Synthesis of 3-Phenyl-2*H*-1,4-benzoxazin-2-one. Revision of Some Structural Assignments

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The reported synthesis of 3-phenyl-2*H*-1,4-benzoxazin-2-one (II) *via* bromination of *o*-acetamidophenyl phenacyl ether (Scheme) leads in fact to the 7-bromo-3-phenyl-2*H*-1,4-benzoxazin-2-ol (VIII). The structure of the other synthetic intermediates is also revised and a one-step synthesis of the lactone II is reported by condensation of methyl phenylglyoxalate and *o*-aminophenol.

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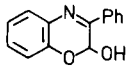
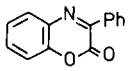
In connection with a study on the chemistry of 1,4-benzoxazines (2), we reported that autoxidation of 3-phenyl-2*H*-1,4-benzoxazine in acid medium gives, besides 2-phenylbenzoxazole, the hemiacetal I and the lactone II.



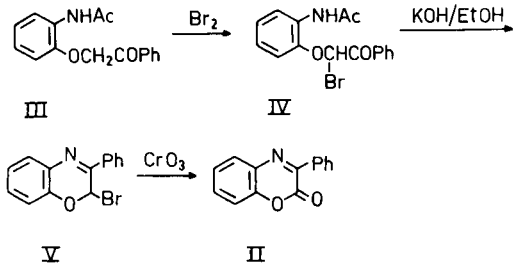
I



II

While I was hitherto unknown, a route had been previously reported by Tishchenko and Minakova (3) for the synthesis of the lactone II involving chromic oxidation of 2-bromo-3-phenylbenzoxazine (V) derived from the phenacyl ether III by selective bromination (4) at the methylene group and subsequent cyclization (Scheme). Surprisingly, the compound formulated as V was reported to remain unchanged after prolonged refluxing in ethanolic potassium hydroxide.

The poor characterization of all products in the Scheme and the marked difference (*ca.* 80°) in the melting points between our lactone II and the reported 3-phenyl-2*H*-1,4-benzoxazin-2-one, the latter identified on the basis of some nitrogen analysis, lead us to reinvestigate the described sequence of reactions.

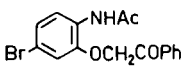


III IV V II

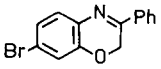
SCHEME

Bromination of *o*-acetamidophenyl phenacyl ether (III) in dioxane-ether gave as reported a colourless compound, m.p. 157-158°, which did not have the α-bromoketone structure IV but VI with the bromine atom located in position 4 of the benzene ring. This assignment followed mainly from the pmr spectrum (deuteriochloroform) showing in the aromatic region a doublet at δ 8.28 (J = 8 Hz) attributable to the proton adjacent to the acetamido group, a doublet centered at δ 7.12 (J = 8 and 2 Hz) assigned to C-4 proton, and a doublet (partially overlapped with the signals of H-4) at δ 7.04 (J = 2 Hz) attributable to C-6 proton.

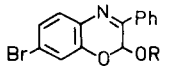
As expected, cyclization of the bromination product of III under the conditions described by Tishchenko and Minakova (3), afforded VII in the place of V, as evidenced by the pmr spectrum characterized by a sharp 2H singlet at δ 5.01 attributable to the methylene protons at C-2.



VI



VII



VIII R=H

IX R=CH_3

In our hands, chromic oxidation of VII, repeated several times exactly as described, gave a fine colourless powder which, however, on tlc (silicagel, eluent benzene) resulted in a mixture consisting mainly of some unchanged starting material and a slower-moving new product. This latter product, isolated in pure form making use of a lower solubility in chloroform, was identified as the bromohemiacetal VIII, $C_{14}H_{10}BrNO_2$, on the basis of the following evidence.

The mass spectrum showed diagnostic peaks at m/e 303 (M^+, 32), 266 (98), and 264 (100%), while the pmr spectrum (heptadeuterio-*N*,*N*-dimethylformamide) exhibited a complex multiplet at δ 8.1-7.4 for eight aromatic protons, and an 1H singlet at δ 6.46 attributable (2) to the hemiacetal methylene proton of structure VIII. The ir spectrum (Nujol) provided no clear evidence for the presence of the OH group which, however, could be evidenced by the reaction of VIII with methanol saturated with hydrochloric acid leading to the corresponding methyl acetal IX.

As expected, chromic oxidation of 3-phenyl-2*H*-1,4-benzoxazine gave a 47% yield of the hemiacetal I but only a trace amount of the lactone II. Attempts to obtain this latter by dehydrogenation of 3-phenyl-2*H*-1,4-benzox-

azine under various conditions were unsuccessful, but oxidation with selenium dioxide in dioxane-water (5) gave the lactone II in poor yield (16%). Once again the main product of this reaction, strictly resembling the aereal oxidation of phenylbenzoxazine (2), was the hemiacetal I (29%) which could not be converted into the lactone II by further oxidation.

Notably, bromination of the hemiacetal I under the conditions described above gave only the bromo derivative VIII, while the same reaction with 2-phenyl-2*H*-1,4-benzoxazine afforded a 60% yield of the hemiacetal I, presumably by hydrolysis of the corresponding 2-bromo derivative during the work-up procedure.

Having defined the actual course of the reported reactions (Scheme), attention was finally directed to the preparation of an authentic sample of the lactone II, which was eventually obtained by direct condensation of methyl phenylglyoxalate and *o*-aminophenol.

As expected, the synthetic compound (67% yield) was identical in all respects with the lactone II previously obtained by air oxidation of 3-phenyl-2*H*-1,4-benzoxazine.

EXPERIMENTAL

2-Acetamido-4-bromophenyl Phenacyl Ether (VI).

Following the procedure described by Tishchenko and Minakova (3), a solution of bromine (0.2 ml.) in dioxane (5 ml.) was added dropwise with continuous stirring to a solution of *o*-acetamidophenyl phenacyl ether (1.1 g.) in 25 ml. of dioxane-ether (2:3, v/v) standing at room temperature. After the addition the reaction mixture was diluted with water, the organic layer was separated and the aqueous layer was extracted with chloroform. Evaporation of the combined organic extracts afforded a solid residue which was crystallized from methanol to give VI, 1.2 g. (85% yield), m.p. 157-158° (lit. (3) 146-147°); mass spectrum: m/e (relative intensity) 349 (44), 347 (44), 307 (34), 305 (34), 202 (7), 200 (8), 188 (32), 186 (34) and 105 (100%); uv (methanol): λ max 216, 248, 288 nm (log ϵ 4.56, 4.50, 3.80); ir (chloroform): ν max 3380 and 3280 (NH) and 1690 cm^{-1} (C=O, amide and arylketone); pmr (deuteriochloroform): δ 8.7 (1H, br, NH, removed by D-exchange), 8.28 (1H, d, J = 8 Hz, H-3), 7.9 and 7.5 (5H, m, COPh), 7.12 (1H, dd, J = 8 and 2 Hz, H-4) and 7.04 (1H, d, J = 2 Hz, H-6). On irradiation at H-3 signal the double doublet at δ 7.12 changed to a doublet (J = 2 Hz), thus indicating the partially overlapped doublet of H-6.

Anal. Calcd. for $C_{16}H_{14}BrNO_3$: C, 60.77; H, 4.46; Br, 25.27; N, 4.43; M, 347.0180. Found: C, 60.42; H, 4.48; Br, 25.36; N, 4.41; M^+ 347.0157.

7-Bromo-3-phenyl-2*H*-1,4-benzoxazine (VII).

A solution of VI (2.1 g.) in 20% ethanolic potassium hydroxide (35 ml.) and water (3 ml.) was refluxed for *ca.* 1 hour. After cooling the crystals which separated were collected by filtration and recrystallized from methanol to give VII (0.92 g., 50% yield) as pale yellow plates, m.p. 157°: mass spectrum: m/e (relative intensity) 289 (100), 288 (58), 287 (100), 286 (42), 180 (12) and 103 (82%); uv (methanol): λ max 212, 253, 303, 337 (log ϵ 4.30, 4.21, 4.10, 4.12); pmr (deuteriochloroform): δ 7.9 (2H, cm, H-2′ and H-6′) and 7.3 (6H, cm, remaining ArH), 5.01 (2H, s, CH_2).

Anal. Calcd. for $C_{14}H_{10}BrNO$: C, 58.35; H, 3.50; Br, 27.73; N, 4.86; M, 286.9946. Found: C, 58.09; H, 3.50; Br, 27.96; N, 4.71; M^+ 286.9938.

Oxidation of VII with Chromic Anhydride.

In a typical experiment, to a suspension of VII (288 mg.) in *t*-butyl alcohol (4 ml.), chromic anhydride (200 mg.) was added and the mixture was stirred vigorously for 20 minutes at 70-75°. After cooling the mixture was diluted dropwise with water (4 ml.) and the brownish precipitate which formed was collected by filtration, dried over phosphorus pentoxide *in vacuo*, and extracted with hot chloroform (150 ml.). The resulting solution on cooling gave VIII (100 mg., 33% yield) as fine, colourless needles, m.p. 250-251°; mass spectrum: m/e (relative intensity) 305 (23), 303 (23), 277 (16), 276 (98), 275 (18), 274 (100) and 196 (65%); uv (methanol): λ max 208, 249, 322 (log ϵ 4.29, 4.05, 4.20, 4.23); pmr (DMF-D_7): δ 8.1 and 7.4 (8H, cm, ArH) and 6.46 (1H, s, CH).

Anal. Calcd. for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; Br, 26.27; N, 4.61; M, 302.9895. Found: C, 55.39; H, 3.36; Br, 26.28; N, 4.50; M^+, 302.9870.

7-Bromo-2-methoxy-3-phenyl-2*H*-1,4-benzoxazine (IX).

A solution of VIII (60 mg.) in methanol saturated with dry hydrochloric acid (20 ml.) was allowed to stand at room temperature for 18 hours. The reaction mixture was then concentrated *in vacuo* to a small volume, diluted with chloroform, washed with aqueous sodium bicarbonate, and evaporated. Preparative tlc of the residue on silica with benzene gave, besides some unchanged starting material (20 mg.), the methyl acetal IX (37 mg., 58% yield) which crystallized from methanol as colourless needles, m.p. 92-93°: mass spectrum: m/e (relative intensity) 319 (98), 317 (100), 304 (34), 302 (36), 288 (32), 286 (32), 276 (70) and 274 (72%); pmr (deuteriochloroform): δ 8.1 and 7.4 (8H, cm, ArH), 5.82 (1H, s, CH) and 3.53 (3H, s, CH_3).

Anal. Calcd. for $C_{15}H_{12}BrNO_2$: M, 317.0052. *Exact Mass.* Found: M^+, 317.0047.

Oxidation of 3-Phenyl-2*H*-1,4-benzoxazine with Chromic Anhydride.

To a solution of 3-phenyl-2*H*-1,4-benzoxazine (210 mg.) in *t*-butyl alcohol (5 ml.), chromic anhydride (200 mg.) was added and the mixture was stirred at 70° for 20 minutes. After cooling, the reaction mixture was diluted with water and extracted with chloroform. Evaporation of the organic layer afforded a residue which was crystallized from ethyl acetate to give the hemiacetal I (69 mg.) m.p. 230-232°. Preparative tlc of the mother liquor on silica gel in chloroform-methanol (9:1) gave an additional 23 mg. of compound I (total yield 47%).

Oxidation of 3-Phenyl-2*H*-1,4-benzoxazine with Selenious Acid.

A solution of selenium dioxide (111 mg.) in dioxane (5 ml.)-water (1 ml.) was added all at once to a stirred solution of 3-phenyl-2*H*-1,4-benzoxazine (210 mg.). After filtration, the mixture was evaporated to dryness and the residue was fractionated by preparative tlc on silica with benzene to give mainly 2-phenylbenzoxazole (10 mg., 5% yield), the hemiacetal I (65 mg., 29% yield) and the lactone II (35 mg., 16% yield).

Bromination of 3-Phenyl-2*H*-1,4-benzoxazine.

A solution of bromine (0.05 ml.) in dioxane (2 ml.) was added dropwise at room temperature to a solution of 3-phenyl-2*H*-1,4-benzoxazine (209 mg.) in dioxane-ether (6 ml., 1:2; v/v), kept under a nitrogen atmosphere. After the addition (*ca.* 30 minutes) the reaction mixture was diluted with water and ex-

tracted three times with ethyl acetate. The combined extracts, dried over sodium sulphate, were evaporated to dryness and the residue was crystallized from ethyl acetate to give 135 mg. (60% yield) of the hemiacetal I, m.p. 230-232°.

Bromination of 3-phenyl-2*H*-1,4-benzoxazine with two molar equivalents of bromine (0.1 ml.) and work-up of the reaction mixture as above gave 173 mg. (57% yield) of VIII m.p. 250-251° (from chloroform) identical in all respects to a sample obtained from chromic oxidation of VII.

Bromination of 3-Phenyl-2*H*-1,4-benzoxazin-2-ol (I).

A solution of bromine (0.025 ml.) in dioxane (1 ml.) was added dropwise at room temperature to a solution of the hemiacetal I (112 mg.) in dioxane-ether (6 ml., 1:2, v/v), kept under a nitrogen atmosphere. Upon completion of the addition (*ca.* 30 minutes) the reaction mixture was stirred at room temperature for an additional 30 minutes before being worked-up as usual to give 140 mg. (92% yield) of VIII m.p. 250-251° (from chloroform) identical in all respects to a sample obtained by chromic oxidation of VII.

3-Phenyl-2*H*-1,4-benzoxazin-2-one (II).

To a suspension of *o*-aminophenol (550 mg.) in xylene (10 ml.) methyl phenylglyoxalate (850 mg.) was added and the *p*H of the mixture was adjusted to *ca.* 4 by dropwise addition of glacial acetic acid. The mixture was then heated under stirring at *ca.* 100° for 18 hours. After cooling, the reaction mixture was diluted with ether, washed with 2*N* sodium hydroxide and water, dried and evaporated to dryness. Crystallization of the residue from methanol gave II (750 mg., 67% yield) as pale yellow needles, m.p. 120-121°.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.28. Found: C, 75.28; H, 4.20; N, 6.28.

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