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The Synthesis of 5-Fluoro- and 7-Methyl-indole and -tryptophane

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5-Fluoroindole was prepared in 4 steps in 46% overall yield from *m*-fluorotoluene. 7-Methylindole was prepared in 2 steps from 2,6-dimethylaniline. Both compounds were transformed to the corresponding tryptophanes in high yields. The final hydrolytic step was carried out in aqueous acidic medium.

Various methods are known for the synthesis of nuclear substituted indoles and tryptophanes. Very often, however, the yields in - and the ease of - these preparations leave much to be desired. Actually no one method was found uniformly useful for the synthesis of the various substituted indoles and in practice the most suitable synthetic method has to be chosen in each case with the nature and the place of the substituent on the indole nucleus in mind (2,3). The synthesis of the title compounds may illustrate this point. 5-Fluoroindole has been prepared by the Fischer indole synthesis (4), by Reissert's method (5) and from indolines (6). In the present synthesis this compound is obtained in 46% overall yield in four steps (from *m*-fluorotoluene) *via* the corresponding benzyl bromide, benzyl cyanide to the 2-nitro-4-fluorobenzyl cyanide which is cyclized reductively (7) without any difficulties (8) to 5-fluoroindole.

The synthesis of 7-methylindole has been described (9). Other methylindoles have been synthesized *via* the Madelung synthesis (10). In this method only half of the quantity of N-formyl-*o*-toluidine employed for cyclization can yield the indole, the rest being recovered as the free toluidine. Therefore other methods have been employed for the synthesis of methyl derivatives of indoles and tryptophanes (11, 12). However, the application of the Madelung synthesis to N-formyl-2,6-dimethylaniline (obtained quantitatively by formylation of the commerically available 2,6-dimethylaniline) did produce the 7-methylindole in 42.5% yield (85% of theory) under relatively mild and easy conditions, probably because the N-formylanilino group is flanked here by two methyl groups in the ortho position (instead of one, which is necessary). This might make an easier and more quantitative cyclization possible.

For the conversion of the indoles to tryptophanes the now classical method of conversion to gramines and condensation with diethyl N-formylaminomalonate to diethyl skatyl-N-formylaminomalonates was used and uniformly high yields were obtained. For the final hydrolytic step to the tryptophanes an aqueous acidic medium was used in order to avoid some of the complications encountered with aqueous alkali. Decomposition or polymerization of the sensitive indole nucleus due to this medium were negligible and a clear and clean reaction solution could be obtained at the end by neutralization and filtration prior to the final precipitation of the free tryptophanes.

EXPERIMENTAL (13)

m-Fluorobenzyl bromide.

This compound was prepared by direct bromination of *m*-fluorotoluene and was obtained in 85% yield after distillation under reduced pressure, b.p. 88°/20 mm. Reported b.p. 80°/13 mm. (14), 196-200° (15). It was also obtained in 65% yield by bromination of *m*-fluorotoluene with N.B.S. in carbon tetrachloride.

Anal. Calcd. for C_7H_6BrF: C, 44.4; H, 3.2; F, 10.1. Found: C, 44.7; H, 3.2; F, 10.5.

m-Fluorobenzyl cyanide.

To a boiling solution of 9.4 g. (0.05 mole) of *m*-fluorobenzyl bromide in 100 ml. of absolute ethanol was added a solution of 3.2 g. of potassium cyanide in the minimum amount of water. The mixture was refluxed with stirring for three hours, then most of the ethanol was distilled off under reduced pressure and the cooled residue poured into water. The aqueous solution was extracted several times with ether; the combined extracts were dried and the ether distilled off to leave a residue which was distilled *in vacuo*, b.p. 117-119°/22 mm., 113-114°/18 mm. (52% yield), reported b.p. 229-230° (15).

Anal. Calcd. for C_8H_6FN: F, 14.1. Found: F, 13.8.

For large scale preparation the crude *m*-fluorobenzyl bromide was treated directly with absolute ethanol and aqueous potassium cyanide. Yields of 67-74% of *m*-fluorobenzyl cyanide (based on *m*-fluorotoluene used) were obtained.

2-Nitro-5-fluorobenzyl cyanide.

A mixture of 24 ml. of concentrated sulfuric acid and 24 ml. of concentrated nitric acid (70%) was cooled and stirred in an ice-salt bath and 10 g. (0.074 mole) of *m*-fluorobenzyl cyanide were added with stirring at such a rate that the temperature was kept below -10°. After the addition was complete the solution was stirred in the cold for one more hour and then poured on ice. A yellow oil was precipitated which crystallized on stirring and the supernatant acid solution was decanted. The solid material was dried and recrystallized from a minimum of methanol and gave 11 g. (75% yield) of yellow crystals, m.p. 65°.

Anal. Calcd. for $C_8H_5FN_2O_2$: C, 53.3; H, 2.8; F, 10.5. Found: C, 53.2; H, 3.1; F, 10.3.

5-Fluoroindole.

Eighteen g. (0.1 mole) of 2-nitro-5-fluorobenzyl cyanide were dispersed in 150 ml. of absolute ethanol together with 5 g. of 10% Pd/C. The mixture was hydrogenated under a pressure of 60 lbs./sq. inch and only the theoretical amount of hydrogen was taken up. The catalyst was filtered and the solvent was distilled off under reduced pressure. The residue was purified by steam distillation and gave 11 g. (84%) of white solid, m.p. 44°, reported m.p. 46° (4,5,6).

Anal. Calcd. for C_8H_6FN: C, 71.1; H, 4.4; N, 10.4. Found: C, 71.0; H, 4.6; N, 10.0.

Instead of purification by steam distillation, the residue can be distilled under reduced pressure. The fraction boiling at 110-120°/1 mm. was collected and the 5-fluoroindole recrystallized from hexane.

N-Formyl-2,6-dimethylaniline.

This compound was obtained in 96% yield by formylation of 2,6-dimethylaniline with acetic anhydride - formic acid (16), m.p. 167-168° (from ethanol); reported m.p. 164-165° (17).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.5; H, 7.4; N, 9.4. Found: C, 72.6; H, 7.3; N, 9.7.

7-Methylindole.

Fourteen and nine-tenths g. (0.1 mole) of N-formyl-2,6-dimethylaniline were dissolved in a mixture of 17 g. of potassium *t*-butoxide in 110 ml. of *t*-butyl alcohol. The mixture was heated under a stream of nitrogen on an air bath until all the *t*-butyl alcohol was distilled off. The temperature was then raised gradually during 10 minutes and 2,6-dimethylaniline distilled off. Finally the mixture was kept at about 320° for 5 minutes and then cooled. Water was then added and the dark mixture steam distilled; 5.6 g. (85%) of 7-methylindole was obtained, m.p. 82° (from hexane), reported m.p. 85° (18).

Anal. Calcd. for C_9H_9N: C, 82.5; H, 6.9. Found: C, 82.7; H, 6.8.

5-Fluorogramine.

A solution of 13.5 g. (0.1 mole) of 5-fluoroindole in 100 ml. of dioxane was added to a solution of 8 ml. (3 g.) of formaldehyde, 9.6 ml. (4.5 g.) of dimethylamine and 100 ml. of glacial acetic acid in 100 ml. of dioxane and left to stand for 24 hours at room temperature. An aqueous solution of 30% sodium hydroxide was then added with cooling to the reaction mixture until the solution was strongly alkaline. 5-Fluorogramine was thus precipitated quantitatively, filtered and dried, m.p. 150° (from benzene), reported m.p. 139-140° (5), m.p. 145-146° (19).

Anal. Calcd. for $C_{11}H_{13}FN_2$: C, 68.8; H, 6.8; F, 9.9. Found: C, 69.0; H, 6.9; F, 10.2.

7-Methylgramine.

This compound was prepared similarly from 7-methylindole. It was obtained in 91% yield, m.p. 115-117° (from benzene), reported m.p. 114° (10).

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.6; H, 8.5; N, 14.9. Found: C, 76.5; H, 8.7; N, 15.4.

5-Fluoroskatyl-N-formylaminomalonate.

A mixture of 96 g. (0.5 mole) of 5-fluorogramine, 101.5 g. (0.5 mole) of diethyl N-formylaminomalonate and 7.5 g. of powdered sodium hydroxide in 1.9 l. of dry toluene was refluxed with stirring under an atmosphere of nitrogen. Dimethylamine was evolved and after 3 hours the reaction product began to separate. After 8 hours the reaction was complete and the precipitate filtered; 163 g. (93%) of product was obtained, m.p. 180° (from isopropyl alcohol).

Anal. Calcd. for $C_{17}H_{19}FN_2O_5$: C, 58.3; H, 5.4; F, 5.4. Found: C, 58.5; H, 5.7; F, 5.5.

7-Methylskatyl-N-formylaminomalonate.

This compound was prepared similarly from 7-methylgramine. It was obtained in 78% yield, m.p. 179° (from xylene or isopropyl alcohol).

Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.4; H, 6.4. Found: C, 62.1; H, 6.4.

5-Fluorotryptophane.

One hundred sixty-three g. (0.465 mole) of 5-fluoroskatyl-N-formylaminomalonate was dispersed in 1.8 l. of dilute hydrochloric acid (prepared from 300 ml. of concentrated hydrochloric acid (10 *N*) and 1000 ml. of water) and refluxed with stirring. The solid dissolved very gradually while a strong evolution of carbon dioxide was observed. After solution was complete reflux and stirring were continued for one more hour and then the hot somewhat coloured solution was neutralized with concentrated sodium hydroxide to *p*H 7 and filtered from a small amount of tarry material. The clear and colourless filtrate was cooled and treated slowly with glacial acetic acid until precipitation set in. The amino acid was then left to crystallize, finally collected and dried over potassium hydroxide, m.p. 260°, reported m.p. 267° (20).

Anal. Calcd. for $C_{11}H_{11}FN_2O_2$: F, 8.6. Found: F, 8.3.

7-Methyltryptophane.

Two and one-tenth g. (0.00607 mole) of 7-methylskatyl-N-formylaminomalonate was dispersed in 40 ml. of 5% hydrochloric acid and refluxed with stirring under a stream of nitrogen until all the ester dissolved and the evolution of carbon dioxide ceased. The hot coloured solution was then treated with activated charcoal, filtered and neutralized while still hot with concentrated aqueous sodium hydroxide to *p*H 5 and quickly filtered from some precipitated tarry material. Upon cooling 1.1 g. (83.5% yield) of 7-methyltryptophan precipitated from the solution and was collected, m.p. 287° (from methanol-water), reported m.p. 296° (10).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.4. Found: C, 65.6; H, 6.4.

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