Chloromethylation of 7-Methoxyisoflavone

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Chloromethylation of flavones has already been carried out by Nakazawa and Matsuura(1) and by Da Re and Verlicchi(2) to give 6- and 8-chloromethyl derivatives from acacetin 7-methyl ether and 8-chloromethyl derivative from 7-methoxy-3-methylflavone respectively, and of flavanones by Matsuoka(3), but that of isoflavone has not yet been reported. Now the chloromethylation of 7-methoxyisoflavone (II) has been carried out.

For the reaction are available two methods, those are by the action of formaline or paraformaldehyde(2) and hydrochloric acid and by that of chloromethyl methyl ether and acetic acid(1,3).

In this experiment, II was chloromethylated by the paraformaldehyde-hydrochloric acid method to give 7-methoxy-8-chloromethylisoflavone (III), colorless needles, m. p. 143~144°C, in 59% yield. The structure of III was confirmed by converting it into 8-acetoxymethyl derivative IV by the action of sodium acetate and acetic anhydride, and further by an alkaline hydrolysis of IV into 8-hydroxymethyl derivative V, which was identical with the authentic sample prepared from 7-hydroxy-8-formylisoflavone(4) (VI) by another route: Reduction of VI by the Meerwein-Ponndorf method or by sodium borohydride[*2] furnished 8-hydroxymethyl derivative VII, which was methylated by diazomethane to give V as shown in the Chart.

The chlorine atom of III is fairly reactive: The methoxy- or ethoxy-methyl derivative (VIII or IX) was obtained by the action of sodium

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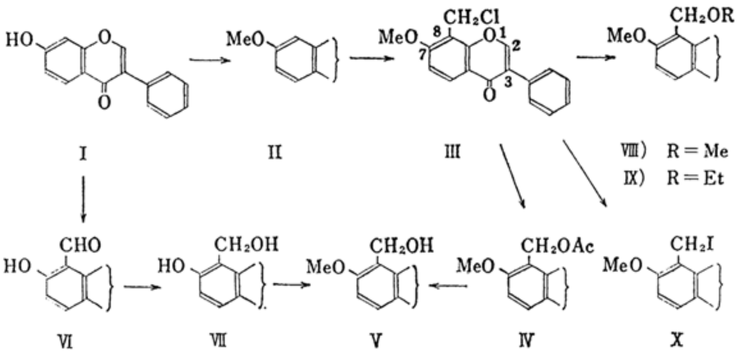
1) K. Nakazawa and S. Matsuura, *J. Pharm. Soc. Japan*, **73**, 481, 484 (1953).

2) P. Da Re and L. Verlicchi, *Ann. Chim. (Rome)*, **46**, 904 (1956).

3) K. Matsuoka, *J. Chem. Soc. Japan, Pure Chem. Sec., (Nippon Kagaku Zasshi)*, **80**, 64 (1959).

4) K. Fukui and Y. Kawase, This Bulletin, **31**, 693 (1958).

[*2] It was confirmed that this reagent does not affect the isoflavone nucleus.



methoxide or ethoxide and the iodomethyl derivative X by the action of potassium iodide in acetone, and only the acetoxymethyl derivative IV instead of the reduced compound was obtained by the action of zinc and acetic acid. An attempted chloromethylation of 7-hydroxyisoflavone (I) by the similar method was unsuccessful.

Experimental[*3]

7-Methoxyisoflavone (II).—*a) By Methyl Iodide.* To a stirred mixture of 7-hydroxyisoflavone (I) (30 g.), anhydrous potassium carbonate (30 g.) and anhydrous acetone (350 ml.) was added dropwise a solution of methyl iodide (18 g.) in acetone (50 ml.), and the mixture was refluxed for 6 hr. and then treated as usual to give II, m. p. 156~157°C (from benzene), identical with the other sample; yield 21.5 g. (67%).

b) By Diazomethane.—To a suspension of I (20 g.) in benzene (500 ml.) was added an ethereal solution of diazomethane (prepared from 7.8 g. of nitrosomethylurea), and the mixture was allowed to stand for 2 days. By the usual treatment, 9.8 g. (46.5%) of II was obtained through recrystallization from benzene; m. p. 156~157°C.

Found: C, 76.06; H, 4.66. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80%.

7-Methoxy-8-chloromethylisoflavone (III).—A mixture of II (9.8 g.), paraformaldehyde (4 g.), acetic acid (98 ml.) and concentrated hydrochloric acid (49 ml.) was saturated with hydrogen chloride under stirring and heating at 60~70°C, and then was allowed to stand at room temperature over night. The solid product obtained was washed with water and recrystallized from acetone to give III in colorless needles, m. p. 143~144°C, giving a positive Beilstein test; yield 7.1 g. (59%). IR: 1645 cm^{-1} (γ-pyrone).

Found: C, 67.29; H, 4.43. Calcd. for $C_{17}H_{13}O_3Cl$: C, 67.89; H, 4.36%.

7-Methoxy-8-acetoxymethylisoflavone (IV).—*a) From III by Sodium Acetate and Acetic Anhydride.* —A mixture of III (2 g.), anhydrous sodium acetate (1.4 g.) and acetic anhydride (20 ml.) was heated for 3 hr. on an oil-bath (170~180°C). By the usual treatment, 1.7 g. of IV was obtained in colorless needles, m. p. 197~198°C (from ethanol). IR: 1720 (acetate), 1650 cm^{-1} (γ-pyrone).

Found: C, 70.21; H, 4.92. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98%.

b) From III by Zinc and Acetic Acid.—A mixture of III (0.3 g.), zinc powder (1 g.) and acetic acid (80%, 5 ml.) was heated at 80°C for 2 hr., and the resulting mixture was poured into water. The crystalline product obtained was recrystallized from ethanol to give IV, m. p. 196~198°C.

c) From V.—A mixture of V (0.2 g.), sodium acetate (0.15 g.) and acetic anhydride (2 ml.) was treated similarly as described for a) to give IV, m. p. 196~198°C.

7-Hydroxy-8-hydroxymethylisoflavone (VII).—*a) By the Meerwein-Ponndorf Method.*—To a solution of 7-hydroxy-8-formylisoflavone[4)] (VI) (0.5 g.) in absolute isopropyl alcohol (15 ml.) was added aluminum isopropoxide (prepared from 2.75 g. of aluminum ribbon and 30 ml. of isopropyl alcohol), and the mixture was heated on an oil-bath for 4 hr., most of the solvent was distilled off in the meantime. Dilute sulfuric acid was added to the residue, and the crystalline product obtained was recrystallized from ethanol then from ethyl acetate to give VII in colorless microcrystals, m. p. 172°C (decomp.); yield 0.2 g. IR: 3300~2400 (OH), 1620 cm^{-1} (γ-pyrone).

Found: C, 71.56; H, 4.54. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%.

b) By Sodium Borohydride.—A solution of sodium borohydride (0.2 g.) in water (100 ml.) was added to a solution of VI (1 g.) in 1% aqueous sodium hydroxide (50 ml.), and the solution was heated at 60~70°C for 2 hr. on a steam-bath. The cooled solution was acidified with dilute hydrochloric acid, and the crystalline product obtained was recrystallized from ethanol then from ethyl acetate; m. p. 172°C (decomp.), identical with the other sample.

7-Methoxy-8-hydroxymethylisoflavone (V).—*a) From VII.*—To a suspensin of VII (0.1 g.) in benzene (150 ml.) was added an ethereal solution of diazomethane (prepared from 1.5 g. of nitrosomethylurea), and the mixture was allowed to stand over night. The solvent was removed, and the residual product was washed with 5% aqueous sodium hydroxide then was recrystallized from benzene to give V in colorless microcrystals, m. p. 185~186°C. IR: 3300 (OH), 1625 cm^{-1} (γ-pyrone).

Found: C, 72.23; H, 5.03. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%.

[*3] Melting points are uncorrected and infrared spectra were measured in Nujol.

b) From IV.—A mixture of IV (0.5 g.), ethanol (5 ml.) and 0.5 N ethanolic potassium hydroxide (2 ml.) was refluxed for 1.5 hr. The cooled solution was diluted with water and the crystalline product obtained was recrystallized from benzene to give V in colorless microcystals, m. p. 186~187°C, identical with the other sample; yield 0.2 g.

Found: C, 72.51; H, 5.02. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%.

7-Methoxy-8-methoxymethylisoflavone (VIII).—To a solution of III (1.5 g.) in benzene (100 ml.) was added methanolic sodium methoxide (prepared from 0.1 g. of sodium and 5 ml. of methanol), and the mixture was refluxed for 4 hr. The resulting mixture was filtered, the solvent was distilled off, and the residual product was crystallized from ethanol to give VIII in colorless needles, m. p. 142~143°C; yield 1 g.

Found: C, 72.58; H, 5.47. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44%.

7-Methoxy-8-ethoxymethylisoflavone (IX). — A similar treatment of III with sodium ethoxide furnished IX in colorless needles, m. p. 115~117°C (from acetone).

Found: C, 72.80; H, 5.68. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85%.

7-Methoxy-8-iodomethylisoflavone (X).—A mixture of III (1 g.), potassium iodide (1 g.) and acetone (20 ml.) was refluxed for 1.5 hr. The acetone was distilled off, and the residual product was washed with water and then was crystallized from acetone to give X in colorless needles, m. p. 166~167°C, giving a positive Beilstein test; yield 1 g.

Found: C, 51.98; H, 3.39. Calcd. for $C_{17}H_{13}O_3I$: C, 52.06; H, 3.34%.

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