INVESTIGATION OF THE TRANSFORMATIONS OF 2-CARBOMETHOXY-5-HYDROXYBENZOFURAN

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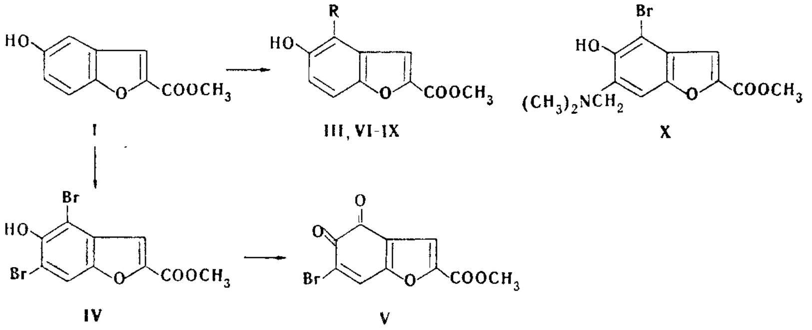
In the electrophilic substitution reactions (bromination, nitration, diazo coupling, Sommelet formylation, and aminomethylation) of 2-carbomethoxy-5-hydroxybenzofuran substituents primarily enter the 4 position.

It has been observed that substituents enter the 6 position in the bromination and nitration of 2-methyl-3-carbethoxy-5-hydroxybenzofuran, whereas in diazo coupling they enter the 4 position [1]. In order to ascertain the effect of a carbethoxy group on the orientation of substituents it seemed of interest to study the electrophilic substitution reaction of 5-hydroxybenzofuran with an ester group in the 2 position.

We synthesized 2-carbomethoxy-5-hydroxybenzofuran (I) by esterification of 2-carboxy-5-hydroxybenzofuran (II), which was obtained by demethylation of the appropriate 5-methoxybenzofuran derivative [2]. We obtained 2-carbomethoxy-4-bromo-5-hydroxybenzofurans (III) in 90% yield by bromination of I with an equivalent amount of bromine, whereas the action of excess bromine under more severe conditions gave 2-carbomethoxy-4,6-dibromo-5-hydroxybenzofuran (IV). 2-Carbomethoxy-4,5-dioxo-6-bromobenzofuran (V) is formed by oxidation of IV with nitric acid.

The nitration, diazo coupling, aminomethylation, and Sommelet formylation of I led primarily to replacement of the hydrogen atom in the 4 position to give the corresponding 4-substituted I (VI-IX). 2-Carbomethoxy-4-bromo-5-hydroxy-6-dimethylaminomethylbenzofuran (X) is formed in the aminomethylation of III.



III R=Br; VI R=NO$_2$; VII R=p-CH$_3$C$_6$H$_4$N$_2$; VIII R=CH$_2$N(CH$_3$)$_2$; IX R=CHO

The structures of III and VI-IX were established by means of PMR spectroscopy. Doublets of the 6-H and 7-H protons with a spin-spin coupling constant (SSCC) of 8 Hz are observed in the spectra of these compounds, and the signal of the 3-H proton has the form of a singlet, the position of which (7.25-8.06 ppm) depends on the character of the substituent introduced into the ring.

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Thus, whereas the shielding effect of the carbethoxy group in 2-methyl-3-carbethoxy-5-hydroxybenzofuran hinders bromination and nitration in the 4 position, this is not the case in I, and substituents primarily enter the 4 position in all electrophilic substitution reactions.

EXPERIMENTAL METHOD

The PMR spectra of deuterochloroform solutions were recorded with a JNM 4H-100 JEOL spectrometer with hexamethyldisiloxane as the internal standard.

2-Carboxy-5-hydroxybenzofuran (II). A mixture of 2.06 g (0.01 mole) of 2-carbethoxy-5-methoxybenzofuran [2] and 8 g (0.07 mole) of pyridine hydrochloride was stirred in a stream of nitrogen at 190-200° for 1 h, after which it was cooled and poured into 20 ml of 10% hydrochloric acid. The resulting precipitate was removed by filtration to give a product with mp 252-254° (from water) in 84% yield. Found %: C 60.6; H 3.5. $C_9H_6O_4$. Calculated %: C 60.7; H 3.4.

Compound II was also obtained from 2-carboxy-5-methoxybenzofuran [2] in 59% yield.

2-Carbomethoxy-5-hydroxybenzofuran (I). A stream of hydrogen chloride was bubbled through a refluxing solution of 5.2 g (29 mmole) of II in 100 ml of methanol for 6 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration to give I with mp 168-169° (from aqueous methanol) in 81% yield. Found %: C 62.5; H 4.1. $C_{10}H_8O_4$. Calculated %: C 62.5; H 4.2.

2-Carbomethoxy-4-bromo-5-hydroxybenzofuran (III). A solution of 0.8 g (5 mmole) of bromine in 8 ml of glacial acetic acid was added gradually at room temperature to a suspension of 1 g (5 mmole) of I in 10 ml of glacial acetic acid, after which the mixture was stirred for 4 h. The resulting precipitate was removed by filtration to give III with mp 163-164° (from methanol) in 90% yield. PMR spectrum, δ, ppm:* 7.42 s (3-H), 7.08 d (6-H), and 7.38 d (7-H). Found %: C 44.5; H 2.7; Br 29.6. $C_{10}H_7BrO_4$. Calculated %: C 44.3; H 2.6; Br 29.5.

2-Carbomethoxy-4,6-dibromo-5-hydroxybenzofuran (IV). A solution of 1.6 g (10 mmole) of bromine in 8 ml of glacial acetic acid was added gradually to a refluxing solution of 1 g (5 mmole) of I in 10 ml of glacial acetic acid, after which the mixture was refluxed for 6 h and the acid was removed by vacuum distillation. The residue was recrystallized from aqueous methanol to give IV with mp 155-156° in 55% yield. Found %: C 34.0; H 1.8; Br 46.1. $C_{10}H_6Br_2O_4$. Calculated %: C 34.3; H 1.7; Br 45.7

2-Carbomethoxy-4,5-dioxo-6-bromobenzofuran (V). A 2.5-ml (37 mmole) sample of nitric acid (sp. gr. 1.4) was added at 20° to a solution of 0.55 g (1.6 mmole) of IV in 10 ml of chloroform, after which the mixture was stirred for 1-2 min. It was then washed with water, and the chloroform was removed by vacuum distillation to give V with mp 164-165° (from ethyl acetate) in 74% yield. Found %: C 42.1; H 1.8; Br 28.2. $C_{10}H_5BrO_5$. Calculated %: C 42.1; H 1.8; Br 28.0.

2-Carbomethoxy-4-nitro-5-hydroxybenzofuran (VI). A solution of 0.63 ml (7.7 mmole) of nitric acid (sp. gr. 1.35) in 7 ml of glacial acetic acid was added gradually at 10-12° to a suspension of 1 g (5 mmole) of I in 30 ml of glacial acetic acid, after which the mixture was stirred at the same temperature for 2 h. It was then poured into water, and the resulting precipitate was separated to give VI with mp 204-205° (from alcohol) in 72% yield. PMR spectrum, δ, ppm: 8.11 s (3-H), 7.74 d (6-H), and 8.07 d (7-H). Found %: C 50.7; H 3.1; N 6.1. $C_{10}H_7NO_6$. Calculated %: C 50.6; H 3.0; N 5.9.

2-Carbomethoxy-4-(p-tolylazo)-5-hydroxybenzofuran (VII). A solution of p-toluenediazonium chloride prepared from 0.7 g (6.5 mmole) of p-toluidine, 1.5 ml of concentrated hydrochloric acid, 5 ml of water, and a saturated aqueous solution of 0.5 g (7.2 mmole) of sodium nitrite was added with stirring at 3-5° to a solution of 1 g (5 mmole) of I in 20 ml of dioxane and 20 ml of 5% NaOH, after which the reaction mixture was stirred at 0° for 3 h. It was then acidified with hydrochloric acid, and the resulting precipitate was removed by filtration to give VII with mp 254-255° (from acetic acid) in 84% yield. PMR spectrum,

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*Here and subsequently, s is singlet and d is doublet.

δ, ppm: 7.89 s (3-H), 7.07 d (6-H), and 7.62 d (7-H). Found %: C 65.4; H 4.2; N 9.3. $C_{17}H_{14}N_2O_4$. Calculated %: C 65.8; H 4.5; N 9.0.

2-Carbomethoxy-4-dimethylaminomethyl-5-hydroxybenzofuran (VIII). A solution of 0.5 g (2.6 mmole) of I in 10 ml of dioxane and 1 ml (7.4 mmole) of bisdimethylaminomethane was refluxed for 3 h, after which the dioxane and excess amine were removed by vacuum distillation to give VIII with mp 127-128° (from aqueous methanol) in 77% yield. PMR spectrum, δ, ppm: 7.29 s (3-H), 6.83 d (6-H), and 7.24 d (7-H). Found %: C 62.5; H 6.0; N 5.6. $C_{13}H_{15}NO_4$. Calculated %: C 62.6; H 6.0; N 5.6. The hydrochloride of VIII was obtained from the base in quantitative yield and had mp 235-236° (from acetone–methanol). Found %: Cl 12.2. $C_{13}H_{15}NO_4 \cdot HCl$. Calculated %: Cl 12.4.

2-Carbomethoxy-4-formyl-5-hydroxybenzofuran (IX). A mixture of a solution of 1 g (0.01 mole) of I in 10 ml of glacial acetic acid and 3 g (0.02 mole) of urotropin was heated on a steam bath for 3 h, after which 10 ml of 10% hydrochloric acid was added, and the mixture was heated for another 30 min. The solution was cooled, and the resulting precipitate was removed by filtration to give IX with mp 166-167° (from 50% acetic acid) in 26% yield. PMR spectrum, δ, ppm: 7.42 s (3-H), 7.08 d (6-H), and 7.38 d (7-H). Found %: C 60.0; H 3.6. $C_{11}H_8O_5$. Calculated %: C 60.0; H 3.6.

2-Carbomethoxy-4-bromo-5-hydroxy-6-dimethylaminomethylbenzofuran (X). This compound, with mp 155-156° (from ethanol), was obtained in 40% yield by the method used to prepare VIII. Found %: C 47.6; H 4.2; Br 24.8; N 4.1. $C_{13}H_{14}BrNO_4$. Calculated %: C 47.6; H 4.3; Br 24.4; N 4.3. The hydrochloride of X was obtained in quantitative yield from the base and had mp 196-197° (from acetone–methanol–ether). Found %: Cl 9.6. $C_{13}H_{14}BrNO_4 \cdot HCl$. Calculated %: Cl 9.7.

LITERATURE CITED

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