

Synthesis of 4*H*-Furo[3,2-*b*]indoles. II (1,2).
Bromination, Acylation and Nitration of 4*H*- and 4-Benzoylfuro[3,2-*b*]indoles

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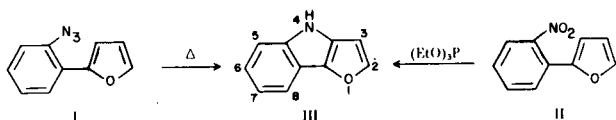
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Monobromination and monoacylation at the 2-position of 4*H*-furo[3,2-*b*]indole ring (III) were facilitated by the benzoyl group in the 4-position; subsequent nitration attempts were unsuccessful.

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In a previous paper, we reported that 4*H*-furo[3,2-*b*]indole (III) was prepared by the thermolysis of 2-(2-azidophenyl)furan (I) and the deoxygenation of 2-(2-nitrophenyl)furan (II) with triethyl phosphite as shown in Scheme I (2). In this paper, we describe that the reaction of III with various electrophiles was attempted to acquaint us with the chemical properties of III.

Scheme I



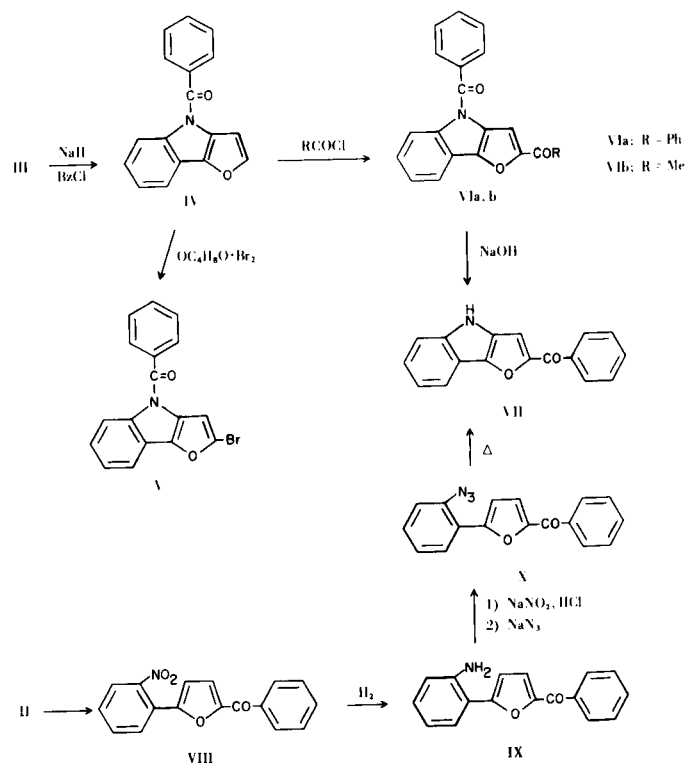
In the literature relating to 4*H*-thieno[3,2-*b*]indole which has a structure similar to that of III, Smith, *et al.*, reported only the preparation of its ring system and did not describe its chemical properties (3). We reported that the Vilsmeier formylation of III gave 4*H*-furo[3,2-*b*]indole-2-carboxaldehyde (2). Thus, it is estimated that the active position of III relative to electrophiles will be the C₂-position as in the furan ring.

An attempt to brominate III by reaction with pyridinium hydrobromide perbromide (4) gave only black intractable material which was not possible to characterize. When dioxane dibromide was used as the brominating reagent in pyridine or dioxane, the result was identical. Reaction of III with benzoyl chloride in carbon disulfide involving Lewis acids (aluminum chloride, zinc chloride or stannic chloride) at 0° gave only an amorphous dark brown solid. Similarly, nitration of III with fuming nitric acid in acetic anhydride failed. Although the Friedel-Crafts acylation of indole has been rarely reported (6), the acylation of indole was only reported to produce amorphous solids (8). Since compound III incorporates an enamino-keto structure in its molecule, it is probably more unstable in acidic medium than furan and indole.

We, therefore, prepared the compound containing a benzoyl group at the nitrogen atom as a protecting group for the purpose of reducing the instability in an acidic

medium, and carried out the reaction of electrophiles. 4-Benzoylfuro[3,2-*b*]indole (IV) was obtained from substituted III by sodium hydride with benzoyl chloride in dimethylformamide. Bromination of V with dioxane dibromide in pyridine at 0-2° gave 2-bromo-4-benzoylfuro[3,2-*b*]indole (V). Elimination of the benzoyl group of V with 33% sodium hydroxide solution gave the same intractable black solid as the attempted direct bromination of III. Acylation of IV with benzoyl chloride or acetyl chloride in carbon disulfide containing aluminum chloride gave 2,4-dibenzoylfuro[3,2-*b*]indole (VIa) and 2-acetyl-4-benzoylfuro[3,2-*b*]indole (VIb), respectively. The structure of V and VIa,b were supported by spectral data and elemental analysis as shown in the experimental. Compound VIa was treated with sodium hydroxide solution to

Scheme II



give 2-benzoyl-4*H*-furo[3,2-*b*]indole (VII). Compound VII was shown to be identical to the compound prepared below by mixed melting point and the ir spectrum. 2-Benzoyl-5-(2-nitrophenyl)furan (VIII) was prepared from II by the Friedel-Crafts reaction. The reduction of VIII gave 2-benzoyl-5-(2-aminophenyl)furan (IX). The diazonium salt of IX reacted with sodium azide to give 2-benzoyl-5-(2-azidophenyl)furan (X). Compound VII was prepared by the thermolysis of X in boiling *o*-dichlorobenzene. In the nmr spectra, the C₃-proton of VIa was shown at 1.55 ppm higher field than its proton of VII due to the shielding of the C₄-phenyl group. On the other hand, nitration of V with fuming nitric acid in acetic anhydride at -50° gave only black-brown amorphous solids.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were measured with a Jasco IRA-1 spectrometer using the pressed potassium bromide discs and the nmr spectra were recorded on a JEOL-PS-100 spectrometer using TMS as an internal standard. The mass spectra were taken with a Hitachi RMU-6 spectrophotometer.

Attempted Bromination of 4*H*-Furo[3,2-*b*]indole (III).

To a solution of 1 g. (6.4 mmoles) of III in 10 ml. of pyridine was added slowly 2.05 g. (6.4 mmoles) of pyridinium hydrobromide perbromide dissolved in 7 ml. of pyridine at 0-1°. When the addition was complete, the solution was poured into cold ether and filtered off. The cold ether solution was washed several times with cold diluted hydrochloric acid solution. The residual ether solution was then washed first with cold diluted sodium hydroxide solution, then with water and dried over magnesium sulfate. The solvent was removed and the residue became of colored black (m.p. >280°). The ether solution gave a positive halogen (Beilstein) test. Thus, tetrachloromethane was added to the ether solution. The ether was removed by concentrating the solution. The nmr spectrum was measured in the tetrachloromethane solution; nmr δ (tetrachloromethane): 7.34 (1H, br, NH), 7.23 (4H, m, C₅-8-H), 6.32 (1H, s, C₃-H). It was expected that the product by bromination of III would give 2-bromo-4*H*-furo[3,2-*b*]indole. At this writing, this has not been established.

4-Benzoylfuro[3,2-*b*]indole (IV).

To a solution of 1 g. (6.4 mmoles) of III in 5 ml. of dimethylformamide was added 0.16 g. (6.7 mmoles) of sodium hydride at room temperature and the mixture stirred for half an hour. To the mixture was then added 0.95 g. (6.8 mmoles) of benzoyl chloride and stirred for 1 hour at room temperature and poured into 100 ml. of ice-water. The resulting product was filtered off and recrystallized from methanol to give 1.3 g. (78%) of IV as colorless needles, m.p. 98-99°; ir ν cm⁻¹: 1670 (C=O); nmr δ (deuteriochloroform): 8.37 (1H, m, aromatic-H), 7.48 (8H, m, aromatic-H), 7.27 (1H, d, J = 2 Hz, C₂-H), 5.57 (1H, d, J = 2 Hz, C₃-H); ms: (m/e) 261 (M⁺).

Anal. Calcd. for C₁₇H₁₁NO₂: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.40; H, 3.94; N, 5.21.

2-Bromo-4-benzoylfuro[3,2-*b*]indole (V).

To a solution of 1 g. (3.8 mmoles) of IV in 10 ml. of pyridine was added slowly 1 g. (4 mmoles) of dioxane dibromide dissolved in 5 ml. of pyridine at 0-2°. After half an hour, the reaction mixture was poured into 80 ml. of cold ether and washed several times with cold diluted hydrochloric acid solution. The residual

ether solution was then washed first with cold diluted sodium hydroxide solution, then with water and dried over magnesium sulfate. After evaporation of the ether, the residue was recrystallized from ethanol to give 0.8 g. (61%) of V as colorless needles, m.p. 131-132°, dec.; ir ν cm⁻¹: 1680 (C=O); nmr δ (DMSO-d₆): 8.29 (1H, m, aromatic-H), 7.61 (8H, m, aromatic-H), 5.59 (1H, s, C₃-H); ms: (m/e) 339 (M⁺).

Anal. Calcd. for C₁₇H₁₀BrNO₂: C, 60.02; H, 2.96; N, 4.12. Found: C, 60.23; H, 2.75; N, 3.89.

2,4-Dibenzoylfuro[3,2-*b*]indole (VIa).

To a mixture of 0.54 g. (3.8 mmoles) of benzoyl chloride and 1.52 g. (11.4 mmoles) of aluminum chloride in 10 ml. of carbon disulfide was added 1 g. (3.8 mmoles) of IV dissolved in 10 ml. of carbon disulfide at 10° under stirring. After the addition, the reaction mixture was stirred at room temperature for 1 hour and poured into 100 ml. of ice-water. The resulting product was filtered off and washed with 5% sodium hydroxide solution, then with water. Recrystallization from acetone gave 0.8 g. (57%) of VIa as pale yellow needles, m.p. 166-167°; ir ν cm⁻¹: 1680, 1610 (C=O); nmr δ (DMSO-d₆): 8.36 (1H, m, aromatic-H), 7.70 (13H, m, aromatic-H), 6.08 (1H, s, C₃-H); ms: (m/e) 365 (M⁺).

Anal. Calcd. for C₂₄H₁₅NO₃: C, 78.89; H, 4.14; N, 3.83. Found: C, 78.65; H, 3.89; N, 3.62.

2-Acetyl-4-benzoylfuro[3,2-*b*]indole (VIb).

A compound VIb was prepared from IV with acetyl chloride by the procedure described for VIa as yellow prisms, m.p. 170-171° (from benzene-petroleum benzin) in 43% yield.

Anal. Calcd. for C₁₉H₁₃NO₃: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.21; H, 4.30; N, 4.45.

2-Benzoyl-4*H*-furo[3,2-*b*]indole (VII).

A mixture of 1 g. (2.7 mmoles) of VIa in 10 ml. of 33% sodium hydroxide solution was heated at 80° for 5 hours. After cooling, the reaction mixture was filtered off and recrystallized from methanol to give 0.6 g. (84%) of VII as yellow scales, m.p. 210-211°; ir ν cm⁻¹: 3240 (NH), 1600 (C=O); nmr δ (DMSO-d₆): 11.27 (1H, br, NH), 7.63 (1H, s, C₃-H), 7.60 (9H, m, aromatic-H); ms: (m/e) 261 (M⁺).

Anal. Calcd. for C₁₇H₁₁NO₂: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.97; H, 4.13; N, 5.16.

2-Benzoyl-5-(2-nitrophenyl)furan (VIII).

To a mixture of 23 g. (0.16 mole) of benzoyl chloride and 42 g. (0.32 mole) of aluminum chloride in 300 ml. of carbon disulfide was added 30 g. (0.16 mole) of II in 60 ml. of carbon disulfide at room temperature under stirring. After the addition, the reaction mixture was stirred at room temperature for 1.5 hours and poured into 2,000 ml. of ice-water. The resulting product was filtered off and recrystallized from methanol to give 43 g. (93%) of VIII as yellow needles, m.p. 129-130°; ir ν cm⁻¹: 1645 (C=O); ms: (m/e) 293 (M⁺).

Anal. Calcd. for C₁₇H₁₁NO₄: C, 69.62; H, 3.78; N, 4.78. Found: C, 69.88; H, 3.66; N, 4.71.

2-Benzoyl-5-(2-aminophenyl)furan (IX).

A solution of 29.3 g. (0.1 mole) of VIII in 250 ml. of dioxane was hydrogenated over 3 g. of 5% palladium-charcoal at room temperature. When hydrogen had been absorbed, the catalyst was filtered off. After evaporation of the solvent, the residue was recrystallized from methanol to give 23.1 g. (88%) of IX as yellow needles, m.p. 124-125°; ir ν cm⁻¹: 3480, 3350 (NH₂), 1620 (C=O); nmr δ (DMSO-d₆): 7.51 (1H, d, J = 3.8 Hz, C₃-H), 7.31 (9H, m, aromatic-H), 7.10 (1H, d, J = 3.8 Hz, C₄-H), 5.72 (2H, bs, NH₂); ms: (m/e) 263 (M⁺).

Anal. Calcd. for C₁₇H₁₃NO₂: C, 77.55; H, 4.98; N, 5.32.

Found: C, 77.77; H, 4.81; N, 5.14.

2-Benzoyl-5-(2-azidophenyl)furan (X).

A mixture of 32.6 g. (0.12 mole) of IX in 15 ml. of concentrated hydrochloric acid was cooled in ice-salt-bath. To the cold solution was added 8.5 g. of sodium nitrite in 30 ml. of water. The cold reaction mixture was then allowed to stand with frequent stirring for 45 minutes and then to the cold diazonium solution was added dropwise a solution of 16.3 g. of sodium azide in 45 ml. of water. After the addition, the solution was allowed to stand at room temperature for half an hour. The reaction mixture was poured into 1,000 ml. of water, filtered off, and recrystallized from ether to give 30 g. (84%) of X as pale brown prisms, m.p. 67-68°; ν cm^{-1} : 2250 (N_3), 1610 (C=O); ms: (m/e) 289 (M^+).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{N}_3\text{O}_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.72; H, 4.01; N, 14.71.

2-Benzoyl-4H-furo[3,2-b]indole (VII).

A solution of 6 g. (28 mmoles) of X in 10 ml. of *o*-dichlorobenzene was added dropwise to 30 ml. of boiling *o*-dichlorobenzene under stirring. During the reaction, nitrogen gas evolved and the solution changed to reddish brown color. After evaporation of the solvent, the residue was recrystallized from methanol to give 3.8 g. (70%) of VII as yellow scales, m.p. 211-212°, which was identified by mixed melting point and ir with those of VII prepared from VIa.

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