

THE SYNTHESIS OF 2,2'-SUBSTITUTED 5,5'-BIPYRIMIDINES*

V. KRCHŇÁK and Z. ARNOLD

*Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Sciences, 166 10 Prague 6*

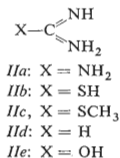
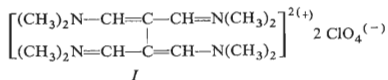
Received March 12th, 1974

Condensation of the double trimethinium perchlorate *I* with basic components *II* gave 2,2'-substituted 5,5'-bipyrimidines *IIIa–IIIc*. On methylation of compound *IIIb* bis(methylthio) derivative *IIIe* was obtained which on its hydrolysis afforded dihydroxy derivative *IIIf*.

The reaction of trimethinium salts with a component giving rise to a N—C—N grouping (guanidine, thiourea, amidines) represents a versatile synthesis of the pyrimidine nucleus^{1–3}. The preparation of bipyrimidines, described in this paper, represents an extension of this method.

Not many bipyrimidines are known yet, but the first one was already prepared about the middle of last century by Bayer⁴ on reaction of barbituric acid with glycerol. The major part of described bipyrimidines was obtained by connection of two pyrimidine rings^{5–9} using Ullmann's reaction of halogeno derivatives, best bromo pyrimidines. Another method of preparation of bipyrimidine derivatives consists in a simultaneous formation of both pyrimidine rings¹⁰. The method used by us here belongs to the second group.

The starting compound in our synthesis was the double trimethinium salt *I* (ref.¹¹). We investigated the reaction of this salt with guanidine, thiourea, formamidine, S-methylthiourea and urea. The reaction was carried out in ethanol; a solution of 1M sodium methoxide was added dropwise to a refluxing mixture containing the salt *I* and a 120% excess of the condensation component *II*. On condensation with the salt *I* guanidine and thiourea afforded corresponding bipyrimidines *IIIa* and *IIIb*.



* Part XXIX in the series Synthetic Reactions of Dimethylformamide; Part XXVIII: This Journal 38, 2641 (1973).

mixture was refluxed for 2 hours, cooled, dimethylamine removed in vacuum and the pyrimidine formed isolated and purified.

2,2'-Diamino-5,5'-bipyrimidine (IIIa): The separated product was filtered off, dissolved in a small amount of 2M-HCl and precipitated with diluted alkali solution, then centrifuged and washed with water. Yield 0.25 g (33%), the sample does not melt up to 360°C. For analysis the product was reprecipitated. For $C_8H_8N_6$ (188.2) calculated: 51.1% C, 4.3% H, 44.7% N; found: 50.9% C, 4.3% H, 44.7% N. Mass spectrum: $M^+ = 188$. IR spectrum (KBr): $\nu(NH_2)$ 3310, 3145 cm^{-1} ; $\delta(NH_2)$ 1657, 1602 cm^{-1} ; $\gamma(NH_2)$ 650 cm^{-1} ; ν (ring) 1549 cm^{-1} .

2,2'-Dimercapto-5,5'-bipyrimidine (IIIb): From the reaction mixture a dark precipitate (see below) was filtered off, the filtrate was purified with charcoal until only yellow, and neutralized with glacial acetic acid. The precipitated product was centrifuged, washed with water and dried. Yield 0.32 g, the substance does not melt up to 360°C. The insoluble fraction after filtration was dissolved in 1M-NaOH, the solution was purified with charcoal and neutralized with acetic acid. The precipitated product was centrifuged, washed with water and dried. Yield 0.34 g of a yellow substance which did not melt up to 360°C. Total yield 0.66 g of compound *IIIb* (30%). For analysis the sample was purified by double precipitation from 1M-NaOH. For $C_8H_6N_4S_2$ (222.3) calculated: 43.2% C, 2.7% H, 25.2% N, 28.8% S; found 42.5% C, 2.8% H, 24.2% N, 26.9% S. Mass spectrum $M^+ = 222$; (high resolution) found 222.00339, calculated 222.00324. IR spectrum (KBr): $\nu(SH)$ 2520 cm^{-1} ; ν (ring) 1619, 1581, 1565 cm^{-1} .

2-Methoxy-2'-methylthio-5,5'-bipyrimidine (IIIc): The reaction mixture was carefully neutralized with hydrochloric acid, methanol and ethanol were distilled off and the residue (0.4 g) was separated by column chromatography on silica gel (containing 10% of water) with methanol. Yield, 0.2 g of compound *IIIc* (21%), m.p. 205–220°C, and 0.07 g of compound *IIIc* (8%), m.p. 210–218°C. For analysis compound *IIIc* was crystallized from methanol, m.p. 215–220°C. For $C_{10}H_{10}N_4OS$ (234.2) calculated: 51.9% C, 4.3% H, 23.9% N, 13.7% S; found: 52.2% C, 4.9% H, 23.9% N, 13.9% S. Mass spectrum (high resolution): found 234.1479; calculated: 234.1480. IR spectrum ($CHCl_3$): $\delta(CH_3)_{as}$ 1479 cm^{-1} ; $\nu(O-CH_3)$ 1034 cm^{-1} ; ν (ring) 1607, 1585, 1550, 1409, 1390 cm^{-1} ; $-OCH_3$, $-SCH_3$: $\nu(CH)_{as}$ 2930 cm^{-1} ; $\nu(CH)_s$ 2870 cm^{-1} ; $-SCH_3$: $\delta(CH_3)_s$ 1302 cm^{-1} .

Condensation of the Methinium Salt *I* with Formamidine

A. Sodium methoxide solution (1M; 20 ml) was added dropwise over half-an-hour into a boiling solution of 1.8 g (0.004 mol) of methinium salt *I* and 1.5 g (0.012 mol) of formamidine acetate in 30 ml of ethanol and the mixture was refluxed for 2 hours. After cooling the liberated dimethylamine and ammonia were evaporated, the mixture neutralized with hydrochloric acid and filtered with charcoal. The filtrate was evaporated under reduced pressure and the residue extracted three times with 15 ml of dichloromethane. The extracts were combined, the solvent evaporated and the product *IV* crystallized from a small amount of ethanol. Yield 0.3 g, m.p. 105–110°C, after recrystallization from ethanol m.p. 110–111°C.

B. Formamidine acetate (3 g; 0.024 mol) was added into a solution of 1.8 g (0.004 mol) of methinium salt *I* in 40 ml of acetonitrile at room temperature and the mixture was refluxed for 2 hours. After cooling it was filtered, the filtrate evaporated under reduced pressure and the product extracted with three 15 ml portions of dichloromethane. The extracts were combined, dichloromethane distilled off and the product crystallized from a small volume of ethanol. Yield 0.38 g, m.p. 108–110°C, after recrystallization from ethanol m.p. 110–111°C. For $C_6H_{14}ClN_3O_4$ (227.6) calculated: 31.6% C, 6.1% H, 18.5% N, 15.5% Cl; found: 31.5% C, 6.2% H, 18.5% N,

15.2% Cl. UV spectrum (ethanol) $\lambda_{\max} = 246 \text{ nm}$ ($\epsilon = 3.16$); IR spectrum (CHCl_3): $\nu(\text{C}=\text{N})$ 1613 cm^{-1} ; $-\text{N}(\text{CH}_3)_2$: $\nu(\text{CH})$ 2810 cm^{-1} . The melting point, UV and IR spectrum of this sample were identical with those of an authentic sample¹².

2,2'-Dimethoxy-5,5'-bipyrimidine (IIIc)

Sodium methoxide solution (1M; 30 ml) was added dropwise over 30 minutes into a boiling solution of 1.8 g (0.004 mol) of methinium salt *I* and 1.4 g of S-methylthiuronium sulfate (0.01 mol) in 30 ml of ethanol and the mixture refluxed for 3 hours. After cooling dimethylamine was removed in vacuum and the mixture neutralized with hydrochloric acid. Methanol and ethanol were distilled off and the product extracted with benzene (3 \times 20 ml). The extracts were combined and benzene evaporated. Yield 0.3 g (34%), m.p. 208–220°C (from benzene). Sample for analysis was crystallized from ethanol, m.p. 216–221°C. For $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_2$ (218.1) calculated: 55.0% C, 4.6% H, 25.7% N; found: 54.5% C, 4.6% H, 25.8% N. Mass spectrum (high resolution): found 218.08037; calculated: 218.0804. IR spectrum (CHCl_3): $\delta(\text{CH}_3)_{\text{as}}$ 1427 cm^{-1} , $\delta(\text{CH}_3)_{\text{s}}$ 1415 cm^{-1} , $\delta(\text{OCH}_3)$ 1035 cm^{-1} , $\nu(\text{ring})$ 1595, 1549, 1400 cm^{-1} , $-\text{OCH}_3$: $\nu(\text{CH})_{\text{as}}$ $2960, 2935 \text{ cm}^{-1}$, $\nu(\text{CH})_{\text{s}}$ 2860 cm^{-1} .

2,2'-Bis(methylthio)-5,5'-bipyrimidine (IIIe)

Dimethyl sulfate (0.33 ml; 0.0035 mol) was added dropwise and under stirring into an ice-cold solution of 0.22 g (0.001 mol) of compound *IIIb* and 0.31 g (0.0055 mol) of potassium hydroxide in 2 ml of water and the mixture was stirred for 20 minutes. The separated product was filtered off with suction, washed and dried. Yield 0.2 g (80%), m.p. 213–218°C, after crystallization from methanol m.p. 218–219°C (lit.⁷ 210–212°C). For $\text{C}_{10}\text{H}_{10}\text{N}_4\text{S}_2$ (250.3) calculated: 48.0% C, 4.0% H, 22.4% N, 25.6% S; found: 48.0% C, 4.0% H, 22.3% N, 25.5% S. IR spectrum (CHCl_3): $\nu(\text{CH}-\text{SCH}_3)$ $2925, 2850 \text{ cm}^{-1}$; $\nu(\text{ring})$ 1579, 1532, 1515 cm^{-1} .

2,2'-Dihydroxy-5,5'-bipyrimidine (IIIf)

A mixture of 10 ml of 12% hydrochloric acid and 0.25 g (0.001 mol) of compound *IIIc* was heated at 100°C for two hours, then evaporated on a rotatory evaporator and the residue dissolved in dilute ammonia, the solution filtered with charcoal and the product precipitated by neutralization with hydrochloric acid. The precipitate was filtered off, washed with water and dried. Yield 0.15 g (80%), the substance did not melt up to 360°C. For analysis the sample was reprecipitated. For $\text{C}_8\text{H}_6\text{N}_4\text{O}_2$ (190.2) calculated: 50.5% C, 3.2% H, 29.4% N; found: 50.0% C, 3.6% H, 28.1% N. Mass spectrum: M^+ 190. IR spectrum (KBr): $\nu(\text{NH})$ 2750 cm^{-1} ; (CO) 1777 cm^{-1} , 1743 cm^{-1} ; $\nu(\text{ring})$ 1580 cm^{-1} .

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Translated by Ž. Procházka.