2,3-Benzoxazines. XVIII (1). Synthesis of 4-Methyl-1*H*-2,3-benzoxazine

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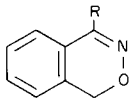
Received August 1, 1972

In previous papers of this series, we described new benzoxazines of type I substituted in position 4 with halogen, carboxy (3), alkoxy (4), amino and hydrazino groups (5). When our research was in progress (6), Barnish and Hauser (7) reported on the elegant synthesis of 4-phenyl-1*H*-2,3-benzoxazine (Ia) starting from *N*,*N*-dimethylbenzylamine (II) and benzonitrile. This route was



Ia, R C_6H_5
Ib, R H
Ic, R CH_3

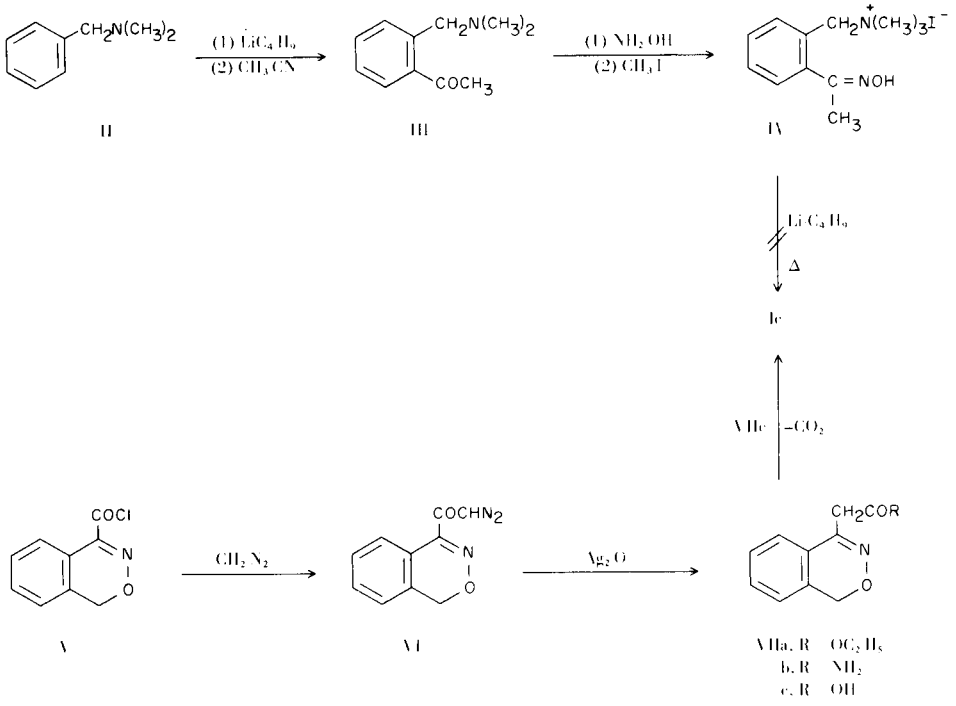
not suitable for the preparation of the unsubstituted parent member Ib, which however was obtained by us starting from 1*H*-2,3-benzoxazine-4-carboxylic acid (3).

Next, we have attempted to extend the method of Barnish to the preparation of the 4-methyl analogue Ic, owing to the potential biological interest of this structure (8).

The ketoamine III, obtained from II, *n*-butyllithium and acetonitrile, was reacted with hydroxylamine and methyl iodide to give the corresponding oxime IV (see Scheme I). This compound was then treated with *n*-butyllithium in tetrahydrofuran and heated at the reflux temperature, but the reaction mixture darkened without evolution of trimethylamine. When dioxane was used as solvent, small quantities of trimethylamine were observed, but the higher temperature probably favored decomposition of the lithio salt of IV and the cyclized derivative Ic was not found in the resulting materials.

Since this method did not appear suitable for the preparation of 4-alkyl-1*H*-2,3-benzoxazines, another syn-

Scheme I



thesis of Ic was developed. The intermediate diazoketone VI, obtained *via* Arndt-Eistert reaction of V (3) with diazomethane, was rearranged in ethanol to the acetate VIIa in the presence of silver oxide. The acetamide derivative VIIb was similarly prepared from VI. Alkaline hydrolysis of VIIa gave high yields of 1*H*-2,3-benzoxazine-4-acetic acid (VIIc) and this method was therefore preferred to the direct rearrangement of VI in aqueous medium. Finally, compound VIIc was smoothly converted into Ic by decarboxylation *in vacuo* at 150°.

The 4-methyl-1*H*-2,3-benzoxazine (Ic) is a colorless oil which can be distilled *in vacuo* without decomposition. Spectroscopic data are consistent with the structure assigned; in particular, the two protons singlet at τ 5.06 and the infrared band at 1565 cm^{-1} (C=N stretching) are characteristic for the 1*H*-2,3-benzoxazine ring (3,8).

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. Distillations were performed *in vacuo* using a bulb tube apparatus (9). Infrared spectra were scanned on a Perkin-Elmer Model 137 spectrometer as liquid films or Nujol mulls. Nmr spectra were recorded on a Varian A-60 (60 Mc/s) spectrometer. Chemical shifts are reported as τ (ppm) relative to internal TMS and the following abbreviations are used: s = singlet, m = multiplet.

o-(Dimethylaminomethyl)acetophenone (III).

A 20% hexane solution of *n*-butyllithium (48 ml., 148 mmoles) was added to a solution of 10 g. (74 mmoles) of dimethylbenzylamine (II) in 200 ml. of anhydrous ether-hexane (1:1) and the solution was left at room temperature for 20 hours in the absence of air. To the resulting solution of *o*-lithiobenzyldimethylamine were slowly added with stirring 6.1 g. (148 mmoles) of acetonitrile and the mixture was refluxed 6 hours under nitrogen. After cooling, the reaction mixture was worked up as described previously (10) to give an oil residue containing some starting amine II. The material was purified by distillation and the fraction of III boiling at 100-105°/10 mm. (3.27 g., 25%) was collected; ir: 3050 (ν aromatic CH), 2830 and 2780 (N-$(CH_3)_2$), 1690 (ν C=O), 1600 and 1580 (ν aromatic C=C), 1260, 1240 ν C-CO-C cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_{11}H_{15}NO$: N, 7.90. Found : N, 8.29.

o-(Dimethylaminomethyl)acetophenone Oxime Methiodide (IV).

An aqueous solution of 3.27 g. (24 mmoles) of sodium acetate hydrate was added to a warm solution of III (3.5 g., 19.75 mmoles) and hydroxylamine hydrochloride (1.68 g., 24 mmoles) in 12 ml. of ethanol. The resulting solution was refluxed for 4 hours, then it was cooled, taken up with water (40 ml.) and neutralized with sodium bicarbonate. Sodium chloride was added, the mixture was extracted three times with ether and the ether layer was dried over sodium sulfate. The solvent was evaporated to give 2.1 g. (55%) of the crude oxime of III as a pale yellow oil. The infrared spectrum was consistent with the expected oxime showing characteristic absorptions at 3500-2300, 1630 and 915 cm^{-1}. This material was dissolved in 20 ml. of ethanol containing 1 ml. of methyl iodide and the solution was refluxed for 1½ hours. After cooling, ether was added and the resulting precipitate was collected and crystallized from 2-propanol to give 1.42 g. (39%) of IV, m.p. 146-148°; ir: 3500-3300 (ν OH), 1630 (ν C=N), 1600 and 1500 (ν aromatic C=C), 915 (ν N-O), 775 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_{12}H_{19}IN_2O$: N, 8.38; I, 37.97. Found: N, 8.10; I, 37.45.

Attempted Cyclization of IV to give Ic.

A 20% hexane solution of *n*-butyllithium (0.85 ml., 2.7 mmoles) was slowly added under nitrogen to a cold suspension of IV (0.76 g., 2.24 mmoles) in 20 ml. of anhydrous dioxane. The mixture was warmed at 90° for 24 hours (a violet solution was observed with a poor development of trimethylamine) and then at the reflux temperature until evolution of the gas had ceased (about 15 hours). Some water-soluble material with a positive test for iodide ion was removed by filtration and the filtrate was evaporated to dryness. The residue was taken up in ether and filtered; the filtrate was concentrated to give an oily residue (about 0.4 g.) which did not contain the benzoxazine Ic (infrared and tlc comparison with an authentic sample obtained from VIIc).

4-Diazoacetyl-1*H*-2,3-benzoxazine (VI).

A solution of 6.0 g. (3.07 mmoles) of 1*H*-2,3-benzoxazine-4-carboxylic acid chloride (V) (3) in 90 ml. of ether was added dropwise at 0° to 470 ml. of an 1.2% ether solution of diazomethane. After the addition was completed, the solution was stirred at room temperature for 2 hours. The solvent and the excess of diazomethane were evaporated under reduced pressure without heating and the residue was taken up with isopropyl ether and cooled. The precipitate was collected by filtration, yielding pale yellow crystals (4 g., 65%) of crude VI, m.p. 110-112° dec.; ir: 3100 (ν CH), 2120 ($\nu_{asym.}$ N_2), 1640 (ν C=O), 1540 (ν C=N), 1020 (benzoxazine ring), 775 and 730 cm^{-1} (γ aromatic CH).

1*H*-2,3-Benzoxazine-4-acetic Acid, Ethyl Ester (VIIa).

A fine suspension of silver oxide (prepared from an aqueous solution of 0.8 g. of silver nitrate and 1.95 ml. of sodium hydroxide) in 40 ml. of anhydrous ethanol was added portionwise to a stirred solution of VI (4 g., 9.9 mmoles) in 120 ml. of ethanol at 60°. The reaction mixture was then stirred and heated to boiling for one hour and the catalyst was separated by filtration. After decoloration with Anticromos, the solution was evaporated to dryness and the residue was crystallized from isopropyl ether to yield 2.8 g. (64%) of VIIa, m.p. 71-72°; ir: 1735 (ν C=O), 1610 and 1500 (ν aromatic C=C), 1560 (ν C=N), 1200 and 1020 ($\nu_{asym.}$ and $\nu_{sym.}$ C-O-C), 770 and 720 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 6.20; N, 6.68.

1*H*-2,3-Benzoxazine-4-acetamide (VIIb).

A solution of 2.5 g. (12.4 mmoles) of VI in 20 ml. of dioxane was slowly added to a 10% aqueous ammonia solution (20 ml.) containing 3.9 ml. of a 10% silver nitrate solution at 60°. The reaction mixture was then refluxed for 2 hours with stirring. After filtration, the solution was evaporated *in vacuo* to dryness and the residue was triturated with water. The solid was collected and crystallized from ethanol, to give 0.9 g. (38%) of VIIb, m.p. 145-146°; ir: 3400 and 3200 ($\nu_{asym.}$ and $\nu_{sym.}$ NH_2), 1670 (ν C=O), 1630 (amide II), 1560 (ν C=N), 1400 (amide III), 1020 (benzoxazine ring), 760 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.50; N, 14.69.

1*H*-2,3-Benzoxazine-4-acetic Acid (VIIc).

Potassium hydroxide (0.45 g., 8 mmoles) was added to a solution of 1.5 g. (6.84 mmoles) of VIIa in 45 ml. of 90% ethanol and the resulting solution was left at room temperature for 15 hours. After evaporation *in vacuo*, the residue was taken up in water and acidified with 10% hydrochloric acid. The mixture was cooled and the precipitate collected to yield 1.05 g. (80%) of crude acid VIIc. A sample was further purified for analysis by crystallization from 80% ethanol, m.p. 97-98° dec.; ir: 2700-2200 (ν OH), 1720 (ν C=O), 1610 and 1490 (ν aromatic C=C), 1570 (ν C=N), 1020 (benzoxazine ring), 930 (γ OH), 770 cm^{-1} (γ aromatic CH); nmr (DMSO-d_6): τ 6.23 (s, 2H, CH_2CO), 5.07 (s, 2H, CH_2O), 4.0-2.3 (broad s, 1H, COOH), 2.9-2.3 (m, 4H, aromatic H).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.92; H, 4.94; N, 7.13.

4-Methyl-1*H*-2,3-benzoxazine (Ic).

Compound VIIc (0.55 g., 2.88 mmoles) was introduced in a bulb tube (9) and heated at 150° for 15 minutes. After the carbon dioxide evolution ceased, the oil residue was distilled at 70°/0.1 mm. to give 0.4 g. (94%) of pure Ic; ir: 1610 and 1490 (ν aromatic C=C), 1565 (ν C=N), 1015 (benzoxazine ring), 770 and 720 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): τ 7.64 (s, 3H, CH_3), 5.06 (s, 2H, CH_2), 3.0-2.3 (m, 4H, aromatic H).

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.20; H, 6.29; N, 9.30.

Acknowledgements.

The authors thank Dr. B. Gioia for the nmr spectra, Mr. G. Tuan for the ir spectra, and Mr. A. Restelli for the microanalyses.

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