

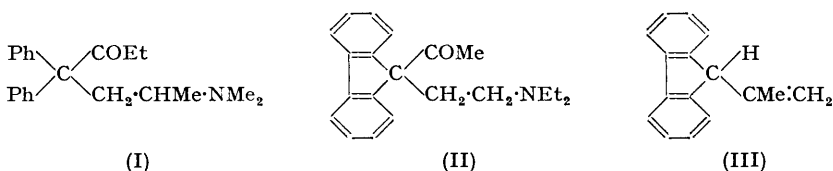
24. Fluorene Derivatives related to Amidone.

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The synthesis of 9-acetyl- and 9-carbethoxy-9-diethylaminoethylfluorene is recorded.

THE high analgesic potency of Amidone (I) (Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 369) suggested the examination of its fluorene analogue, in which the two phenyl groups are linked in the *ortho*-positions. The experiments now described were undertaken with the object of preparing compounds of this type. They were discontinued after the publication by Ginsburg and Baizer (*J. Amer. Chem. Soc.*, 1949, **71**, 1500) of a note reporting the synthesis of the fluorene ketone probably having the same basic side-chain as Amidone.

9-Cyano-9-diethylaminoethylfluorene was prepared from the potassium salt of 9-cyanofluorene and 2-chloroethyldiethylamine and was treated with methylmagnesium iodide, to give 9-acetyl-9-diethylaminoethylfluorene (II). These reactions were based on the Amidone synthesis of Schultz, Robb, and Sprague (*ibid.*, 1947, **69**, 2454). A procedure based on the alternative Amidone synthesis of Easton, Gardner, and Stevens (*ibid.*, p. 2941) gave anomalous results; the potassium salt of 9-cyanofluorene reacted with propylene oxide to give 9-isopropenylfluorene (III). Its structure followed from the fact that it differed from 9-isopropylideneffluorene but was hydrogenated to 9-isopropylfluorene (Maitland and Tucker, *J.*, 1929, 2559).



Ethyl 9-diethylaminoethylfluorene-9-carboxylate (cf. II) was prepared on account of its structural resemblance to some of the compounds found to have analgesic activity by Macdonald *et al.* (*Brit. J. Pharmacol.*, 1946, **1**, 4).

EXPERIMENTAL

9-Cyano-9-diethylaminoethylfluorene.—Potassium (3 g.), in small pieces, was added to a solution of 9-cyanofluorene (15 g.) in dry dioxan (100 c.c.), in an atmosphere of nitrogen. After 2 hours' boiling, all the potassium had reacted. The yellow potassium salt of 9-cyanofluorene crystallised. After being cooled to 50° the suspension was treated with 2-chloroethyldiethylamine (Tchoubar and Letellier-Dupré, *Bull. Soc. chim.*, 1947, **14**, 792), and the mixture then boiled for an hour. It was cooled and filtered from potassium chloride, and the dioxan removed under reduced pressure. The residual amber-coloured oil (23 g.) was dissolved in ether (100 c.c.), and the solution extracted with 1% hydrochloric acid. The aqueous extract was clarified with charcoal and basified. The free base, recovered by ether-extraction, formed a yellow oil (21.2 g.) which solidified when cooled and rubbed with a little light petroleum (b. p. 60–80°). Recrystallisation from this solvent gave 9-cyano-9-diethylaminoethylfluorene as colourless rhombic plates, m. p. 59.5–60.5° (Found: C, 82.8; H, 7.5; N, 10.0. $C_{20}H_{22}N_2$ requires C, 82.7; H, 7.6; N, 9.6%). Its *hydrochloride* formed colourless needles (from ethanol-ethyl acetate), m. p. 205–206° (Found: C, 73.6; H, 7.0; N, 8.9. $C_{20}H_{22}N_2 \cdot HCl$ requires C, 73.5; H, 7.1; N, 8.6%), and its *picrate* crystallised from ethanol in yellow needles, m. p. 157–160° (decomp.) (Found: C, 60.6; H, 4.8; N, 14.0. $C_{26}H_{25}O_7N_5$ requires C, 60.1; H, 4.8; N, 13.5%).

9-Acetyl-9-diethylaminoethylfluorene (II).—A solution of the aforesaid base (2.9 g.) in *n*-butyl ether (30 c.c.) was added dropwise to a stirred Grignard solution prepared under nitrogen from methyl iodide (5.7 g.), magnesium turnings (0.97 g.), and *n*-butyl ether (40 c.c.). Stirring was continued at 70–80° for 3 hours. The mixture was cooled and decomposed with concentrated hydrochloric acid (8 c.c.). The clear solution was decanted and the residue was treated with water (20 c.c.) and boiled. The brown oil which separated on cooling became

solid when rubbed. It was the *hydriodide* (4 g.) of (II) and crystallised from ethanol in colourless needles, m. p. 194—195° (after sintering) (Found: C, 58.5; H, 5.9; N, 3.4. $C_{21}H_{25}ON, HI$ requires C, 57.9; H, 6.0; N, 3.2%). 9-Acetyl-9-diethylaminoethylfluorene (II), extracted with ether after basification of the hydriodide solution, formed a colourless highly refractive oil, b. p. 153—154°/0.4 mm. (Found: C, 81.6; H, 7.7; N, 4.4. $C_{21}H_{25}ON$ requires C, 82.0; H, 8.2; N, 4.6%). The *hydrochloride*, prepared with ethanolic hydrogen chloride, formed colourless needles (from ethanol-ethyl acetate), m. p. 192—193° (Found: C, 73.4; H, 7.5; N, 4.2. $C_{21}H_{25}ON, HCl$ requires C, 73.3; H, 7.6; N, 4.1%). The *oxime*, prepared from a solution of the hydriodide (0.2 g.) and hydroxylamine hydrochloride (0.07 g.) in pyridine (1 c.c.) at room temperature overnight, formed colourless plates (from aqueous ethanol), m. p. 156—157° (Found: C, 78.4; H, 7.9; N, 8.4. $C_{21}H_{26}ON_2$ requires C, 78.2; H, 8.1; N, 8.7%).

9-Diethylaminoethylfluorene.—This was obtained in an attempt to prepare (II) from fluorene by condensation in the presence of potassium methoxide, first with ethyl acetate and then with 2-chloroethyldiethylamine, the reactions being carried out in boiling ether. The 9-diethylaminoethylfluorene so obtained formed a pale yellow oil, b. p. 156—158°/0.8 mm. (Found: C, 85.3; H, 8.6; N, 4.7. $C_{19}H_{23}N$ requires C, 86.0; H, 8.7; N, 5.3%). Its *perchlorate* crystallised from ethanol in rosettes of colourless needles, m. p. 181—182.5° (Found: C, 62.0; H, 6.6; N, 3.3. $C_{19}H_{23}N, HClO_4$ requires C, 62.4; H, 6.6; N, 3.8%). The base regenerated from the pure perchlorate, when treated with ethereal hydrogen chloride, gave the *hydrochloride* which crystallised from ethanol-ethyl acetate (1 : 8) in colourless hygroscopic needles, m. p. 127—129° (Found: C, 75.1; H, 7.9; N, 4.6. $C_{19}H_{23}N, HCl$ requires C, 75.6; H, 8.0; N, 4.6%). The *methiodide*, also prepared from a sample of base purified through the perchlorate, formed colourless flakes (from ethyl acetate), m. p. 157° (Found: C, 58.8; H, 6.3; N, 3.3. $C_{20}H_{26}NI$ requires C, 59.0; H, 6.4; N, 3.4%).

The same base, identified by mixed m. p. of the 3 derivatives, was formed when a solution of 9-cyano-9-diethylaminoethylfluorene (0.5 g.) in 30% methanolic potassium hydroxide (7 c.c.) was boiled under reflux for 48 hours.

9-isoPropenylfluorene.—The potassium compound of 9-cyanofluorene (4.9 g.) was prepared in dioxan (40 c.c.) with sliced potassium (1 g.). Propylene oxide (6 g.) was added to the cooled suspension and the mixture was heated under gentle reflux for an hour, during which the yellow potassium salt became replaced by a fine white suspension. After cooling, the solution was filtered and then boiled with charcoal for 15 minutes. Removal of the solvent under reduced pressure yielded a brown oil which solidified when cooled (4.8 g.). Recrystallisation from methanol gave colourless plates of 9-isopropenylfluorene, m. p. 97—98° (Found: C, 93.0; H, 7.0. $C_{16}H_{14}$ requires C, 93.2; H, 6.8%). Microhydrogenation over palladium black led to absorption of hydrogen corresponding to one ethylenic bond. Hydrogenation of the hydrocarbon (0.1 g.) in acetic acid (10 c.c.) over palladium-charcoal (0.15 g.) gave 9-isopropylfluorene, m. p. 55°, alone or mixed with an authentic specimen (Maitland and Tucker, *loc. cit.*).

Ethyl 9-Diethylaminoethylfluorene-9-carboxylate Hydrochloride.—Potassium (0.23 g.), in thin slices, was added to a solution of ethyl fluorene-9-carboxylate (1.4 g.) in dry ether (5 c.c.) under nitrogen. When the vigorous reaction had subsided, dry ethanol (0.3 c.c.) was added and the mixture kept at room temperature until reaction was complete. A solution of 2-chloroethyldiethylamine (0.67 g.) in ether (5 c.c.) was then added and the whole boiled for an hour. The filtered solution was twice extracted with dilute hydrochloric acid. Basification of the aqueous extract yielded an oil which was extracted with ether, and the extract was dried (Na_2SO_4). Passage of hydrogen chloride gave a resinous precipitate (1.15 g.). This was dissolved in ethyl acetate, and a little ether added. Ethyl 9-diethylaminoethylfluorene-9-carboxylate hydrochloride crystallised in rhombic plates, m. p. 159—160° (Found: C, 70.2; H, 7.4; N, 4.0. $C_{22}H_{27}O_2N, HCl$ requires C, 70.7; H, 7.5; N, 3.7%). The free base, which decomposed on distillation at 0.4 mm., gave a *methiodide* which formed small colourless needles (from dioxan), m. p. 156° (Found: C, 57.0; H, 6.3; N, 3.0. $C_{23}H_{30}O_2NI$ requires C, 57.6; H, 6.3; N, 2.9%).