[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY]

# Fluorine-Substituted 1,2-Benzanthracene and 3,4-Benzophenanthrene Derivatives and Related Compounds

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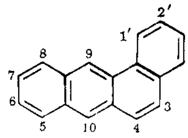
In order to study the influence of fluorine substitution on the biological properties of carcinogenic polycyclic hydrocarbons, 3-fluoro-9-methyl- and -9,10-dimethyl-1,2-benzanthracene have been synthesized from the condensation product of phthalic anhydride with 4-fluoro-1-naphthylmagnesium bromide *via* the anthrone derivative (IV). An attempt to elaborate from (IV) the system of cholanthrene failed. The keto acid (IX) formed from 4-methylphthalic anhydride and 1-fluoronaphthalene was converted into 3-fluoro-6-methyl-1,2-benzanthracene. 3-Fluoro-6,10- and -7,10-dimethyl-1,2-benzacridine (XV, XVI) have been prepared by conventional methods. Starting from the maleic anhydride adduct of 1-(cyclohex-1-enyl)-4-fluoronaphthalene, 2-fluoro-9,10-dimethyl-3,4-benzophenanthrene has been obtained.

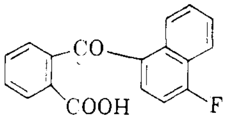
The influence, on the carcinogeneity of polycyclic substances having fluorine substitution, especially in the K-region, is being studied at present in a number of laboratories.[1-3] The results of these studies may contribute to our understanding of the process of carcinogenesis. The reason for this expectation lies in the fact that the electron localization energies involved in electrophilic substitution—such as the rate-determining step in the carcinogenic process is assumed to be—will decrease steeply in the immediate neighborhood of a fluorine-substituted carbon atom. The most important polycyclic systems studied so far[4,5] are the fluorine derivatives of 2-acetaminofluorene[2,3] and those of 1,2-benzanthracene.[1] The present study supplements the data on the latter system and adds two 1,2-benzacridines[6] and one 3,4-benzophenanthrene derivative. A preliminary report on some of the results has been published.[7]

The following fluoro-1,2-benzanthracenes have been described before: 4′-fluoro-, 3-fluoro-, 10-methyl-3-fluoro-, -4-fluoro-, -6-fluoro-, -7-fluoro-, -3′-fluoro-, -4′-fluoro-, and 8-fluoro-10-methyl-.

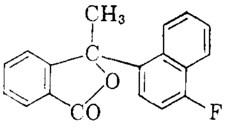


The present paper describes the synthesis of 3-fluoro-9,10-dimethyl-(V) and 3-fluoro-9-methyl-1,2-benzanthracene (VI) as well as of 3-fluoro-6-methyl-1,2-benzanthracene.

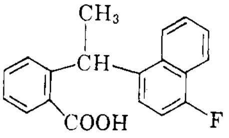
The condensation of 4-fluoro-1-naphthylmagnesium bromide with phthalic anhydride led to the keto acid I. The reaction of I with methylmagnesium bromide gave in the usual manner the lactone II of *o* - [*α* - hydroxy - *α* - (4 - fluoro - 1-naphthyl)ethyl]benzoic acid, which was converted by successive reduction to III and cyclization into 3-fluoro-9-methyl-1,2-benzanthr-10-one (IV). The reaction of IV with methylmagnesium iodide gave



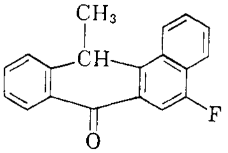
I



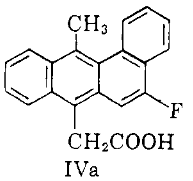
II



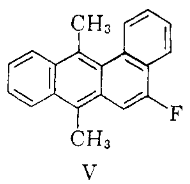
III



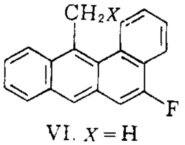
IV



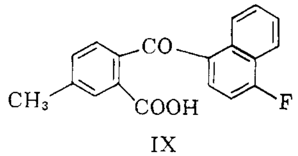
IVa



V



VI. $X = H$
VII. $X = Br$
VIII. $X = CN$



IX

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[1] (a) M. S. Newman, D. Mac Dowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959); (b) M. S. Newman, S. Swaminathan, and R. Chatterji, *J. Org. Chem.*, **24**, 1961 (1959); (c) M. S. Newman and R. H. B. Galt, *J. Org. Chem.*, **25**, 214 (1960); (d) U. S. Newman, and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

[2] (a) T. L. Fletcher, M. J. Namkung, H. L. Pan, and N. H. Wetzel, *J. Org. Chem.*, **25**, 996 (1960); (b) T. L. Fletcher, M. J. Namkung, N. H. Wetzel, and H. L. Pan, *J. Org. Chem.*, **25**, 1342 (1960); (c) T. L. Fletcher, N. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959).

[3] M. Dahlgard, J. D. Bokil, and F. E. Ray, *J. Org. Chem.*, **25**, 951 (1960).

[4] See also N. P. Buu-Hoï and P. Jacquignon, *J. Chem. Soc.*, 4173 (1952).

[5] See also N. P. Buu-Hoï, R. Royer, M. Hubert-Harbat, and P. Mabille, *J. Chem. Soc.*, 3584 (1953).

[6] For the carcinogeneity of substituted 1,2-benzacridines, see P. Daudel, B. Chenon, N. P. Buu-Hoï, P. Jacquignon, A. Lacassagne, G. Prodi, G. Vallée, R. Vasquez, and F. Zajdela, *Bull. Soc. chim. biol.*, **42**, 135 (1960).

[7] E. D. Bergmann, J. Blum, S. Butanaro, and A. Heller, *Tetrahedron Letters*, March 1959, p. 15.

TABLE I

ULTRAVIOLET SPECTRA [mμ (log ε)].

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1,2-Benzanthracene[b,9] | | | 254<br>(4.56) | 266.5<br>(4.60) | 276.5<br>(4.85) | 287<br>(4.95) | 299.5<br>(3.99) | 312.5<br>(3.63) | 327.5<br>(3.80) | 341<br>(3.87) | 358<br>(3.69) | 365.5<br>(3.41) | 375.5<br>(2.73) | 384.5<br>(3.07) |
| V[a] | | | | | | | 289<br>(4.65) | 300<br>(4.68) | | | | 366<br>(3.78) | | |
| VI[a] | | | | | | | 285<br>(4.78) | 295<br>(4.38) | | 348<br>(3.79) | | | | 396<br>(3.04) |
| VII[b] | 220<br>(4.48) | 236<br>(4.44) | 257<br>(4.61) | | | 282<br>(4.73) | | 293<br>(4.72) | | 343<br>(3.81) | | 356<br>(3.79) | 375<br>(3.48) | 396<br>(3.28) |
| VIII[b] | 227<br>(4.58) | | 258<br>(4.62) | | | 283<br>(4.73) | 287<br>(4.72) | 303<br>(4.22) | 324<br>(3.78) | 336<br>(3.81) | | 352<br>(3.70) | 370<br>(3.27) | 392<br>(3.15) |
| 3-Fluoro-6-methyl-1,2-benzanthracene | | | 263<br>(4.51) | | | 284<br>(4.65) | | 294<br>(4.65) | 330 (infl)<br>(3.72) | 342<br>(3.82) | | 359<br>(3.78) | 375 (infl)<br>(3.40) | 399<br>(3.30) |
| 1,2-Benzacridine[10] | | | | | 270 | | | | 334.5 | 349 | | | 368 | 387 |
| XV[a] | | | 264<br>(4.52) | | 272<br>(4.58) | 284<br>(4.71) | | 294<br>(4.64) | 322<br>(3.83) | 336<br>(3.89) | | 355<br>(3.83) | 374<br>(3.90) | 395<br>(3.95) |
| XVI[a] | | | | | 274<br>(4.65) | 283<br>(4.72) | 285<br>(4.75) | 296<br>(4.70) | | 342<br>(3.88) | | | 369<br>(3.92) | 390<br>(3.90) |

[a] Chloroform as solvent. [b] Ethanol as solvent.

V, and the reduction of IV with zinc and alkali yielded VI.

Some experiments may be mentioned designed to convert IV into a fluoro derivative of cholanthrene by reaction with ethyl bromoacetate and zinc. The product, after alkaline hydrolysis, gave in 59% over-all yield 3-fluoro-9-methyl-10-anthrylacetic acid (IVa), which showed the violet fluorescence to be expected of its structure; however, all attempts at cyclizing this compound failed.

In experiments carried out to elaborate from VI more highly condensed ring systems, *N*-bromosuccinimide gave easily the bromomethyl compound VII and this, with potassium cyanide, gave VIII. However, it was impossible to hydrolyze the cyano group of VIII or to cause VIII to cyclize directly.

For the synthesis of 3-fluoro-6-methyl-1,2-benzanthracene, 4-methylphthalic anhydride was subjected to reaction with 1-fluoronaphthalene and aluminum chloride. The keto acid formed (in 35–40% yield) was homogeneous; its structure IX was proven by decarboxylation to 4-fluoro-1-naphthyl *p*-tolyl ketone, which was synthesized by an unambiguous route; for comparison the *m*-tolyl isomer has also been prepared. Analogous condensations with 3-substituted phthalic anhydrides have been carried out.[8]

The acid X, obtained by reduction of IX, was cyclized to the enol form XI of the anthrone XII. The latter could be obtained in the normal manner by isomerization of XI, but proved refractory to Grignard and Reformatsky reagents as well as to ethyl cyanoacetate in the presence of piperidine acetate. Only reduction could be carried out successfully, yielding 3-fluoro-6-methyl-1,2-benzanthracene.

In view of the biological similarity of 1,2-benzanthracene and 1,2-benzacridine, two fluoro derivatives of the latter highly carcinogenic compound were prepared, *viz.*, 3-fluoro-7,10- and 3-fluoro-6,10-dimethyl-1,2-benzacridine (XV, XVI). They were formed when the naphthylamine derivatives (XIII and XIV) were heated with a mixture of *zinc and aluminum* chlorides and acetic anhydride. This cyclization reaction failed when analytically pure zinc chloride was employed as condensing agent in the classical manner.

Also with regard to spectrographic properties, the benzanthracenes and benzacridines are similar

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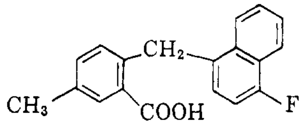
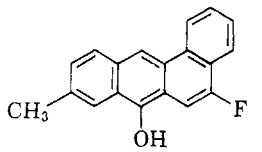
[8] M. S. Newman and C. M. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **72**, 5191 (1950); M. S. Newman and P. C. Scheuer, *J. Am. Chem. Soc.*, **78**, 5004 (1956); H. N. Stephens, *J. Am. Chem. Soc.*, **43**, 1920 (1921); E. H. Huntress, K. Pfister, and K. H. T. Pfister, *J. Am. Chem. Soc.*, **64**, 2845 (1942); M. Bentov, and E. D. Bergmann, *Bull. soc. chim. France*, 1316 (1961).

[9] R. N. Jones, *J. Am. Chem. Soc.*, **62**, 148 (1940); **67**, 2123 (1945).

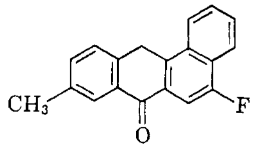
[10] A. Cheutin, N. P. Buu-Hoï, O. Chalvet, R. Daudel, M. Pages, M. Roux, and R. Royer, *Compt. rend.*, **241**, 52 (1955).



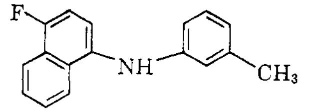
X



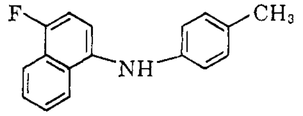
XI



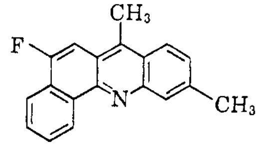
XII



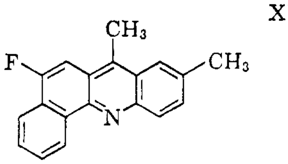
XIII



XIV



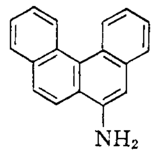
XV



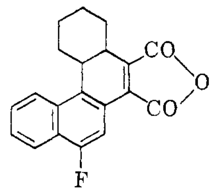
XVI

to each other, as can be seen from Table I. This similarity is not unexpected.

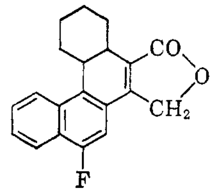
In connection with these experiments an attempt was made to prepare a fluoro derivative of the carcinogenic 3,4-benzophenanthrene. As the transformation of 1-amino-3,4-benzophenanthrene (XVII)[11] into the corresponding fluoro compound failed, the following somewhat devious route was employed. From cyclohexanone and 4-fluoro-1-naphthylmagnesium bromide, 1-(cyclohex-1-enyl)-4-fluoronaphthalene was obtained, which reacted smoothly with maleic anhydride (but not with *p*-benzoquinone, which caused carbonization) at 200°. The product distilled with evolution of gas and, according to its analysis and spectrum, contained two hydrogen atoms fewer than expected; it is formulated as XVIII. While the fluorine-free parent substance[12] could be dehydrogenated smoothly, XVIII lost the fluorine atom both upon dehydrogenation (with palladium or sulfur) and decarboxylation. Reduction of XVIII with lithium aluminum hydride gave a mixture of two phthalides of practically identical spectrum (XIX, XX) and of the diol (XXI), which was the major product. Although the three products could be separated without difficulty, it sufficed to treat the crude reaction product with phosphorus and hydriodic acid. The compound formed (XXII) had all the properties of 2-vinylnaphthalene; it absorbed oxygen slowly on exposure to air and became discolored. Dehydrogenation with selenium at 320–330° led to the desired 2-fluoro-9,10-dimethyl-3,4-benzophenanthrene (XXIII), an oil which gave a well defined complex with 2,4,7-trinitrofluorenone and had the absorption spectrum characteristic of a methylated 3,4-benzophenanthrene (last absorption bands at 373 and 381 mμ).[13,14]



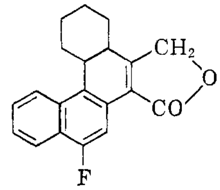
XVII



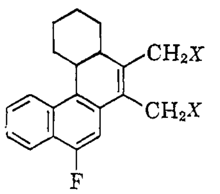
XVIII



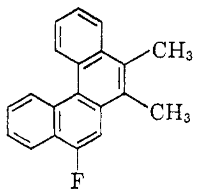
XIX



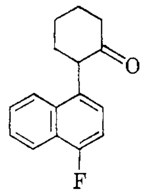
XX



XXI. $X = OH$
XXII. $X = H$



XXIII



XXIV

An attempt was also made to construct the 3,4-benzophenanthrene system from 2-(4-fluoro-1-naphthyl)cyclohexanone (XXIV), which was obtained easily from 4-fluoro-1-naphthylmagnesium bromide and 2-chlorocyclohexanone. However, the reaction of XXIV with ethyl bromoacetate and zinc gave the desired hydroxy acid in a yield of only 10%; this route was, therefore, abandoned.

## EXPERIMENTAL

All melting points are uncorrected.

*o-(4-Fluoro-1-naphthoyl)benzoic acid* (I).[1a] To a boiling suspension of 13.3 g. of phthalic anhydride in 60 ml. of benzene, a Grignard solution, prepared from 22.5 g. of 1-bromo-4-fluoronaphthalene and 2.4 g. of magnesium in 100 ml. of ether, was added, and the mixture refluxed for 2 hr. and decomposed with 100 ml. of 18% hydrochloric acid and 100 g. of ice. The product was steam distilled and the residue extracted with 10% sodium hydroxide solution. Addition of 10% hydrochloric acid yielded I which was recrystallized from toluene; m.p. 161°; yield, 15.5 g. (53%). $\nu_{max}^{KBr}$ 3050 (H-bonded OH), 1665 (carbonyl), 1142 (C—F) cm.$^{-1}$

*Anal.* Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7; F, 6.5. Found: C, 73.7; H, 4.0; F, 6.4.

*Lactone* II *of o-[α-hydroxy-α-(4-fluoro-1-naphthyl)ethyl]-benzoic acid.* To a hot solution of 13 g. of I in 250 ml. of ether and 200 ml. of benzene, a Grignard solution prepared from 6.6 g. of magnesium and 16.7 g. of methyl bromide in 200 ml. of ether was added. The mixture was refluxed for 2 hr. and decomposed with cold 25% sulfuric acid, and the

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(11) M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949).

(12) F. Bergmann and J. Szmuszkowicz, *J. Am. Chem. Soc.*, **69**, 1367 (1947).

(13) G. M. Badger and I. S. Walker, *J. Chem. Soc.*, 3238 (1954).

(14) R. N. Jones and E. Spinner, *Spectrochimica Acta*, **16**, 1060 (1960).

organic layer washed with water, 5% sodium carbonate solution and again with water, and concentrated. Recrystallization of the residue from ethanol gave 7.7 g. (60%) of colorless crystals, m.p. 140°. $\bar{\nu}_{\max}^{\text{KBr}}$ 1754 (lactone), 1128 (C—F) cm.$^{-1}$

*Anal.* Calcd. for $C_{19}H_{13}FO_2$: C, 78.1; H, 4.4; F, 6.5. Found: C, 78.0; H, 4.4; F, 6.6.

*o-[α-(4-Fluoro-1-naphthyl)ethyl]benzoic acid* (III). (a) To amalgamated zinc, prepared from 8.25 g. of zinc, 0.82 g. of mercuric chloride, 0.5 ml. of concd. hydrochloric acid, and 12.5 ml. of water, a solution of 15 g. of II in 25 ml. of glacial acetic acid, and 50 ml. of hydrochloric acid were added. The mixture was refluxed for 10 hr., during which, in intervals of 2 hr., 25 ml. of hydrochloric acid and 8.5 ml. of glacial acetic acid were added. The hot solution was filtered and concentrated and the residue recrystallized from nitromethane to give 6.1 g. (40%) of colorless needles, m.p. 169°.

*Anal.* Calcd. for $C_{19}H_{15}FO_2$: C, 77.5; H, 5.1; F, 6.5. Found: C, 77.6; H, 5.2; F, 6.8.

(b) A mixture of 5 g. of II, 4 g. of red phosphorus, 100 ml. of glacial acetic acid and 2 ml. of water was refluxed for 24 hr., filtered while still hot, and poured into 500 ml. of water containing some sodium bisulfite. The precipitate was reprecipitated from its solution in 10% sodium carbonate solution by 10% hydrochloric acid and recrystallized from nitromethane. Thus, 4.5 g. of colorless needles of m.p. 170.5° was obtained. Unchanged II (0.5 g.) did not dissolve in the carbonate solution; after recrystallization from methanol, it melted at 140°. III showed $\bar{\nu}_{\max}^{\text{KBr}}$ 1680 (acid carbonyl), 1150 (C—F) cm.$^{-1}$

*3-Fluoro-9-methyl-1,2-benzanthr-10-one* (IV). A solution of 10 g. of III in 100 ml. of concd. sulfuric acid was kept at room temperature for 3 hr. and then poured onto ice. The yellowish precipitate was recrystallized from ethanol and formed yellowish needles, m.p. 130°; yield, 8.3 g. (88%); $\bar{\nu}_{\max}^{\text{KBr}}$ 1655 (carbonyl), 1150 (C—F) cm.$^{-1}$

*Anal.* Calcd. for $C_{19}H_{13}FO$: C, 82.5; H, 4.7; F, 6.9. Found: C, 82.8; H, 4.6; F, 7.2.

*3-Fluoro-9-methyl-10-anthrylacetic acid* (IVa). To 10 g. of mossy zinc, activated with a crystal of iodine, a mixture of 37 g. of IV, 25 g. of ethyl bromoacetate, and 300 ml. of dry benzene was added so that the solvent boiled continuously. The reaction was completed by additional heating of the mixture for 2 hr. and the product poured into 1 l. of 40% sulfuric acid. The solvent was removed with steam and the residual brown oil refluxed for 15 min. with 500 ml. of a 15% solution of potassium hydroxide in ethanol. The solution was filtered and acidified with 18% hydrochloric acid, and the precipitate recrystallized from xylene; 21 g. (59%) of yellowish crystals was obtained, m.p. 212–213°, which showed in solution an intense violet fluorescence.

*Anal.* Calcd. for $C_{22}H_{15}FO_2$: C, 79.2; H, 4.7; F, 6.0. Found: C, 79.1; H, 5.0; F, 6.4.

Cyclization experiments on the acid were carried out without success with the following reagents: polyphosphoric acid (up to 170°), hydrofluoric acid, sulfuric acid, chlorosulfonic acid, boron trifluoride etherate. Also the chloride of the acid did not give the desired ketone with stannic chloride (without solvent or in carbon disulfide) or with aluminum chloride in benzene or nitrobenzene.

*3-Fluoro-9-methyl-1,2-benzanthracene* (VI). A mixture of 5 g. of IV, 5 g. of zinc dust, and 500 ml. of 10% aqueous sodium hydroxide solution was refluxed for 6 hr. and the organic product taken up in benzene. Evaporation gave colorless crystals of 3-fluoro-9,10-dihydro-10-hydroxy-9-methyl-1,2-benzanthracene, m.p. 130°, which were converted into VI by adding to their concentrated ethanolic solution a drop of concentrated hydrochloric acid. The oily product which precipitated was diluted in benzene and chromatographed on alumina [eluent: benzene–petroleum ether (b.p. 40–70°) (1:5)]; yield, 4.1 g. (87%); m.p. 54°. A solution of VI showed a strong violet fluorescence.

*Anal.* Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found: C, 87.4; H, 5.4; F, 7.5.

*3-Fluoro-9,10-dimethyl-1,2-benzanthracene* (V). A warm solution of 2 g. of IV in 100 ml. of benzene was added to a Grignard solution prepared from 1 g. of magnesium, 10 g. of methyl iodide, and 100 ml. of ether. The mixture was stirred at room temperature for 2 hr. and decomposed with 10% sulfuric acid. The residue from the organic layer was dissolved in benzene and chromatographed on alumina [eluent: benzene-petroleum ether (1:1)]. Recrystallization from cyclohexane gave 1.52 g. (75%) of yellowish needles, m.p. 94°, which showed in solution a strong violet fluorescence.

*Anal.* Calcd. for $C_{20}H_{15}F$: C, 87.6; H, 5.5; F, 6.9. Found: C, 87.9; H, 5.5; F, 7.2.

*9-Bromomethyl-3-fluoro-1,2-benzanthracene* (VII). A mixture of 2.6 g. of VI, 1.78 g. of *N*-bromosuccinimide and 30 ml. of carbon tetrachloride was refluxed for 45 min. and the filtered solution diluted with 20 ml. of petroleum ether. Yellowish needles (2.1 g.) were obtained; concentration of the mother liquor gave an additional crop of 1.25 g. (total yield, 96%). The melting point (199°) was not raised by recrystallization from carbon tetrachloride.

*Anal.* Calcd. for $C_{19}H_{12}BrF$: C, 67.3; H, 3.5; F, 5.6. Found: C, 67.3; H, 3.8; F, 5.4.

*9-Cyanomethyl-3-fluoro-1,2-benzanthracene* (VIII). When 2 g. of VII was refluxed for 3 hr. with 2 g. of potassium cyanide, 80 ml. of acetone, 50 ml. of acetonitrile, and 10 ml. of water, a strong violet fluorescence appeared. The reaction product was poured into 1 l. of water and the yellow solid washed with water, dried and recrystallized twice from nitromethane. Thus, 1.2 g. (81%) of yellowish needles of m.p. 209° was obtained; their solution in benzene was strongly fluorescent.

*Anal.* Calcd. for $C_{10}H_{12}FN$: C, 84.3; H, 4.2; F, 6.7; N, 4.9. Found: C, 83.9; H, 4.1; F, 7.1; N, 4.8.

We did not succeed in hydrolyzing VIII by treatment with sulfuric, hydrochloric and hydrobromic acid in water or alcohol as solvents nor in cyclizing VIII with hydrofluoric or polyphosphoric acid; alcoholic alkali gave only traces of acid after refluxing the compound with it for several days. The alkaline solution was diluted with water, filtered from most of the starting material and acidified with 10% hydrochloric acid. (3-Fluoro-1,2-benz-9-anthryl)acetic acid was recrystallized from xylene and formed colorless crystals of m.p. 274–275° dec.

*Anal.* Calcd. for $C_{20}H_{13}FO_2$: C, 79.0; H, 4.3; F, 6.2. Found: C, 78.6; H, 4.1; F, 6.5.

*2-(4-Fluoro-1-naphthoyl)-5-methylbenzoic acid* (IX). The first of the following methods is more convenient for small, the second for larger quantities.

(a) To a mixture of 16.2 g. of 4-methylphthalic anhydride[15] and 26.6 g. of finely powdered aluminum chloride, 18 g. of 1-fluoronaphthalene was added at 0°. The mixture was stirred for 5 min.; a very viscous mass resulted which was decomposed with ice and concentrated hydrochloric acid. The organic material was extracted with benzene and the extract washed with 18% hydrochloric acid and water and concentrated.

The residue was dissolved in 10% sodium carbonate solution, reprecipitated with 10% hydrochloric acid and recrystallized twice from xylene. Thus, 10.3–12.3 g. (35–40%) of colorless crystals, m.p. 174–175°, was obtained.

(b) A mixture of 14.6 g. of 1-fluoronaphthalene, 16.2 g. of 4-methylphthalic anhydride, 26.6 g. of aluminum chloride and 100 ml. of carbon disulfide was refluxed with stirring until the evolution of hydrogen chloride ceased (4–6 hr.), decomposed with ice and hydrochloric acid and treated with steam. The work-up was as in (a); m.p. 174–175°; yield, 35–40%.

*Anal.* Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.2; F, 6.2. Found: C, 74.1; H, 4.6; F, 6.6.

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(15) D. Craig, *J. Am. Chem. Soc.*, 72, 3732 (1950).

*(4-Fluoro-1-naphthyl) p-tolyl ketone.* (a) A solution of 6 g. of *p*-tolunitrile in 100 ml. of benzene was added to a Grignard solution, prepared from 1.2 g. of magnesium and 11.2 g. of 1-bromo-4-fluoronaphthalene in 60 ml. of ether. A quantity of 50 ml. of ether was distilled and the mass refluxed for 12 hr. and decomposed with 150 ml. of ice water and 50 ml. of concd. hydrochloric acid. The organic solvents were removed by steam distillation, and the remaining ketimine hydrochloride was refluxed for 2 hr. with 50 ml. of concd. hydrochloric acid, 100 ml. of water, 50 ml. of glacial acetic acid, and 50 ml. of toluene. After dilution with 300 ml. of water, the toluene layer was separated and the aqueous phase twice extracted with toluene. The combined toluene solutions were poured into 150 ml. of 10% sodium hydroxide solution, and the toluene was removed by steam distillation. The ketone was extracted with benzene and purified by distillation. It formed a yellowish, viscous oil of b.p. 189–191° (2 mm.) and could not be induced to crystallize; yield, 12 g. (92%).

*Anal.* Calcd. for $C_{18}H_{13}FO$: C, 81.8; H, 4.9; F, 7.2. Found: C, 81.9; H, 5.1; F, 7.2.

*The 2,4-dinitrophenylhydrazone* was recrystallized from methanol and formed crystals, m.p. 268°.

(b) A mixture of 1 g. of the acid (IX) and of 1 g. of its cupric salt was heated at 240° for 20 min. Flash-distillation in a vacuum of 5 mm. gave 0.7 g. of a viscous oil which could not be induced to crystallize. It was converted into its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p., 268°.

*(4-Fluoro-1-naphthyl) m-tolyl ketone.* The preparation followed exactly the lines indicated for the *para*-isomer. The ketone boiled at 194–197° (3 mm.) and crystallized upon trituration with ether. Recrystallization from methanol yielded 9.5 g. (72%) of colorless crystals, m.p. 72°.

*Anal.* Calcd. for $C_{18}H_{13}FO$: C, 81.8; H, 4.9; F, 7.2. Found: C, 81.6; H, 5.2; F, 7.4.

*The 2,4-dinitrophenylhydrazone* melted at 216° after recrystallization from methanol.

*2-[(4-Fluoro-1-naphthyl) methyl]-5-methylbenzoic acid* (X). A mixture of 5 g. of IX, 4 g. of red phosphorus, 2 ml. of hydriodic acid, 100 ml. of glacial acetic acid, and 2 ml. of water was refluxed for 50 hr., filtered while still hot, and diluted with 500 ml. of water containing 0.5 g. of sodium bisulfite. The precipitate was recrystallized from toluene; m.p. 226°; yield, 3.6 g. (75%).

*Anal.* Calcd. for $C_{19}H_{15}FO_2$: C, 77.5; H, 5.1; F, 6.5; Found: C, 77.8; H, 5.4; F, 6.4.

*3-Fluoro-6-methyl-1,2-benzanthr-10-ol* (XI). A mixture of 5 g. of the foregoing compound and 30 ml. of anhydrous hydrogen fluoride was kept at room temperature until the liquid had evaporated. The residue was treated with 100 ml. of water and then formed yellow crystals of m.p. 165°. Recrystallization from toluene gave cubes of the same melting point; yield, 4.2 g. (92%). The infrared spectrum showed the hydroxyl band (3420 cm.$^{-1}$), but no trace of the carbonyl absorption characteristic for the tautomer (XII).

*Anal.* Calcd. for $C_{19}H_{13}FO$: C, 82.5; H, 4.7; F, 6.9. Found: C, 82.6; H, 4.8; F, 6.8.

*3-Fluoro-6-methyl-1,2-benzanthr-10-one* (XII). When 4 g. of the foregoing compound was refluxed for 8 hr. with 100 ml. of toluene, light yellow crystals separated on cooling, which showed, after recrystallization from toluene or much benzene, m.p. 299–300° dec.; yield, 3.1 g. (77%). The infrared spectrum (absorption at 1630 cm.$^{-1}$: no hydroxyl absorption) indicated that the transformation of the enol into the keto form was complete.

*Anal.* Calcd. for $C_{19}H_{13}FO$: C, 82.5; H, 4.7; F, 6.9. Found: C, 82.3; H, 4.8; F, 6.6.

The product did not enter into reaction with methylmagnesium iodide, vinylmagnesium bromide, ethyl bromoacetate and zinc, or ethyl cyanoacetate in the presence of piperidine acetate. In all cases, only partial isomerization to XI took place.

*3-Fluoro-6-methyl-1,2-benzanthracene.* A mixture of 2.5 g. of XI or XII, 3.1 g. of zinc dust, and 150 ml. of 10% sodium hydroxide solution was refluxed for 8 hr. The solid product was dissolved in hot benzene and the solution washed with 10% hydrochloric acid and concentrated. The concentrated solution was chromatographed on alumina, a 1:1 mixture of benzene and petroleum ether serving as eluent. From the first, strongly fluorescent fraction, 1.9 g. (81%) of colorless, shiny needles was obtained, m.p. 172–173°, unchanged by recrystallization from benzene.

*Anal.* Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found: C, 87.4; H, 5.1. F, 7.6.

*4-Fluoro-1-naphthylamine hydrochloride.*[16] A solution of 38.2 g. of 4-fluoro-1-nitronaphthalene in 100 ml. of absolute ethanol was reduced catalytically in the presence of 0.6 g. of palladium on charcoal (10%). The filtered solution was poured into 200 ml. of 18% hydrochloric acid and the crystalline product reprecipitated from its solution in hot water by addition of concentrated hydrochloric acid; m.p. 280° dec.; yield, 37 g. (94%).

*N-(m-Tolyl)-4-fluoro-1-naphthylamine* (XIII). From 28.5 g. of the foregoing compound, the amine was set free by treatment with 10% sodium hydroxide solution and isolated by extraction with benzene and concentration of the solution. The mixture of the residue with 16 g. of freshly distilled *m*-toluidine and 0.5 g. of iodine was heated at 250–260° for 14 hr. (until the evolution of gas had almost ceased), cooled and dissolved in 200 ml. of benzene. This solution was washed with 100 ml. of 10% hydrochloric acid, the solid was filtered and the solution washed with 30% sodium hydroxide solution and saturated salt solution. The product distilled at 208° (5 mm.) as a yellow oil which crystallized upon trituration with methanol. Thus, 24.5 g. (65%) of colorless cubes of m.p. 53° was obtained.

*Anal.* Calcd. for $C_{17}H_{14}FN$: C, 81.2; H, 5.6; F, 7.6; N, 5.6. Found: C, 81.2; H, 5.2; F, 7.7; N, 5.5.

*N-(p-Tolyl)-4-fluoro-1-naphthylamine* (XIV). The condensation with *p*-toluidine was carried out as above, but the temperature of condensation was 230–240° and its duration 7 hr. The product distilled at 187–188° (2 mm.); m.p. 74–75° after recrystallization from methanol; yield, 18 g. (49%).

*Anal.* Calcd. for $C_{17}H_{14}FN$: C, 81.2; H, 5.6; F, 7.6; N, 5.6. Found: C, 81.6; H, 5.2; F, 7.8; N, 5.6.

*3-Fluoro-7,10-dimethyl-1,2-benzacridine* (XV). It has been found that analytically pure zinc chloride does not catalyze the cyclization of XIII or XIV; it has to be supplemented with aluminum chloride. A mixture of 10 g. of zinc chloride (analytical grade, freshly fused, and powdered), 2.5 g. of aluminum chloride (technical, powdered), 12.5 g. of XIII and 12.5 g. of acetic anhydride was heated, with stirring, at 150–160° for 24 hr. After cooling, an excess of 20% aqueous potassium hydroxide was added and the product extracted with benzene. The extract was washed with water and concentrated; the product boiled at 228–240° (3.5 mm.) and crystallized from methanol in form of yellowish needles of m.p. 168–170°. For purification, it was converted in benzene solution into its yellow picrate, which after recrystallization from nitrobenzene melted at 227–228° dec. and was decomposed with dilute ammonia. The base thus obtained was recrystallized repeatedly from a 1:5 mixture of benzene and methanol and melted at 173–175°. Alternatively, chromatography on alumina and elution with benzene–petroleum ether (3:1), followed by recrystallization from ethanol–benzene (5:1), gave 5.1 g. (37%) of pure product, m.p. 175°.

*Anal.* Calcd. for $C_{19}H_{14}FN$: C, 82.9; H, 5.1; F, 6.9; N, 5.1. Found: C, 82.9; H, 5.0; F, 7.2; N, 4.9.

*3-Fluoro-6,10-dimethyl-1,2-benzacridine* (XVI). The cyclization was carried out as above; the product boiled at 235–245° (5 mm.) and was recrystallized from methanol, giving yellow crystals of m.p. 165–170°, and after purification through the picrate (m.p. 220° dec. after recrystallization

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[16] G. I. Niemann, W. Gueffroy, and W. Winkelmueller, *Ann.*, 487, 270 (1931).

from nitrobenzene) or through chromatography, m.p. 174°; yield, 4.4 g. (32%).

*Anal.* Calcd. for $C_{19}H_{14}FN$: C, 82.9; H 5.1; F, 6.9; N, 5.1. Found: C, 83.2; H, 5.6; F, 6.8; N, 5.0.

*2-(4-Fluoro-1-naphthyl)-cyclohexanone* (XXIV). A solution of 13.2 g. of 2-chlorocyclohexanone in 50 ml. of anhydrous ether was added, during 20 min. and with agitation, to a Grignard solution, prepared from 2.45 g. of magnesium, 22.5 g. of 1-bromo-4-fluoronaphthalene and 100 ml. of ether. After 15 min., the solvent was distilled until the viscous, foaming mass filled about half of the 500-ml. flask. Then 70 ml. of benzene was added and the bluish mass refluxed for 8 hr. with vigorous agitation. After decomposition and work-up, the product boiled under 5 mm. pressure from 200 to 230°. Renewed distillation gave a fraction of b.p. 194° (3 mm.) which gave beautiful, transparent platelets upon trituration with 50 ml. of ethanol. Recrystallization from the same solvent led to 4.5 (19%) of the ketone (XXIV), m.p. 135.5°; $\lambda_{max}^{C_2H_5OH}$ 223 (5.73); 275 (shoulder; 3.74); 285 (3.79); 320 mμ (2.90).

*Anal.* Calcd. for $C_{16}H_{15}FO$: C, 79.4; H, 6.2; F, 7.9. Found: C, 79.0; H, 6.4; F, 7.9.

*The 2,4-dinitrophenylhydrazone,* long orange needles of m.p. 177–178°, was purified by recrystallization from a mixture of benzene and ethanol.

*Anal.* Calcd. for $C_{22}H_{19}FN_4O_4$: C, 62.5; H, 4.5; F, 4.5. Found: C, 62.3; H, 4.3: F, 4.5.

From the ethanolic mother liquor of XXIV a viscous second product was obtained by evaporation. It boiled at 181–182° (2 mm.) and crystallized upon trituration with methanol. Recrystallization from the same solvent gave 6.8 g. of glistening, colorless prisms, m.p. 126°, the nature of which has not been elucidated.

*Anal.* Found: C, 81.6; H, 5.1; F, 11.8.

*1-Carboxymethyl-2-(4-fluoro-1-naphthyl)cyclohexanol.* A mixture of 2.42 g. of XXIV, 1.2 ml. of ethyl bromoacetate, and 15 ml. of benzene was added in small portions to 0.65 g. of mossy zinc, activated with a little iodine. When the spontaneous reaction had subsided (10 min.), the mixture was refluxed for 2 hr., hydrolyzed with ice water, and brought to *p*H 3 with hydrochloric acid. The organic layer was washed with 5% sodium hydrogen carbonate solution, dried, and concentrated and the oily residue refluxed for 10 min. with a solution of 2 g. of potassium hydroxide in 20 ml. of ethanol. The solution was diluted with 50 ml. of water, extracted with ether, and acidified with 10% hydrochloric acid. The acid was obtained as an oil which was extracted with benzene; the residue of this solution crystallized with, and was recrystallized from, a mixture of petroleum ether and benzene; yield, 0.25 g. (8%). $\lambda_{max}^{C_2H_5OH}$ 224 (4.70); 275 (shoulder; 3.74); 287 (3.46); 314 (2.93); 321 mμ (3.04).

*Anal.* Calcd. for $C_{18}H_{19}FO_3$: C, 71.5; H, 6.3; F, 6.3. Found: C, 71.5; H, 6.6; F, 6.5.

From the mother liquors, a second acidic product (1.1 g.) was obtained, which was recrystallized from a mixture of xylene and ligroin and formed colorless needles of m.p. 141.5–142.5°. When larger batches than the above one were used, the separation of the two compounds proved somewhat tedious, but the second one was always formed in larger quantities. Its structure has not been elucidated.

*Anal.* Found: C, 70.1; H, 6.3; F, 6.7.

*1-(Cyclohex-1-enyl)-4-fluoronaphthalene.* A solution of 26 g. of cyclohexanone in 100 ml. of benzene was added to a Grignard solution, prepared from 7 g. of magnesium and 56 g. of 1-bromo-4-fluoronaphthalene in a mixture of 300 ml. of ether and 100 ml. of benzene, and the mixture refluxed for 2 hr. and decomposed with 40% sulfuric acid. The organic layer was washed with 5% sodium hydroxide solution and saturated sodium chloride solution, dried, and distilled. The product (29 g.; 52%) boiled at 152° (3 mm.) and crystallized upon standing in the refrigerator.

*Anal.* Calcd. for $C_{16}H_{15}F$: C, 85.0; H, 6.6; F, 8.4. Found: C, 85.2; H, 6.6; F, 8.2.

A small second fraction [b.p. 178–180° (2.5 mm.)] was, according to the analysis *1-(4-fluoro-1-naphthyl)cyclohexanol.*

*Anal.* Calcd. for $C_{16}H_{17}FO$: C, 78.7; H, 7.0; F, 7.8. Found: C, 78.7; H, 7.2; F, 7.6.

*2-Fluoro-4b,5,6,7,8a-hexahydro-3,4-benzophenanthrene-9,10-dicarboxylic acid anhydride* (XVIII). A mixture of 23 g. of the foregoing cyclohexenyl derivative and 60 g. of maleic anhydride was heated at 220–230° for 4 hr.; the excess of the maleic anhydride was distilled *in vacuo.* The residue was then distilled at 0.5 mm: the product frothed very heavily, obviously because of decomposition (loss of hydrogen), and only very slowly could a suitable distillate be obtained (4 hr.). The latter was extracted with 200 ml. of toluene and the yellow extract concentrated and treated with petroleum ether (the toluene-insoluble part was free of fluorine). Thus, 14 g. (43%) of the yellow anhydride was obtained from cyclohexane, m.p. 154°.

*Anal.* Calcd. for $C_{20}H_{15}FO_3$: C, 74.5; H, 4.7; F, 5.9. Found: C, 74.7; H, 4.3; F, 6.1.

*Reduction of* XVIII. A solution of 10 g. of XVIII and 10 g. of lithium aluminum hydride in 300 ml. of dry tetrahydrofuran was refluxed and stirred for 5 hr. After dilution with 300 ml. of ether, the excess reagent was destroyed by addition of ethyl acetate and the product decomposed with water and hydrochloric acid. The aqueous layer was extracted twice with 100 ml. of benzene, and the combined organic layers were concentrated. The residue (6.5 g.) was treated with 2 ml. of cyclohexane and 10 ml. of benzene and gave 0.1 g. of colorless crystals, from cyclohexane-benzene, m.p. 173–175°, of the phthalide (XIX or XX). $\lambda_{max}^{CHCl_3}$ 257 (4.68); 315 (4.08); 345 (3.58); 362 (3.65); 390 mμ (2.53). $\tilde{\nu}_{max}^{KBr}$ 1740 cm.$^{-1}$

*Anal.* Calcd. for $C_{20}H_{17}FO_2$: 77.9; H, 5.5; F, 6.2. Found: C, 77.7; H, 5.3; F, 6.2.

Concentration of the cyclohexane-benzene mother-liquor and trituration of the residue with cyclohexane gave again 0.1 g. of crystals, which were recrystallized twice from cyclohexane and melted at 137°, representing the isomeric phthalide (XX or XIX). $\lambda_{max}^{CHCl_3}$ 258 (4.72); 343 (3.41); 360 (3.50); 390 mμ (2.45). $\tilde{\nu}_{max}^{KBr}$ 1750 cm.$^{-1}$

*Anal.* Calcd. for $C_{20}H_{17}FO_2$: C, 77.9; H, 5.5; F, 6.2. Found: C, 77.9; H, 5.6; F, 6.1.

The oily product obtained after removal of the above two compounds was the diol (XXI). When the reduction of XVIII was continued for 30 hr., only the diol was obtained. It was used directly for the following step.

*2-Fluoro-9,10-dimethyl-4b,5,6,7,8,8a-hexahydro-3,4-benzophenanthrene* (XXII). A mixture of 12 g. of the diol (XXI), 15 g. of red phosphorus, 3 g. of iodine, 3 ml. of water, and 200 ml. of glacial acetic acid was refluxed for 48 hr., filtered while still hot, and poured into water, containing some sodium hydrogen sulfite. The benzene solution of the reddish oil that precipitated, was washed with 25% sodium hydroxide solution and saturated sodium chloride solution and concentrated. The product distilled at 180–183° (2 mm.) and formed a yellowish oil (6 g.; 56%) which was fairly unstable in contact with the atmosphere.

*Anal.* Calcd. for $C_{20}H_{21}F$: C, 85.7; H, 7.5; F, 6.8. Found: C, 85.6; H, 7.7; F, 6.3.

The oil gave a very well defined orange-colored complex with 2,4,6-trinitrofluorenone (in benzene-ethanol, 1:1). The complex was recrystallized from the same solvent mixture; m.p. 144–145°.

*Anal.* Calcd. for $C_{33}H_{26}FN_3O_7$: C, 66.5; H, 4.4. Found: C, 66.2; H, 4.5.

*2-Fluoro-9,10-dimethyl-3,4-benzophenanthrene* (XXIII). A mixture of 5 g. of the foregoing compound with 3 g. of selenium powder was heated at 320–330° for 26 hr. The dark residue was powdered and extracted with 100 ml. of boiling benzene. The filtered extract was concentrated and the residue dissolved in petroleum ether and subjected twice to chromatography on activated alumina. The first fraction, which showed a greenish fluorescence, represented the product (2.8 g.; 57%), which was identified by its spectrum

($\lambda_{max}^{CHCl_3}$ 255 (shoulder; 4.10); 287 (3.98); 323 (shoulder; 3.32); 342 (shoulder; 2.50); 373 (1.53); 381 mμ (1.75)) and the dark-orange-colored 2,4,6-trinitrofluorenone derivative, from benzene, m.p. 175–176°.

*Anal.* Calcd. for $C_{33}H_{20}FN_3O_7$: C, 67.3; H, 3.4; F, 3.2. Found: C, 67.1; H, 3.6; F, 2.9.

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[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

# Derivatives of *cis*- and *trans*-3-Stilbazoles

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*cis*- and *trans*-3-Stilbazole derivatives each containing a carboxy, carboxamido or cyano group in the alpha or beta position were prepared. Stereochemical assignments were made on the basis of their ultraviolet spectra and confirmed by chemical transformations.

In our search for new medicinal agents we have prepared a number of *cis*- and *trans*-3-stilbazole derivatives each containing a carboxy, carboxamido, or cyano group in the alpha or beta position.[1] The stereochemistry of stilbazole derivatives has been studied in only a few instances[2–4] and although the synthesis of *trans*-3-stilbazole (VII) was described by Beard and Katritzky[5] while this work was in progress, no attention has been given to the stereochemistry of derivatives of 3-stilbazole. Thus, the configuration of the precursor of VII, α-carboxy-3-stilbazole[5–7] (V) has not been discussed and a number of β-cyano-3-stilbazoles have been described[8,9] without mention of their stereochemistry.

On the other hand, the geometrical isomers of stilbene derivatives have been carefully studied[10] and it has been found possible to make structural assignments on the basis of their ultraviolet spectra[10–12] even when only one of a pair of geometrical isomers is available.[13,14] Most stilbene derivatives exhibit two *major* absorption bands in their ultraviolet spectra. The band at the lower wave length is the more intense for *cis*-stilbenes and that at the higher wave length is more intense for the *trans* isomers.[12,14] This useful observation is valid in the stilbene series even when the double bond is substituted with a cyano, carboxy, or carboxamido group[12] and has now been found to apply for the corresponding stilbazole derivatives (see Table II.)

The Perkin condensation of sodium phenylacetate with benzaldehyde is known to give the more stable *cis*-α-carboxystilbene.[15] Therefore, it is not surprising that when 3-pyridinealdehyde was condensed with sodium phenylacetate in the presence of acetic anhydride the product was shown by its ultraviolet spectrum to be *cis*-β-carboxy-3-stilbazole[16] (I). Similarly, the α-carboxy-3-stilbazole V formed under the conditions described by Beard and Katritzky[5] was found to have the *cis* configuration. These stereochemical assignments made on the basis of ultraviolet spectra were confirmed by chemical transformations. Thus the decarboxylation of I using copper chromite in quinoline solution[17] gave the new *cis*-3-stilbazole (II) which was readily isomerized to the *trans* isomer (VII) with iodine in nitrobenzene.[17] Furthermore, I was converted *via* the acid chloride to the corresponding *cis*-β-carboxamido-3-stilbazole (III) which, upon dehydration with *p*-toluene-

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[1] In order to facilitate discussion of their stereochemistry and interconversions, these compounds are named as derivatives of *cis*- and *trans*-3-stilbazole following the precedent of Codington and Mosettig.[12] Thus compound I is named *cis*-β-carboxy-3-stilbazole although in *Chemical Abstracts* the name *trans*-α-phenyl-3-pyridineacrylic acid would probably be used.

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