the temperature of the water bath was kept not higher than 60° and as soon as practically no more ether distilled, heating was discontinued and the distilling flask cooled *. The residue, after the addition of 175 ml of 10 % sodium hydroxide solution, was steam-distilled (condenser with tap-water, receiver in ice-water). The pale yellow crystals were filtered off on a glass filter, drained as dry as possible and then further dried by keeping them in a non-evacuated desiccator, set aside in a cool place, over a mixture of equal parts of sodium hydroxide pellets and calcium chloride.

The dried crystalline material, which should consist almost entirely of the two possible isomers of mononitro-3,5-dimethylfluorobenzene, was subjected to a systematic fractional crystallization from methanol, applying the classical procedure (*cf.* for instance Morton [22]). As the result of these operations two pale yellow substances which differed distinctly as to their crystalline forms, but had about the same value of their melting points, were obtained. (Further recrystallizations of the two products from a solvent mixture di-*n*-butyl ether — light petroleum 1:2 (v/v) did not alter the melting points.) One of the two products (A) consisted of octahedral crystals of m. p. 56—57°; yield 30 g. This substance was predominant in the first crop of crystals, obtained from the methanolic solution. The other product (B) was made up of very thin needles melting at 57—58°; yield 9 g. A mixture of equal parts of A and B was found to melt in the range between 31° and 43°. Both compounds sublimed appreciably at room temperature and pressure, A more rapidly than B.

The elementary analyses gave evidence that each substance was a mononitro-3,5-dimethylfluorobenzene. (Found for A: C 56.5; H 4.80. Found for B: C 56.7; H 4.73. Calc. for $C_8H_8FNO_2$ (169.2): C 56.8; H 4.77).

Replacement of the fluorine atom by the methoxy group in A, proved it to be 4-nitro-3,5-dimethylfluorobenzene (*cf.* following section), so apparently B was identical with the other of the two possible isomers, *viz.* 2-nitro-3,5-dimethylfluorobenzene.

Determination of the position of the nitro group in mononitro-3,5-dimethylfluorobenzene A (*cf.* preceding section). A solution of 2.00 g (0.0118 mole) of mononitro-3,5-dimethylfluorobenzene A and 2.9 g (0.052 mole) of potassium hydroxide in 36 ml of methanol was refluxed for six hours. After cooling, the mixture was poured into 150 ml of water. A pale yellow precipitate formed. This was filtered off, washed with water and dried in a desiccator over silica gel. The melting point was found to be 49—50°; yield 1.90 g (89 %, assuming the product to be a nitro-3,5-dimethylanisole). The substance was recrystallized from ethanol under the addition of a little water. Thin, yellow needles melting at 51—52° were obtained; yield 1.7 g (79 %, *cf.* above). Another recrystallization from a

* The desired nitro derivatives are volatile and therefore a prolonged heating to remove the last traces of the ether should be avoided.

solvent mixture di-*n*-butyl ether — light petroleum 1:2 (v/v) did not alter the melting point which agrees with that of 4-nitro-3,5-dimethylanisole [2,3]. (Found: C 59.5; H 6.10. Calc. for $C_9H_{11}NO_3$ (181.2): C 59.7; H 6.12). 4-Nitro-3,5-dimethylanisole was prepared according to the method of Rowe *et al.*[2] (nitration of 3,5-dimethylphenol and subsequent methylation of the 4-nitro derivative). The mixed m. p. showed no depression. If the nitroanisole obtained from compound A had consisted of 2-nitro-3,5-dimethylanisole (recorded [2,3] m. p. 45—46°), admixture of the isomeric 4-nitro-3,5-dimethylanisole would have produced a large depression, such a mixture being an oil at ordinary room temperature (*cf.* Wilds *et al.*[3]).

4-Fluoro-2,6-dimethylaniline. This was made from 4-nitro-3,5-dimethylfluorobenzene by catalytical hydrogenation as described in the preparation of *p*-fluoroaniline. Colourless oil of b. p. 117—118°/14 mm; $n_D^{20} = 1.5352$; yield 72 %. (Found: N 10.3. Calc. for $C_8H_{10}FN$ (139.2): N 10.1. — *Perchlorate:* Colourless crystals from 98 % ethanol; m. p. 235° (decomp.). (Found: C 40.0; H 4.64. Calc. for $C_8H_{11}ClFNO_4$ (239.6): C 40.1; H 4.63).

α-Chloro-4-fluoro-2,6-dimethylacetanilide. The compound was prepared from chloroacetyl chloride and 4-fluoro-2,6-dimethylaniline according to the acetate buffer method given by Löfgren [5,8]. Thin, colourless needles from absolute ethanol; m. p. 193—194°; yield 91 %. (Found: C 55.6; H 5.17. Calc. for $C_{10}H_{11}ClFNO$ (215.7): C 55.7; H 5.14).

α-Diethylamino-4-fluoro-2,6-dimethylacetanilide (VI). This compound was made from diethylamine and α-chloro-4-fluoro-2,6-dimethylacetanilide in the same manner as described above in the synthesis of α-diethylamino-2-fluoroacetanilide. At the distillation the compound appeared as a colourless oil that soon solidified; b. p. 112—113°/0.1 mm; yield 85 %. After recrystallization from light petroleum the melting point was found to be 56—57°. (Found: C 66.7; H 8.46; Equiv. wt. 252. Calc. for $C_{14}H_{21}FN_2O$ (252.3): C 66.6; H 8.39; Equiv. wt. 252). — *Perchlorate:* Colourless, thin needles from 95 % ethanol; m. p. 179—180°. (Found: C 47.9; H 6.27. Calc. for $C_{14}H_{22}ClFN_2O_5$ (352.8): C 47.7; H 6.29).

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