

STUDIES ON PYRAN, ITS ANALOGS, AND RELATED COMPOUNDS

XXVI. An Investigation of 4-Methylesculetin for the Synthesis of Substituted 5,6-Dihydroxybenzofurans*

V. A. Zagorevskii and Z. D. Kirsanova

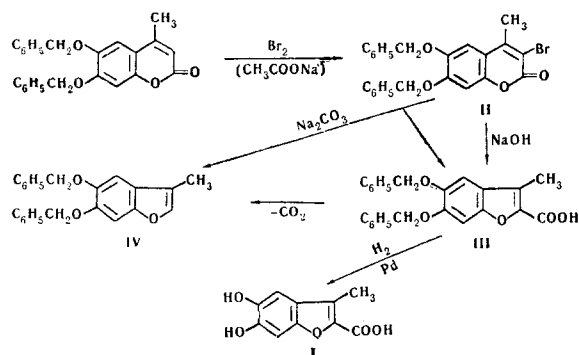
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 4, pp. 598-600, 1968

UDC 547.728.1':814.1

The bromination of 6,7-dibenzyloxy-4-methylcoumarin has given 6,7-dibenzyloxy-3-bromo-4-methylcoumarin and this has been converted by the Perkin reaction into 5,6-dibenzyloxy-3-methylbenzofuran and its 2-carboxy derivative. 5,6-Dihydroxy-3-methylbenzofuran-2-carboxylic acid has been synthesized by the catalytic debenzoylation of the latter compound.

Dihydroxybenzofurans with the hydroxy groups in the benzene nucleus have been little studied. 5,6-Dihydroxybenzofuran with free hydroxyls is completely unknown. There is a small amount of information on 5,6-dialkoxybenzofurans [1-3]. This type of compound has been synthesized by the intramolecular condensation of 2-formyl- or 2-acetyl-4,5-dimethoxyphenoxycetic or -malonic ester [4-6]. 5,6-Dimethoxy-3-phenylbenzofuran-2-carboxylic acid has been obtained from 6,7-dimethoxy-4-phenylcoumarin and its 3-bromo derivative [7]. The reduction of 3-hydroxy-5,6-dimethoxy-2-methylbenzofuran led to 5,6-dimethoxy-2-methylbenzofuran [8]. 3-Bromo-6,7-dihydroxy-4-methylcoumarin (3-bromo-4-methylesculetin) could not be converted into the corresponding dihydroxybenzofuran [9], although this method proved suitable for the 3-halo-6-hydroxycoumarins [10].

We have synthesized 5,6-dihydroxy-3-methyl-2-benzofuran-carboxylic acid (I) from 6,7-dibenzyloxy-3-bromo-4-methylcoumarin (II), which was obtained by the bromination of the known 6,7-dibenzyloxy-4-methylcoumarin [11]. The bromination was carried out in chloroform in the presence of sodium acetate. In experiments without the binding of the hydrogen bromide liberated, debenzoylation took place. By boiling a solution of the bromide II with alcoholic alkali, 5,6-dibenzyloxy-3-methyl-2-benzofurancarboxylic acid (III) was obtained with a yield of 97%.



We succeeded in obtaining I with a yield of ~34% by the catalytic debenzoylation of III. Compound I is readily oxidized by atmospheric oxygen, particularly in solutions in the presence of bases and thereby differs from 4-methylesculetin, which is a fairly stable catechol derivative, and approximates to esculetin. When the bromide II was treated with sodium carbonate in aqueous ethanol, the main reaction product was 5,6-dibenzyloxy-3-methylbenzofuran (IV), which can also be obtained by the decarboxylation of the acid III. By methylation, the acid III was converted into the methyl ester (V), the transesterification of which with 3-dimethylaminopropanol gave the corresponding amino ester (VII).

EXPERIMENTAL

3-Bromo-6,7-dibenzyloxy-4-methylesculetin (II). A solution of 12.09 g (0.0325 mole) of 6,7-dibenzyloxy-4-methylesculetin in 65 ml of dry chloroform, prepared with heating, was cooled to room temperature, and 8.0 g (0.0975 mole) of anhydrous CH_3COONa and, with stirring, 10.38 g (0.065 mole) of bromine in 13 ml of dry chloroform were added. After ~16 hr, the precipitate was filtered off, washed with chloroform and water, and dried. This gave 4 g of II with mp $187^\circ\text{--}189^\circ\text{C}$. The mother solution was treated with petroleum ether and the precipitate was recrystallized from benzene to give an additional 4.7 g of II with mp $188^\circ\text{--}189^\circ\text{C}$. Total yield 59.2%. Mp $190^\circ\text{--}191.5^\circ\text{C}$ (from benzene). Found, %: Br 17.74, 17.86; C 63.74, 63.92; H 4.16, 4.16. Calculated for $\text{C}_{24}\text{H}_{19}\text{BrO}_4$, %: Br 17.70; C 63.87; H 4.24.

5,6-Dibenzyloxy-3-methyl-2-benzofurancarboxylic acid (III). With heating, 2.26 g (0.005 mole) of the bromide II was suspended in 50 ml of ethanol, and 10 ml of 10% NaOH (0.025 mole) was added and the mixture was boiled in the water bath for 1 hr 30 min. The bulk of the solvent was distilled off and the jelly-like residue acidified with ~90 ml of 2 N HCl, left for 1 hr, and filtered, and the residue was washed with water and dried in vacuum over P_2O_5 . This gave 1.88 g (97%) of III, mp $198^\circ\text{--}199^\circ\text{C}$ (decomp., from acetic acid). Found, %: C 74.18, 74.41; H 5.20, 5.16. Calculated for $\text{C}_{24}\text{H}_{20}\text{O}_5$, %: C 74.22; H 5.20.

Methyl 5,6-dibenzyloxy-3-methyl-2-benzofurancarboxylate (V). A mixture of 4.68 g (0.012 mole) of III, 4.96 g (0.036 mole) of ground anhydrous potassium carbonate, and 4.56 g (0.036 mole) of $(\text{CH}_3)_2\text{SO}_4$ in 80 ml of anhydrous acetone was boiled in the water bath for 4 hr and evaporated to dryness, and then water was added and the product was extracted with a mixture of ether (~300 ml) and benzene (~80 ml). The ethereal benzene extract was washed with water to neutrality, dried with Na_2SO_4 , and evaporated to dryness in vacuum. The light-colored residue was triturated with 30 ml of methanol, filtered off, washed with methanol and petroleum ether, and dried in vacuum over P_2O_5 . This gave 4 g (82.5%) of the ester V, mp $122^\circ\text{--}122.5^\circ\text{C}$ (from methanol). Found, %: C 74.84, 74.81; H 5.61, 5.74. Calculated for $\text{C}_{28}\text{H}_{22}\text{O}_5$, %: C 74.63; H 5.51.

3-Dimethylaminopropyl 5,6-dibenzyloxy-3-methyl-2-benzofurancarboxylate (VI). To 7.7 g (0.075 mole) of 3-dimethylaminopropanol and 100 ml of absolute toluene 0.08 g of sodium was added followed

*For part XXV, see [12].

by 6 g (0.015 mole) of the methyl ester V; 50 ml of toluene was distilled off over 1 hr 30 min and then a mixture of 0.77 g of 3-dimethylaminopropanol and 100 ml of absolute toluene containing 0.08 g of sodium was added and again 70 ml of toluene was distilled off over 1 hr 30 min, after which the excess of toluene and the amino alcohol were distilled off in vacuum and the residue was shaken with benzene and filtered from the sodium salt of the acid III. The filtrate was repeatedly washed with water until the alkaline reaction had disappeared and was dried with Na_2SO_4 and evaporated in vacuum. The residue was triturated with petroleum ether, filtered off, and washed with ether to give 2.46 g (35%) of VI with mp $79.5^\circ\text{--}81.5^\circ\text{C}$. For purification, the VI was converted into the hydrochloride (VII) by dissolving it in a mixture of ether and benzene and adding an ethereal solution of hydrogen chloride. The VII was filtered off, washed, transferred to a separating funnel, and shaken with 10% Na_2CO_3 and benzene. The benzene solution was dried with Na_2SO_4 and evaporated in vacuum. The residue was treated with petroleum ether to give 1.71 g of VI with mp $85\text{--}86^\circ\text{C}$ mp $85^\circ\text{--}86^\circ\text{C}$. After crystallization from methanol and from a mixture of petroleum ether and benzene (5:1), mp $85^\circ\text{--}85.5^\circ\text{C}$. Found, %: C 73.74, 73.72; H 6.64, 6.76; N 3.02, 3.13. Calculated for $\text{C}_{29}\text{H}_{31}\text{O}_5\text{N}$, %: C 73.55; H 6.60; N 2.96.

5, 6-Dibenzoyloxy-3-methylbenzofuran (IV). With shaking, a solution of 2.39 g (0.0225 mole) of Na_2CO_3 in 30 ml of water was added to a hot suspension of 3.39 g (0.0075 mole) of II in 75 ml ethanol, and the mixture was boiled for 50 hr. Then it was evaporated to dryness and the residue was treated with 10% Na_2CO_3 (~70 ml) and hot benzene (~130 ml). The insoluble residue was filtered off, boiled for ~5 min with 2 N HCl, and washed with water and ether to give 0.78 g (26.8%) of III; the benzene solution was dried with Na_2SO_4 and evaporated in vacuum to give 1.6 g (62%) of IV with mp $103^\circ\text{--}105^\circ\text{C}$. For purification, the IV was crystallized from a mixture of benzene and petroleum ether (1:2), mp $106^\circ\text{--}107^\circ\text{C}$. Found, %: C 80.34, 80.39; H 5.83, 5.89. Calculated for $\text{C}_{23}\text{H}_{20}\text{O}_3$, %: C 80.19, H 5.85%. Compound IV was also obtained by decarboxylation: 0.59 g of III in 10 ml of dry quinoline in the presence of 0.19 g of copper powder was heated at 220°C for 1 hr and then the copper was filtered off and the quinoline was distilled off. The residue was shaken with 2 N HCl and benzene. The benzene solution was washed with water, 2 N NaOH, and water again, and was dried with Na_2SO_4 and evaporated. The residue was washed with petroleum ether and crystallized from CH_3COOH (with carbon) to give IV. Evaporation of the petroleum ether gave a further portion of IV. Total yield 0.13 g (25%). In this melting point and its R_f value on chromatography in a thin layer of Al_2O_3 the substance was identical with the sample obtained by the method described above.

5, 6-Dihydroxy-3-methyl-2-benzofuran carboxylic acid (I). A solution of 3.88 g (0.01 mole) of III in 500 ml of ethyl acetate and 30 ml of glacial CH_3COOH was added to 4 g of 2.5% Pd/ BaSO_4 in 100 ml of ethyl acetate, and hydrogenation was carried out until 0.02

mole of hydrogen had been absorbed. The catalyst was filtered off, and the filtrate was divided into three portions each of which was evaporated almost to dryness in vacuum on the water bath with protection from atmospheric oxygen. The residues were combined and shaken with water to which a small amount of sodium hydrosulfite had been added, and the light pink residue was filtered off and crystallized from water in the presence of sodium hydrosulfite, giving 0.47 g of I. The two aqueous mother solutions, by evaporation and recrystallization from 50% ethanol in the presence of sodium hydrosulfite gave an additional 0.23 g of I. The total yield was 0.7 g (34%), mp 206°C (decomp.). Found, %: C 57.84, 57.94; H 3.94, 3.88. Calculated for $\text{C}_{10}\text{H}_8\text{O}_5$, %: C 57.68; H 3.87. The substance gave a dark blue coloration with an alcoholic solution of FeCl_3 and it dissolved in aqueous NaHCO_3 .

REFERENCES

1. F. E. King, J. R. Housley, and I. J. King, J. Chem. Soc., 1392, 1954.
2. Garbakhsh Singh, G. V. Nair, and K. P. Aggarwal, J. Sci. Ind. Res., 15B, 190, 1956; C. A. 51, 416, 1957.
3. M. G. Patel and S. Sethna, J. Ind. Chem. Soc., 37, 227, 1960.
4. G. H. Jones, J. B. D. Mackenzie, A. Robertson, and W. B. Whalley, J. Chem. Soc., 562, 1949.
5. W. B. Whalley, J. Chem. Soc., 3479, 1953.
6. S. Tanaka, J. Am. Chem. Soc., 73, 872, 1951.
7. V. K. Ahluwalia, A. C. Mehta, T. R. Seshadri, Tetrah., 4, 271, 1958.
8. S. Muller and P. Richter, Ber., 77, 12, 1944.
9. Z. Jermanowska and Z. Orchowicz, Acta Polon. Pharm., 13, 11, 1956.
10. H. v. Pechmann and E. Hanke, Ber., 34, 109, 1901.
11. L. Velluz and G. Amiard, Bull. Soc. Chim., 1109, 1948.
12. V. A. Zagorevskii and Z. D. Kirsanova, ZhOrKh, 3, 568, 1967.

6 July 1966

Institute of Pharmacology and
Chemotherapy. AMS USSR, Moscow