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

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Received March 12th, 1974

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

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 nucleus¹⁻³. 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 rings⁵⁻⁹ 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.

$$\begin{bmatrix} (\text{CH}_3)_2\text{N}-\text{CH}=\text{C}-\text{CH}=\text{N}(\text{CH}_3)_2 \\ (\text{CH}_3)_2\text{N}=\text{CH}-\text{C}=\text{CH}-\text{N}(\text{CH}_3)_2 \end{bmatrix}^{2(+)} & \text{X-C} \\ \text{NH}_2 \\ I & \text{IIa: X = NH}_2 \\ I \text{Ib: X = SH} \\ I \text{Ic. X = SCH}_3 \\ I \text{Id: X = H} \\ I \text{Ie: X = OH} \\ \end{bmatrix}$$

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

When formamidine was used as condensing component II the azatrimethinium perchlorate of the azamethinium salt IV was isolated from the reaction mixture instead of the expected 5,5'-bipyrimidine. Its formation may be explained by the reaction of formamidine and dimethylamine which is formed on degradation of the enamine grouping of the salt I in the reaction medium. The azatrimethinium salt IV was also isolated when the reaction was carried out in an alternative way, i.e. in acctonitrile without a base. The structure of the azatrimethinium salt IV was proved by comparison of its IV and IR spectra with those of an authentic specimen, prepared in the way described¹².

The reaction course is somewhat complicated when the salt *I* is condensed with S-methylthiourea. During this reaction the 2-methylthio group is substituted by the methoxide anion; from the reaction mixture 2,2'-dimethoxy-5,5'-bipyrimidine (*IIIe*) was isolated if a sufficient amount of methoxide was present. If he reaction was carried out under milder conditions (an equivalent amount of methoxide, shorter reaction time) unsymmetric 2-methoxy-2'-methylthio derivative *IIId* was obtained simultaneously with the already mentioned 2,2'-dimethoxy-5,5'-bipyrimidine (*IIIe*) in an up to 3:1 ratio (in favour of the unsymmetric product *IIId*). 2,2'-Bis(methylthio)bipyrimidine *IIIe*, formed as the primary product of condensation with S-methylthiourea, could not be prepared in this manner; however, it was prepared on methylation of dimercapto derivative *IIIb* with dimethyl sulfate in alkaline medium. Reaction of the salt *I* with urea under the above mentioned conditions did not give dihydroxy derivative *IIIf*. This bipyrimidine was prepared very simply by hydrolysis of 2,2'--bis(methylthio)-5,5'-bipyrimidine (*IIIe*) in 12% boiling hydrochloric acid.

EXPERIMENTAL

The melting points were measured on a Kofler block, the UV spectra on an Optica Milano CF 4 instrument and the IR spectra on a Zeiss, Jena, UR-10 spectrograph. The mass spectra were recorded on an AEI MS-902 apparatus, using double focussing.

Condensation Reaction (preparation of compounds IIIa, IIIb and IIId)

Sodium methoxide (1m; 18 ml) was added dropwise over half-an-hour into a refluxing mixture of 1.8 g (0.004 mol) of the salt I and 0.01 mol of base II (thiourea, urea) or its salt (guanidine hydrochloride, formamidine acetate, isomethylthiuronium sulfate) in 30 ml of ethanol. The

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: $51\cdot1\%$ C, $4\cdot3\%$ H, $44\cdot7\%$ N; found: $50\cdot9\%$ C, $4\cdot3\%$ H, $44\cdot7\%$ N. Mass spectrum: $M^+ = 188$. IR spectrum (KBr): $\nu(NH_2)$ 3310, 3145 cm⁻¹; $\delta(NH_2)$ 1657, 1602 cm⁻¹; $\nu(NH_2)$ 650 cm⁻¹; $\nu(ring)$ 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 (IIId): 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 IIId (21%), m.p. 205—220°C, and 0-07 g of compound IIIe (8%), m.p. 210—218°C. For analysis compound IIId 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 (CHCl₃); δ (CH₃)_{as} 1479 cm⁻¹; ν (O—CH₃) 1034 cm⁻¹; ν (ring) 1607, 1585, 1550, 1409, 1390 cm⁻¹; —OCH₃, —SCH₃: ν (CH)_{as} 2930 cm⁻¹; ν (CH)_s 2870 cm⁻¹; —SCH₃: ν (CH₃)_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. $105-110^{\circ}$ C, after recrystallization from ethanol m.p. $110-111^{\circ}$ 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. $108-110^{\circ}$ C, after recrystallization from ethanol m.p. $110-111^{\circ}$ C. For $C_6H_14CIN_3O_4$ (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,

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15·2% Cl. UV spectrum (ethanol) $\lambda_{\rm max}=246\,{\rm nm}$ ($\epsilon=3\cdot16$); IR spectrum (CHCl₃); ν (C=N) $1613\,{\rm cm}^{-1}$; —N(CH₃)₂: ν (CH) $2810\,{\rm cm}^{-1}$. The melting point, UV and IR spectrum of this sample were identical with those of an authentic sample 12 .

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-methylthiouronium sulfate (0-01 mol) in 30 ml of ethanol and the mixture refluxed for 3hours. 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 × 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 $C_{10}H_{10}N_4O_2$ (218·1) calculated: 55·0% C, 4·6% H, 25·8% N. Mass spectrum (high resolution): found 218·08037; calculated: 218·0804. IR spectrum (CHCl₃): δ (CH₃)_{as} 1427 cm⁻¹, δ (CH₃)_b 1415 cm⁻¹, δ (OCH₃) 1035 cm⁻¹, ν (ring) 1595, 1549, 1400 cm⁻¹, —OCH₃: ν (CH)_{as} 2960, 2935 cm⁻¹, ν (CH)_c 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 $C_{10}H_{10}N_{8}S_{2}$ (250·3) calculated: 48·0% C, 4·0% H, 22·3% N, 25·5% S. IR spectrum (CHCl₃): $v(CH-SCH_{1})$ 2925, 2850 cm⁻¹; v(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 IIIf 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 $C_8H_6N_4O_2$ (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): ν (NH) 2750 cm $^{-1}$; (CO) 1777 cm $^{-1}$, 1743 cm $^{-1}$; ν (ring) 1580 cm $^{-1}$.

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Translated by Ž, Procházka.