FLUORO-DERIVATIVES OF POLYCYCLIC CARCINOGENIC COMPOUNDS

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FROM the strongly ortho-para-directing nature of fluorine atoms in electrophilic reactions of aromatic compounds, and the unusually large reactivity of the ortho-positions, one must conclude that the electrophilic electron localisation energies decrease strongly in the immediate neighbourhood of the fluorine-substituted carbon atom.

Therefore, if one assumes [1,2] that the determining step in the carcinogenic process in an aromatic hydrocarbon is an electrophilic reaction of the "K" region, and if one compares the electrophilic electron localisation energies of the compounds (a) with an unsubstituted "K" region and (b) with fluorine in the "K" region, one arrives at the following predictions:

First possibility: if the electrophilic substitution takes place only at the fluorinated carbon atom, the carcinogenic activity will

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[1] C.A. Coulson, Advances in Cancer Research, Vol. 1, p. 2. New York (1953).

[2] A. Pullman and B. Pullman, Advances in Cancer Research, Vol. 3 p. 117. New York (1955).

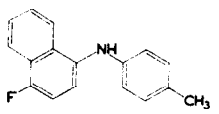
decrease, since this carbon atom will be screened by the fluorine.

Second possibility: if the substitution takes place only at the non-fluorinated atom or simultaneously on both carbon atoms, the carcinogenic activity will increase.

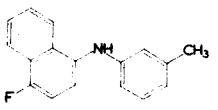
As it seemed interesting to compare these theoretical results with the experiment, a number of fluoro-derivatives of carcinogenic polycyclics has been synthesised. The methods of synthesis are briefly reported here.

(1) 4-Fluoro-1-naphthylamine was condensed in the presence of a trace of iodine with p- and m-toluidine, respectively. The N-p- and m-tolylderivatives so obtained (I, m.p. 74-75°; b.p. 187-189° (2 mm); II, m.p. 53° b.p. 208° (10 mm)) were cyclised with zinc chloride and acetic anhydride to 3-fluoro-5:7-dimethyl-1:2-benzacridine (III, m.p. 174°; picrate, m.p. 218-220° (dec.)) and 3-fluoro-5:8-dimethyl-1:2-benzacridine (IV, m.p. 173-175°; picrate, m.p. 210-213° (dec.)).

(Anal. Found: (III) C, 83.2; H, 5.6; N, 5.0; F, 6.8
(IV) C, 82.9; H, 5.0; N, 4.9; F, 7.2
$C_{19}H_{14}FN$ requires C, 82.9; H, 5.1; N, 5.1; F, 6.9%)



I



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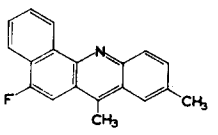

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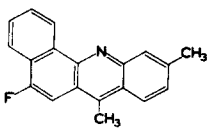
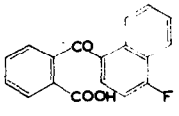


IV

(2) The synthesis of suitably methyl- and fluoro-substituted 1:2-benzanthracenes started from o-(4-fluoro-1-naphthoyl)-benzoic acid (V, from toluene, m.p. 161°), which could be prepared in 53% yield from phthalic anhydride and 4-fluoro-1-naphthylmagnesium bromide (4-fluoro-1-bromonaphthalene boiled at 108° (0.8 mm) and melted at 36°).



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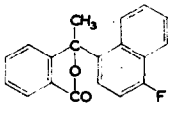

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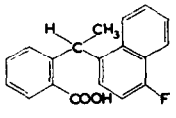
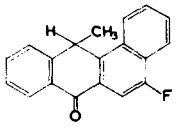
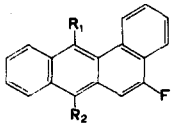


VII



VIII



IX

Reaction of V with methylmagnesium bromide gave the lactone VI (from ethanol, m.p. 140°) which was reduced by zinc and hydrochloric acid in 40% and by phosphorus and hydriodic acid in 100% yield to 4-fluoro-1-α-(o-carboxy-phenyl -ethyl) naphthalene (VII, from nitromethane, m.p. 170.5 - 171°). Cyclisation with sulphuric acid gave in 88% yield 3-fluoro-9-methyl-1:2-benzanthr-10-one (VIII, from ethanol m.p. 130°) and reduction with zinc dust and sodium hydroxide and subsequent dehydration with alcoholic hydrochloric acid, 3-fluoro-9-methyl-1-1:2-benzanthracene (IX,

R_1=CH_3, R_2=H) (m.p. 54°, from ethanol; yield, 87%). (Anal. Found: C, 87.4; H, 5.4; F, 7.5. $C_{19}H_{13}F$ requires C, 87.7; H, 5.0; F, 7.3%). Reaction of VIII with methylmagnesium iodide gave IX (R_1=R_2=CH_3) (from cyclohexane, m.p. 94°; yield, 76%). (Anal. Found: C, 87.9; H, 5.5; F, 7.2. $C_{20}H_{15}F$ requires C, 87.9; H, 5.5; F, 6.9%).

U.V. spectra (in $CHCl_3$) III: 274 mμ (4.65); 283 mμ (4.72); 285 mμ (4.75); 296 mμ (4.70); 342 mμ (3.88); 369 mμ (3.92); 390 mμ (3.90).

IV: 264 mμ (4.52); 272 mμ (4.58); 284 mμ (4.71); 294 mμ (4.64); 322 mμ (3.83); 336 mμ (3.89); 355 mμ (3.83); 374 mμ (3.90); 395 mμ (3.95).

IX: (R_1 = CH_3, R_2 = H): 285 mμ (4.78); 295 mμ (4.38); 348 mμ (3.79); 396 mμ (3.04).

IX: (R_1 = R_2 = CH_3): 289 mμ (4.65); 300 mμ (4.68); 366 mμ (3.78).

A more detailed description of these and related experiments as well as the results of the biological testing of the compounds III, IV and IX (R_1=R_2=CH_3 and R_1=CH_3, R_2=H) will be reported elsewhere.