3-ETHOXY-2-HYDROXYBENZALDEHYDE AS A STARTING COMPOUND FOR SYNTHESIS OF ISOQUINOLINE ALKALOIDS

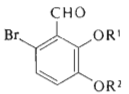
Jan ŠMIDRKAL

Research Institute of Fat Industry, 269 01 Rakovník

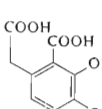
Received July 1st, 1981

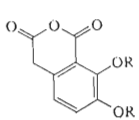
3-Ethoxy-2-hydroxybenzaldehyde (*I*) was used to prepare 6-bromo-2,3-dihydroxybenzaldehyde (*V*), 6-bromo-2,3-methylenedioxybenzaldehyde (*VIa*), 6-bromo-2,3-methylenedioxybenzoic acid (*VIIa*), and for new synthesis of compounds *II*, *IIIa*, *IIIb*, *IV*, *VIb*, *VIIb*, *VIIIa*, *VIIIb*, *IXa* and *IXb*.

Some of the intermediates for total synthesis of isoquinoline alkaloids are difficult to prepare. Thus preparation of 2,3-methylenedioxybenzaldehyde (*IIIa*) for synthesis of the alkaloid sanguinarine includes four reaction steps[1], with an overall yield of 15%. It has been found that the aldehyde *IIIa* can be prepared in two steps in a yield of 70% from 3-ethoxy-2-hydroxybenzaldehyde (*I*), which is a waste product in the industrial production of 3-ethoxy-4-hydroxybenzaldehyde. Dealkylation of *I* with boron tribromide gave 2,3-dihydroxybenzaldehyde (*II*), which was converted by reaction with dibromomethane into 2,3-methylenedioxybenzaldehyde (*IIIa*). The aldehyde *II* was also alkylated with dimethyl sulphate to 2,3-dimethoxybenzaldehyde (*IIIb*).



I, $R^1 = H$; $R^2 = C_2H_5$ — *IV*, $R^1 = H$; $R^2 = C_2H_5$
II, $R^1 = R^2 = H$ — *V*, $R^1 = R^2 = H$
IIIa, $R^1 - R^2 = CH_2$ — *VIa*, $R^1 - R^2 = CH_2$
IIIb, $R^1 = R^2 = CH_3$ — *VIb*, $R^1 = R^2 = CH_3$





VIIIa, $R - R = CH_2$ — *IXa*, $R - R = CH_2$
VIIIb, $R = CH_3$ — *IXb*, $R = CH_3$

6-Bromo-2,3-dimethoxybenzoic acid (*VIIb*) is a starting compound for the synthesis of hydrastine[2], 3,4-methylenedioxyhomophthalic acid (*VIIIa*) for oxysanguinarine[3], anhydride *IXa* for (±)-chelidonine[4], anhydride *IXb* for corydaline[5] and canadine[6]. These compounds can be obtained from the aldehyde *I via* bromoaldehyde *IV* by a route that is shorter than the described ones[1,7]. The bromoaldehyde *IV* can be obtained in one step by conducting the bromination in acetanhydride in the presence of a catalytic amount of sulphuric acid. Dihydroxyaldehyde *V* was obtained from the aldehyde *IV* in a high yield by dealkylation with boron tribromide. Reaction of methylene dibromide with *V* afforded 6-bromo-2,3-methylenedioxybenzaldehyde (*VIa*). Alkylation of *V* with dimethyl sulphate gave 6-bromo-2,3-dimethoxybenzaldehyde (*VIb*). The aldehydes *VIa* and *VIb* were oxidized with potassium permanganate to the corresponding carboxylic acids, *VIIa* and *VIIb*. Reactions of the acids *VIIa* and *VIIb* with ethyl acetoacetate[8], followed by the Claisen retro-cleavage, produced homophthalic acids *VIIIa* and *VIIIb*, which were converted by reaction with acetyl chloride into the respective anhydrides *IXa* and *IXb*.

EXPERIMENTAL

The melting points, determined on the Boetius block, are not corrected. The analytical samples were dried at a pressure of 27 Pa over phosphorus pentoxide at room temperature or at 77°C. The compounds were tested for purity by TLC on silica gel (Silufol UV_{254}, Kavalier), followed under UV light of wave lengths 254 and 366 nm. The UV spectra were measured with a spectrophotometer Unicam SP 8000 (λ_{max}, nm; log ε), IR spectra with a spectrophotometer Unicam SP 2000 G (ν, cm^{-1}) and ^1H NMR spectra with a spectrometer Tesla BS 487 C (80 MHz) (δ, ppm; J, Hz).

2,3-Dihydroxybenzaldehyde (*II*)

To a stirred solution of *I* (8·3 g, 50 mmol) in 100 ml of chloroform was added dropwise at 0°C, in the course of 30 min, a solution of BBr_3 (7·2 ml, 75 mmol) in 50 ml of chloroform. The stirring was continued for 2 h and the mixture was left standing overnight. One hundred ml of water was added, the organic layer was separated, washed with water, dried with sodium sulphate and distilled to remove the solvent. The residue was recrystallized from benzene; yield 5·9 g (86%) of *II*, needles melting at 105–107°C (reported[9] m.p. 105°C). IR spectrum (Nujol): 1 650 (CHO). ^1H NMR spectrum (CD_3OD): 9·97 (1 H, s, CHO), 6·50–7·30 (3 H, m, 4,5,6-H), 4·83 (2 H, bs, 2 × OH).

2,3-Methylenedioxybenzaldehyde (*IIIa*)

A mixture of the aldehyde *II* (6·9 g, 50 mmol), dimethylformamide (110 ml), powdered K_2CO_3 (20·8 g, 0·15 mol), powdered CuO (0·23 g, 2·9 mmol) and CH_2Br_2 (26·1 g, 0·15 mol) was stirred and refluxed for 7 h. The dimethylformamide was removed *in vacuo*, the residue was mixed with 100 ml of water and shaken with two 50 ml portions of ether. The extract was shaken with a 5% solution of NaOH, washed with water, dried with Na_2SO_4 and distilled. The residue was distilled *in vacuo*; yield of *IIIa* 6·1 g (82%), b.p. 129–130°C/1·5 kPa, m.p. 33–34°C (reported[10] m.p. 34°C). IR spectrum ($CHCl_3$): 1 688 (CHO). ^1H NMR spectrum ($CDCl_3$): 10·24 (1 H, s, CHO), 6·80–7·40 (3 H, m, 4,5,6-H), 6·14 (2 H, s, OCH_2O).

2,3-Dimethoxybenzaldehyde (*IIIb*)

To a stirred suspension of the aldehyde *II* (5·5 g, 40 mmol) in water (20 ml) was added dropwise a solution of NaOH (3·2 g, 80 mmol) in 10 ml of water. Then, in the course of 1 h, a solution of NaOH (6 g, 0·15 mol) in 20 ml of water and dimethyl sulphate (22·7 g, 0·18 mol) were added dropwise simultaneously. The mixture was heated for 1 h in a boiling water bath, cooled down and shaken with ether. The extract was shaken with a 5% solution of NaOH, washed with water, dried with Na_2SO_4 and distilled. Vacuum distillation of the residue gave *IIIb* (4·5 g, 68%), b.p. 126–128°C/1·2 kPa, m.p. 54–55°C (reported[11] m.p. 54–55°C). IR spectrum ($CHCl_3$): 1 690 (CHO). ^{1}H NMR spectrum ($CDCl_3$): 10·45 (1 H, s, CHO), 6·95–7·50 (3 H, m, 4,5,6-H), 3·92 and 3·83 (2 × 3 H, 2 × s, 2 × OCH_3).

6-Bromo-3-ethoxy-2-hydroxybenzaldehyde (*IV*)

To a stirred mixture of acetanhydride (37·7 ml, 0·4 mol) and 96% H_2SO_4 (0·1 ml) was slowly added *I* (16·6 g, 0·1 mol). After 1 h acetic acid (100 ml), anhydrous sodium acetate (0·2 g) and iron powder (0·2 g) were added, then bromine (19·2 g, 0·12 mol) was slowly added dropwise at 20°C. After another hour of stirring, 150 ml of water was slowly added dropwise and the mixture was refluxed for 1 h. A small amount of a precipitate was removed by filtration, the filtrate was cooled down, the separated crystals of *IV* were collected on a filter, washed with water, dried in the air and recrystallized from light petroleum (40 ml); yield 11·3 g (46·1%), yellow needles melting at 65–67°C (reported[7] m.p. 68°C). IR spectrum ($CHCl_3$): 1 648 (CHO). ^{1}H NMR spectrum ($CDCl_3$): 12·25 (1 H, s, OH), 10·26 (1 H, s, CHO), 7·05 (1 H, d, J = 8, 5-H), 6·88 (1 H, d, J = 8, 4-H), 4·08 (2 H, q, J = 7, OCH_2CH_3), 1·49 (3 H, t, J = 7, OCH_2CH_3).

6-Bromo-2,3-dihydroxybenzaldehyde (*V*)

To a stirred solution of BBr_3 (18·7 g, 75 mmol) in dichloromethane (106 ml) was added dropwise at 20°C, in the course of 30 min, a solution of *IV* (12·2 g, 50 mmol) in dichloromethane (50 ml). The mixture was stirred for 2 h. Next day 150 ml of water was added, the organic layer was separated, washed with water, dried with Na_2SO_4, and distilled to remove the solvent. The product *V* was recrystallized from benzene; yield 10·5 g (96·5%), yellow needles, m.p. 142 to 144°C. For $C_7H_5BrO_3$ (217·0) calculated: 38·74% C, 2·32% H, 36·82% Br; found: 38·93% C, 2·23% H, 37·06% Br. IR spectrum (KBr): 1 631 (CHO). ^{1}H NMR spectrum (CD_3SOCD_3): 10·70 (2 H, bs, 2 × OH), 10·19 (1 H, s, CHO), 7·10 (1 H, d, J = 9, 5-H), 6·91 (1 H, d, J = 9, 4-H).

6-Bromo-2,3-methylenedioxybenzaldehyde (*VIa*)

A mixture of dimethylformamide (40 ml), *V* (4·34 g, 20 mmol), CH_2Br_2 (10·4 g, 60 mmol), K_2CO_3 (8·3 g, 30 mmol) and powdered CuO (0·1 g) was stirred and heated to 110°C for 4 h. After cooling it was poured into water, the precipitate was collected on a filter, washed with water and recrystallized from 2-propanol. Yield of *VIa* 3·4 g (74·2%), yellow needles, m.p. 158–160°C. For $C_8H_5BrO_3$ (229·1) calculated: 41·95% C, 2·20% H, 34·89% Br; found: 42·09% C, 2·20% H, 34·23% Br. IR spectrum ($CHCl_3$): 1 683 (CHO). ^{1}H NMR spectrum ($CDCl_3$): 10·28 (1 H, s, CHO), 7·10 (1 H, d, J = 8·5, 5-H), 6·81 (1 H, d, J = 8·5, 4-H), 6·15 (2 H, s, OCH_2O).

6-Bromo-2,3-dimethoxybenzaldehyde (*VIb*)

To a stirred mixture of dimethylformamide (20 ml), *V* (4·34 g, 20 mmol) and K_2CO_3 (11 g,

80 mmol) was slowly added dropwise, at 110°C, dimethyl sulphate (6·3 g, 50 mmol). The mixture was stirred and kept at 110°C for 30 min, cooled down, and poured into water. The precipitate was collected on a filter, washed with water and recrystallized from 2-propanol. Yield of *VIb* 3·7 g (76%), needles melting at 77—78°C (reported[2] m.p. 71—73°C) IR spectrum ($CHCl_3$): 1 701 (CHO). ^{1}H NMR spectrum ($CDCl_3$): 10·35 (1 H, s, CHO), 7·31 (1 H, d, J = 9, 5-H), 6·95 (1 H, d, J = 9, 4-H), 3·91, 3·88 (2 × 3 H, 2 × s, 2 × OCH_3).

6-Bromo-2,3-methylenedioxybenzoic Acid (*VIIa*)

To a stirred solution of *VIa* (3·44 g, 15 mmol) in 150 ml of pyridine was slowly added dropwise, at 20°C, a solution of $KMnO_4$ (4·7 g, 30 mmol) in 100 ml of water. The mixture was stirred for 2 h, the precipitated MnO_2 was filtered off and washed with hot pyridine and boiling water. The combined filtrates were concentrated to 50 ml and the precipitate was collected on a filter (recovered *VIa*, 0·97 g, 28·2%). The filtrate was acidified (HCl, 1 : 1) and extracted with ether. The extract was dried with Na_2SO_4 and the ether was distilled off. The product (*VIIa*) was recrystallized from benzene. Yield 1·9 g (51%), yellow needles, m.p. 171—172°C. For $C_8H_5BrO_4$ (245·1) calculated: 39·21% C, 2·06% H, 32·61% Br; found: 39·22% C, 2·27% H, 33·07% Br. IR spectrum (Nujol): 1 681 (COOH). ^{1}H NMR spectrum (CD_3SOCD_3): 7·11 (1 H, d, J = 8·5, 5-H), 6·90 (1 H, d, J = 8·5, 4-H), 6·12 (2 H, s, OCH_2O).

6-Bromo-2,3-dimethoxybenzoic Acid (*VIIb*)

This was prepared in the same way as *VIIa*, except that the mixture was stirred for 6 h. The product (*VIIb*) was recrystallized from a benzene–hexane mixture. Yield 3·0 g (77%), needles melting at 92—93°C (reported[12] m.p. 83—85°C). IR spectrum ($CHCl_3$): 1 712 (COOH). ^{1}H NMR spectrum ($CDCl_3$): 11·50 (1 H, s, COOH), 7·25 (1 H, d, J = 8·5, 5-H), 6·83 (1 H, d, J = 8·5, 4-H), 3·90 and 3·83 (2 × 3 H, 2 × s, 2 × OCH_3).

Anhydride of 3,4-Methylenedioxyhomophthalic Acid (*IXa*)

To a stirred mixture of *VIIa* (2·45 g, 10 mmol), ethyl acetoacetate (20 ml) and powdered CuBr (0·15 g) under an atmosphere of argon was added, in portions, NaH (0·72 g, 30 mmol) and the mixture was stirred for 3 h at 80°C. After cooling 20 ml of water and 10 ml of ether were added. The aqueous phase was separated, shaken with two 20 ml portions of ether and acidified (HCl, 1 : 1). The separated oil was extracted into two 25 ml portions of ether, the ether was evaporated and the residue was mixed with a solution of NaOH (2·5 g in 20 ml H_2O). The solution was stirred for 1 h at 40°C, acidified (HCl, 1 : 1) and cooled down. The precipitate was collected on a filter and dried in the air. The acid *VIIIa* (1·5 g, 67%) was obtained in the form of yellowish crystals melting at 202—204°C (reported[4,12] m.p. 203—204°C). A mixture of the acid *VIIIa* (1·4 g) and acetyl chloride (14 ml) was stirred and refluxed for 6 h. The unreacted acetyl chloride was distilled off and the anhydride *IXa* was recrystallized from benzene; yield 1·3 g (63% based on *VIIa*), m.p. 198—200°C (rep.[4] m.p. 199—200°C and[12] 195°C). IR spectrum (KBr): 1 774, 1 748 (CO). ^{1}H NMR spectrum ($CDCl_3$): 7·35 (1 H, d, J = 8, 6-H), 6·92 (1 H, d, J = 8, 5-H), 6·27 (2 H, s, OCH_2O), 4·17 (2 H, s, CH_2CO).

Anhydride of 3,4-Dimethoxyhomophthalic Acid (*IXb*)

The acid *VIIIb* was prepared by the same procedure as *VIIIa*, except that after acidification with HCl the acid *VIIIb* was taken into ether (2 × 25 ml), the extract was dried with Na_2SO_4

and the ether was evaporated. The acid *VIIIb* (1·4 g, 59%) was obtained as an oil. The anhydride *IXb* was prepared in the same way as *IXa*; yield 1·24 g (56% based on *VIIb*). M.p. 103–105°C, then, at a heating rate of 4°C/min needles crystallized in the melt, their m.p. was 112–114°C. The remelted sample melted at 112–114°C. If the remelted sample was recrystallized from benzene it melted again at 103–105°C and 112–114°C. No decomposition occurred (TLC). The anhydride *IXb* obviously crystallizes in two modifications, which accounts for the discrepant reported data: m.p. 115–117°C (ref.[6]) and 104–105°C (ref.[13]). IR spectrum ($CHCl_3$): 1 815, 1 775 (CO). ^{1}H NMR spectrum ($CDCl_3$): 7·18 (1 H, d, $J = 8$, 6-H), 6·95 (1 H, d, $J = 8$, 5-H), 3·98 (2 H, s, CH_2CO), 3·90, 3·87 (2 × 3 H, 2 × s, 2 × OCH_3).

REFERENCES

1. Sainsbury M., Dyke S. F., Moon B. J.: J. Chem. Soc. (C) *1979*, 1797.
2. Kametani T., Honda T., Inoue H., Fukumoto K.: J. Chem. Soc., Perkin Trans. I *1976*, 1221.
3. Shamma M., Tomlinson H. H.: J. Org. Chem. *43*, 2852 (1978).
4. Cushman M., Choong T.-C., Válko J. T., Koleck M. P.: J. Org. Chem. *45*, 5067 (1980).
5. Cushman M., Dekow F. W.: Tetrahedron *34*, 1435 (1978).
6. Cushman M., Dekow F. W.: J. Org. Chem. *44*, 407 (1979).
7. Brink M.: Acta Univ. Lund. Sect. II *1967*, 12; Chem. Abstr. *69*, 76823 (1968).
8. Bruggink A., McKillop A.: Tetrahedron *31*, 2607 (1975).
9. Pauly H., Schübel C., Lockemann K.: Ann. *383*, 312 (1911).
10. Perkin W. H., Trikojus V. M.: J. Chem. Soc. *1926*, 2935.
11. Rupp E., Linck K.: Arch. Pharm. (Weinheim) *253*, 33 (1915).
12. Haworth R. D., Perkin W. H., Stevens T. S.: J. Chem. Soc. *1926*, 1764.
13. Haworth R. D., Koeffli J. B., Perkin W. H.: J. Chem. Soc. *1927*, 548.

Translated by J. Salák.