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

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Reaction of 5-substituted-2-methylpyrimidines with the Vilsmeyer complex followed by condensation of the resulting immonium salts and acroleins with aromatic amidines has given liquid crystalline 2',5-bipyrimidines.

The intensive study, followed by extensive development of arylpyrimidines in liquid-crystal compositions [1-3] has naturally stimulated interest in liquid-crystalline bipyrimidine systems. Reports have appeared [4-7] on the possibility of modifying the relative contributions of the parameters of liquid-crystalline compounds, depending on the relative orientations of the two pyrimidine rings forming the structural framework. Interest in 2',5-bipyrimidines is primarily due to those features of liquid-crystalline systems which are due to the magnitude and direction of the dipole moment [7-9]. The only known synthesis of 2',5-bipyrimidines is from 5-cyanopyrimidines [7, 8]. The synthesis of the starting materials, however, involves several stages, and their subsequent reactions are frequently complicated by side reactions [10].

A possible route for the construction of the 5-substituted pyrimidine ring is from pyrimidin-2-ylacetic acids [11], by analogy with the reaction of phenylacetic acids with the Vilsmeyer reagent [12]. However, this method of synthesis of the required bipyrimidine system is hardly likely to be successful in view of the ease of conversion of pyrimidin-2-ylacetic acids into 2-methylpyrimidines [11]. The enhanced reactivity of the methyl group in azines, including the 2-position in pyrimidines [13], together with reports of the formylation of activated methylazines by the Vilsmeyer reagent [14, 15] suggested the use of 2-methylpyrimidines as precursors for the synthesis of 2',5-bipyrimidines.

The aim of this investigation was to develop a method for the synthesis of 2',5-bipyrimidines from the readily accessible 5-substituted-2-methylpyrimidines. The formylation of 5-aryl- and 5-alkyl-2-methylpyrimidines (I) with the Vilsmeyer reagent was examined, and it was found that the corresponding immonium salts (II) and acroleins (III) were obtained, which have been reported (see, e.g., [10, 12, 16]) to be standard starting materials for the construction of the 5-substituted pyrimidine ring. Under the conditions used, the pyrimidines (Ic, d) gave both the salts (II) and the acroleins (III), while the pyrimidines (Ia, b) afforded the salts (II) only. Using the salts (IIa-d) and acroleins (IIIc, d) either in the pure state or in admixture with the aromatic amidines (IVa-d), good yields of the 2,5'-disubstituted-2',5'-bipyrimidines (Va-g) were obtained. For example, the bipyrimidine (Va) was obtained by condensing 2-[5'-(p-bromophenyl)pyrimidin-2'-yl]-3-dimethylaminopropenylidenedimethylamine perchlorate (IIa) with the amidine (IVa), and the 2',5-bipyrimidine (Vg) by reacting 2-(5'-heptylpyrimidin-2'-yl)-3-dimethylaminoacrolein (IIId) with the amidine (IVd). When a mixture of the perchlorates of 2-[5'-(p-butylphenyl)pyrimidin-2'-yl]-3-dimethylaminopropenylidenedimethylamine (IIc) and 2-[5'-(p-butylphenyl)pyrimidin-2'-yl]-3-dimethylaminoacrolein (IIIc), obtained by formylation of (Ic) with p-butoxyphenylbenzamidine hydrochloride (IVc) was used, a high yield of the 2',5-bipyrimidine (Vd) was obtained.

This provides a convenient method for the synthesis of 2',5-bipyrimidines from the readily accessible 5-substituted 2-methylpyrimidines (Ia-d) (see below).

All the products showed liquid-crystal properties, and formed predominantly the smectic mesophase over a wide range of temperatures (Table 1). Of the aromatic analogs of the four-ring 2',5-bipyrimidines (Va-d, g), symmetrical dialkyl derivatives of quaterphenyl have been reported which are also smectic (S_A) liquid crystals, but which exist in the liquid-crystal state over a much smaller temperature range (~50°C). This is due to the temperature of transition to the mesophase in these compounds [17] being higher than those in the biypyrimides (Va-d, g). In the vast majority of compounds with a terphenyl framework,

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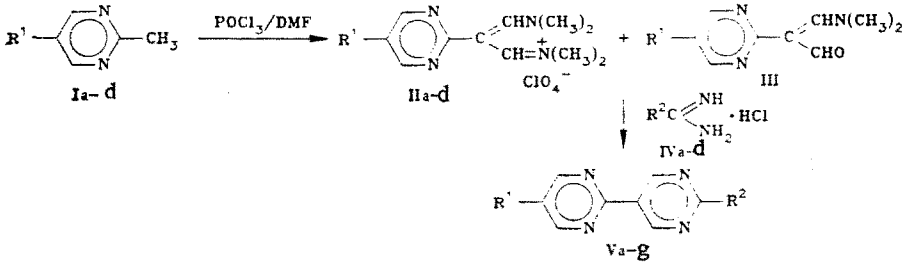

Ia, IIa, Va,b $R^1=C_6H_4Br$-p; Ib IIb Vc $R^1=C_6H_4OC_4H_9$-p, Ic–IIc, Vd $R^1=C_6H_4C_4H_9$-p; Id–IId Ve–g $R^1=C_7H_{15}$; IVa, Va,f $R^2=C_6H_4C_6H_{13}$p IVb, Vb,c,e $R^2=C_6H_4OC_6H_{13}$P; IVc, Vd $R^2=C_6H_4OC_4H_9$-p IVd Vg $R^2=C_6H_4C_6H_4C_5H_{11}$-p

formation of smectic (S_A) and more ordered orthogonal phases B and E ($S_{B,E}$) is typical [18], while the three-ring bipyrimidines (Ve, f) form a nematic in addition to a smectic mesophase. Generally speaking, the visual changes in the texture of the smectic mesophase (pattern, color) in (Va-d) and the change in the type of mesophase in (Ve-g) indicates the tendency of 2',5-bipyrimidines (Va-g) to polymorphism, but determination of the numbers and types of mesophase will require further studies.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer in KBr. Molecular masses were measured by mass spectrometry on a Finnigan MAT 8200 high-resolution instrument. The phase-transition temperatures and the textures of the mesophases were determined on a Boetius micro-hotplate with an RNMK-0.5 visual attachment.

The elemental analyses of (Ia), (IIa), and (Vb) for C, H, and N, and of (IId) and (IIId) for N, were in agreement with the calculated values.

5-(p-Bromophenyl)-2-methylpyrimidine (Ia, $C_{11}H_9BrN_2$). To a boiling suspension of 4.1 g (11.6 mmoles) of 3-(p-bromophenyl)-2-dimethylaminopropenylidenedimethylamine perchlorate [19] and 1.13 g (12 mmoles) of acetamidine hydrochloride in 50 ml of dry pyridine was added with stirring a solution of 1.35 g (25 mmoles) of sodium methoxide in 5 ml of methanol. The mixture was stirred for 8 h at the boil, cooled to 20°C, and poured into 300 ml of cold water. The solid which separated was filtered off, washed with water (3 × 15 ml), and dried to give 1.75 g (60%) of the pyrimidine (Ia), mp 163-164°C (petroleum ether).

2-[5'-p-Bromophenyl)-pyrimidin-2'-yl]-3-dimethylaminopropenylidenedimethylamine Perchlorate (IIa, $C_{17}H_{20}BrClN_4O_4$). To 19.8 ml (250 mmoles) of DMF was added dropwise with stirring at 0°C (bath temp. –5°C) 7.6 ml (80 mmoles) of $POCl_3$. The mixture was then stirred at 20°C for 20 min, again cooled to 0°C, and a suspension of 7.7 g (31 mmoles) of the pyrimidine (Ia) in 20 ml of DMF added in 3-5 portions. The mixture was stirred at 20°C for 4 h, and kept overnight. It was then heated with stirring to 75°C, kept at this temperature for 4 h, cooled to ~20°C, poured onto

TABLE 1. Properties of Bipyrimidines (Va-g)

Compound	Empirical formula	Phase transition temperatures*			ΔT, °C**	Found, m/z***	Calculated, m/z	Yield, %
		T_s	T_n	T_i				
Va	$C_{26}H_{25}BrN_4$	223	—	360	137	472,1256	472,1263	99
Vb	$C_{26}H_{25}BrN_4O$	160	—	259	99			89
Vc	$C_{30}H_{34}N_4O_2$	205	—	356	151	482,2682	482,2682	99
Vd	$C_{28}H_{30}N_4O$	245	—	370	125	438,2440	438,2419	60***
Ve	$C_{27}H_{36}N_4O$	124	208	211	87	432,2886	432,2889	94
Vf	$C_{27}H_{36}N_4$	144	198	200	56	416,2930	416,2940	99
Vg	$C_{32}H_{38}N_4$	154	190	208	54	478,3099	478,3096	56

*Transition temperatures to the smectic (T_s), nematic (T_n), and isotropic (T_i) phases, respectively. Compound (Va) was recrystallized from DMF, (Vb, g) from hexane, (Vc) from ethyl acetate–DMF (1:10), (Vd) from methyl cellosolve, and (Ve, f) from pyridine.

**Mesomorphic state range.

***Calculated on the amidine (IVc).

150 g of crushed ice, and a solution of 12.2 g (0.1 mole) of $NaClO_4$ in 30 ml of alcohol added. The semicrystalline solid which separated was separated from the aqueous layer, and recrystallized from methanol with the addition of activated charcoal to give 5.4 g (38%) of the salt (IIa). IR spectrum: 1080-1110, 1430, 1610 cm^{-1}, mp 265-266°C (decomp.).

The Vilsmeyer complex was reacted similarly with 2 g (11 mmoles) of the pyrimidine (Id) [20] as far as treatment of the reaction mixture with a solution of 6.1 g (50 mmoles) of $NaClO_4$, and the product was then extracted with chloroform (3 × 150 ml), which was then removed in a rotary evaporator. There was obtained a semicrystalline solid containing the salt (IId) and the acrolein (IIId). To this mixture was added 150 ml of diethyl ether, and the solid which separated was filtered off and dried to give the **salt (IId)** ($C_{18}H_{31}ClN_4O_4$) in a yield of 1.75 g (42%). IR spectrum: 1110, 1410, 1610 cm^{-1}, mp 179-180°C (from alcohol–petroleum ether, 1:1).

The ethereal filtrate was evaporated, and passed through a column of alumina (h = 15 cm, d = 3 cm; eluent hexane) to give 1.6 g (51%) of the **acrolein (IIId)** ($C_{16}H_{25}N_3O$). IR spectrum (thin layer): 1680 cm^{-1}, br. Found: m/z 275.1987. Calculated: m/z 275.1998.

A mixture of the salt (IIc) and the acrolein (IIIc) was obtained similarly from 7.5 g of the pyrimidine (Ic) [21] in a yield of 5.5 g [found: m/z 309; IR spectrum, thin layer: 1650 cm^{-1}, br. (C=O], which was used subsequently without separation for the synthesis of the pyrimidine (Vd) (see below).

2-(p-Hexylphenyl)-5'-(p-bromophenyl)-2',5-bipyrimidine (Va). To a boiling suspension of 2 g (4.4 mmoles) of the salt (IIa) and 1.1 g (4.4 mmoles) of the amidine (IVa) in 30 ml of absolute ethanol was added dropwise with stirring a solution of 0.23 g (0.01 mole) of metallic sodium in 10 ml of absolute methanol. The mixture was boiled for 4 h, cooled, the alcohol distilled off, the residue treated with 50 ml of water, and the solid filtered off and dried to give 2 g of the pyrimidine (Va).

Obtained similarly was **2-(p-hexyloxyphenyl)-5'-(p-bromophenyl)-2',5-bipyrimidine (Vb).**

2-(p-Hexyloxyphenyl)-5'-(p-butoxyphenyl)-2',5-bipyrimidine (Vc). To 3.9 ml (50 mmoles) of DMF was added dropwise at 0°C 1.6 ml (17 mmoles) of $POCl_3$. The mixture was stirred for 15 min at 20°C, again cooled to 0°C, and 1.86 g (8 mmoles) of the pyrimidine (Ib) [22] added portionwise. The mixture was kept overnight at 20°C, then for 4 h at 75°C, cooled to 20°C, poured onto 50 g of crushed ice, stirred for 1 h, and 2.1 g (17 mmoles) of dry $NaClO_4$ added portionwise with stirring, whereupon the product separated as a viscous oil. The aqueous layer was decanted, and the residue recrystallized from ethanol with the addition of activated charcoal to give 1.37 g (37%) of 2-[5'-(p-butoxyphenyl)pyrimidin-2'-yl]-3-dimethylaminopropenylidenedimethylamine perchlorate (IIb). IR spectrum: 1100, 1420, 1610 cm^{-1}, mp 154-156°C. The salt (IIb) and 0.80 g (31 mmoles) of the amidine (IVb) were suspended in 30 ml of absolute ethanol, heated to the boil, and a solution of 0.27 g (12 mmoles) of metallic sodium in 5 ml of absolute methanol added dropwise. The mixture was boiled for 6 h, cooled, the solvent removed, and the residue treated with hot chloroform (4 × 50 ml). The chloroform extracts were combined, and the chloroform removed in a rotary evaporator to give 1.5 g of the pyrimidine (Vc).

2-(p-Butoxyphenyl)-5'-(p-butylphenyl)-2',5-bipyrimidine (Vd). To a suspension of 1.1 g of a mixture of the salt (IIc) and the acrolein (IIIc) and 0.8 g (35 mmoles) of the amidine (IVc) in 25 ml of dry pyridine was added with stirring at 100°C a solution of 0.1 g (4 mmoles) of metallic sodium in 5 ml of absolute methanol. The mixture was kept for 6 h, the solution filtered hot, and the filtrate concentrated to a volume of 15 ml and cooled. The solid which separated was filtered off, washed with water (~150 ml), and dried to give 0.9 g of the pyrimidine (Vd).

Obtained similarly from the salt (IId) was **2-(p-hexyloxyphenyl)-5'-heptyl-2',5-bipyrimidine (Ve)**, and from the acrolein (IIId), **2-[p-amyl-(p-biphenylyl)]-5'-heptyl-2',5-bipyrimidine (Vg).**

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REACTION OF 2,3-DIOXOPYRROLO[2,1-*a*]ISOQUINOLINES WITH o-PHENYLENEDIAMINE

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Reaction of 1,2,3,4-tetrahydroisoquinoline enaminoamides with oxalyl chloride gives 2,3-dioxpyrrolo[2,1-a]isoquinolines which react with o-phenylenediamine to give spiro benzimidazolines or condensed quinoxalines, depending on the conditions used.

We have previously obtained 2,3-dioxopyrrolo[2,1-*a*]isoquinolines [1], which are promising synthons [2]. At present, condensed dioxopyrrolines are known principally as dienophiles and reactions of their carbonyl groups have been very little studied. With the preparation of new polycyclic systems in mind, we have studied the reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline with o-phenylenediamine at the dicarbonyl system [3].

The starting 2,3-dioxo-5,5-dimethyl-8,7-$(R^1)_2$-1-R^2-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolines IIa-d are prepared by treating the enamines Ia-d with oxalyl chloride. By using the tertiary amides Ib-d as starting materials we have broadened the scope of the previously described reaction [1].

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