SYNTHESIS OF HETEROCYCLIC COMPOUNDS XXII[1]. PREPARATION OF 6-ARYL-2-THIOXOPYRIMIDINES

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Abstract- The reactions of different ethyl benzylidenecyanoacetates (I) and benzylidenemalononitriles (V) with thiourea in an alcohol-alkoxide medium, provide a new and simple method for the synthesis of 6-aryl-5-cyano-4-oxo-2-thioxohexahydropyrimidines (III) and 4-amino-6-aryl-5-cyano-2-thioxotetrahydropyrimidines (VI), respectively. Similarly, the reaction of ethyl benzylidenemalonate leads to 5-ethoxycarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (XI).

Several methods of synthesis of thioxopyrimidines from α-substituted β-alkoxyacrylonitriles are known[1-10]. All they involve the reaction with ureas or thioacetamides to obtain 2- or 4-thioxopyrimidines, according to the case. In a recent paper[11], the synthesis of 4-oxo-2-thioxopyrimidines through condensation of ethyl cyanoacetate, aldehydes and thiourea, in a potassium carbonate-ethanol basic medium, was reported.

In this paper, the reaction of different ethyl benzylidenecyanoacetates (I) with thiourea (II) in ethanol-sodium ethoxide is studied, by the result of which a method to synthetize 6-aryl-5-cyano-4-oxo-2-thioxohexahydropyrimidines (III) was found. In the same way, the reaction of different benzylidenemalononitriles (V) with thiourea in isopropanol-sodium isopropoxide leads to 4-amino-6-aryl-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidines (VI).

The melting points and yields of the compounds III and VI are summarized in Table 1.

TABLE 1

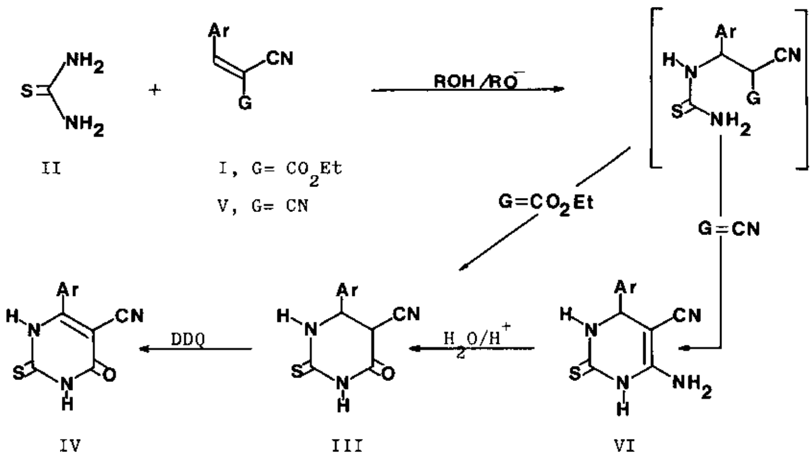
		III		VI	
	Ar	mp (ºC)	Yield (%)	mp (ºC)	Yield (%)
a	C_6H_5	239–240	65	216–217	57
b	p-CH_3-C_6H_4	244–245	82	215–216	63
c	p-CH_3O-C_6H_4	231–232	50	204–206	35
d	m-NO_2-C_6H_4	220–221	30	215–216	21

All products gave satisfactory microanalyses ($C\pm 0.30$, $H\pm 0.34$, $N\pm 0.29$, $S\pm 0.21$)

The formation of the pyrimidines III and VI takes place easily at room temperature and can be explained through condensation of thiourea with the alkylidene compound I or V, followed by cyclization of the adduct (Scheme 1) by attack of the amidic nitrogen to the ethoxycarbonyl or the cyano group, respectively. It should be pointed out that in the reaction between I and thiourea the formation of products through cyclization of the amidic nitrogen with the cyano group has not been observed.

The structure of the compounds obtained was stablished on the basis of spectral data (Tables 2 and 3) and, in some cases, by chemical tests. Thus, the oxidation of IIIc with dichlorodicyanoquinone (DDQ) yields the corresponding 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine IVc that was identified by comparison with the one obtained by Kambe et al[11]. The structure of the pyrimidines VI was confirmed by hydrolisis of VIa with dilute hydrochloric acid to 4-oxo-2-thioxohexahydropyrimidine IIIa.

Scheme 1

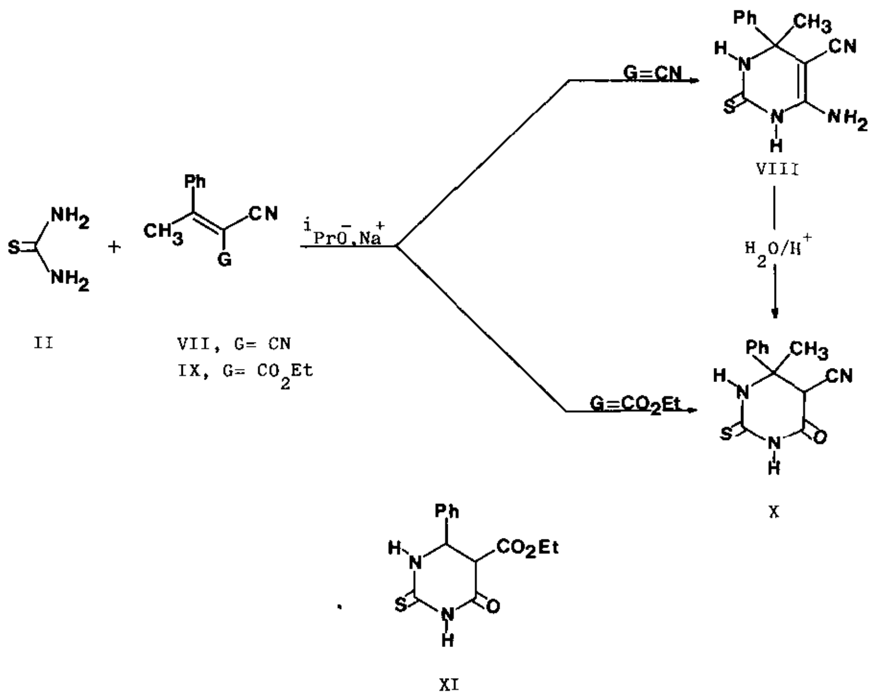


In the reaction of benzylidenemalononitriles V with thiourea, in an ethanol-sodium ethoxide medium, besides the 4-amino-2-thioxo-1,2,3,6-tetrahydropyrimidines VI, the corresponding 2-amino-4-aryl-3,5 dicyano-6-ethoxypyridines are also formed as side products. Their structure was identical to the ones obtained from benzylidenemalononitriles and malononitrile in an ethanol-sodium ethoxide system[12]. The formation of those 6-ethoxypyridines can be explained through condensation of V and malononitrile originated from benzylidenemalononitrile in the basic reaction medium.

The reactions of ethyl β-methylbenzylidenecyanoacetate (IX) and β-methylbenzylidenemalononitrile (VII) with thiourea, in isopropanol-sodium isopropoxide, have also been investigated (Scheme 2). Thus, 5-cyano-6-methyl-6-phenyl-4-oxo-2-thioxohexahydropyrimidine (X) and 4-amino-5-cyano-6-methyl-6-phenyl-1,2,3,6-tetrahydropyrimidine (VIII) were obtained, respectively. Hydrolysis of VIII with concentrated hydrochloric acid in ethanol under reflux affords 4-oxo-2-thioxohexahydropyrimidine X with an almost quantitative yield.

Finally, the reaction of ethyl benzylidenemalonate with thiourea in isopropanol-sodium isopropoxide leads to 5-ethoxycarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (XI) in high yield.

Scheme 2



EXPERIMENTAL

All melting points were determined in open capillary on a Büchi SMP-20 and are uncorrected. IR spectra were performed on a Perkin-Elmer 700. Reported values are the more intense or characteristic peaks. ^{1}H-nmr spectra were recorded on a Varian T-60 A with TMS as internal standard. Mass spectra were registered on a Varian MAT 711. Column chromatographies were carried out on basic alumina 60 Merck.

Benzylidenemalononitriles and ethyl benzylidenecyanoacetates were prepared according to general methods described by Corson[13] and Bertini[14], respectively. Ethyl β-methylbenzylidenecyanoacetate was prepared according to the synthesis described by Cope[15] and β-methylbenzylidenemalononitrile by the method of Mowry[16]. Ethyl benzylidenemalonate was obtained by the procedure of Kroeker and Mc-Elvain[17].

<u>6-Aryl-5-cyano-4-oxo-2-thioxohexahydropyrimidines III (General procedure)</u>.- To a solution of sodium (230 mg) in ethanol (50 ml), thiourea (760 mg, 10 mM) was added. When it became dissolved, 10 mM of the corresponding ethyl benzylidenecyanoacetate (I), dissolved in ethanol, were added. The resulting mixture was stirred at room temperature for 24 hr and after a solid precipitated through addition of 5% acetic acid. This solid was filtered and recrystallised from ethanol to obtain the corresponding hexahydropyrimidine III.

<u>4-Amino-6-aryl-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidine VI (General procedure)</u>.- To a solution of sodium (230 mg) in isopropanol (40 ml), thiourea (760 mg, 10 mM) and the corresponding benzyli-

denemalononitrile V (10 mM), dissolved in isopropanol, were successively added. After 36 hr (Note 1) the reaction mixture was precipitated with 5% acetic acid. The solid was filtered and washed with water. In every cases the different tetrahydropyrimidines VI were recrystallised from ethanol. Experimental results and spectroscopic data of pyrimidines III and VI are summarized in Tables 1-3.

Hydrolysis of VIa: Preparation of 5-cyano-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (IIIa).- 230 mg (1 mM) of VIa were suspended in ethanol (10 ml) and the solution was acidified with 10 % hydrochloric acid (10 ml). The mixture was kept with stirring at room temperature for 12 hr and later the precipitate was filtered, washed with water, dried and recrystallised in ethanol, giving 220 mg of IIIa. Yield: 96%; mp 238-239 ºC.

Oxidation of IIIc: Preparation of 5-cyano-6-(p-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (IVc).- 522 mg (2 mM) of IIIc were suspended in toluene (50 ml) and later DDQ (680 mg, 3 mM) was added. The mixture was refluxed for 8 hr and the resulting solid was filtered and chromatographied in a basic alumina column. IVc was obtained by concentrating the fractions that contained it and further recrystallisation from ethanol. Yield: 43%; mp 281-283 ºC. IR (KBr): ν_{max} = 3200, 3100, 2940, 2230, 2220, 1670, 1600, 1560, 1510, 1460, 1310, 1265, 1220, 1180 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 12.82-12.52 (b. s., 2 H, 1 and 3-H); 7.46, 7.33, 6.93, and 6.80 (q, 4H arom., syst. AB, $\underline{J}$ = 7.8 Hz); 3.73 (s, 3H, OCH_3). MS: m/e (relative intensity)= 259 ($M^{+\cdot}$, 100); 258 (31); 231 (16); 201 (18); 158 (15); 134 (32); 77 (4).

4-Amino-5-cyano-6-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine (VIII).- To a solution of sodium (345 mg) in isopropanol (40 ml), thiourea (1.14 g, 15 mM) and β-methylbenzylidenemalononitrile (2.52 g, 15 mM) were added in successive fractions. The mixture was stirred at room temperature for 36 hr. Ether (15 ml) was added before acidification with 5% acetic acid up to a slightly acidic pH. The precipitate was filtered and washed several times with water and ether. The crystallisation in ethanol with charcoal afforded 1.3 g of VIII. Yield: 36%; mp 249 ºC. IR (KBr): ν_{max} = 3400, 3300, 3210, 3150, 3000, 2195, 1660, 1575, 1470, 1445, 1380, 1265, 1175, cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 9.73 (s, 1H, N-H); 9.60 (s, 1H, N-H); 7.13 (s, 5H arom.); 5.90 (b. s., 2H, NH_2); 1.65 (s, 3H, CH_3). Anal. Calcd. for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93; S, 13.12. Found: C, 58.82; H, 5.06; N, 22.89; S, 13.29 %.

5-Cyano-6-methyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (X) (Procedure A).- To a solution of sodium (230 mg) in isopropanol (30 ml), thiourea (760 mg, 10 mM) was added, followed by slow addition of ethyl β-methylbenzylidenecyanoacetate dissolved in dry isopropanol (30 ml). The mixture was stirred at room temperature for 48 hr. Later it was diluted with ether (15 ml) and acidified with 5% acetic acid. The resulting solid was washed with water and ether, dried and crystallised from ethanol obtaining 1.5 g of X. Yield: 61%; mp 216-217 ºC. IR (kBr): ν_{max} = 3125, 3050, 2930, 2250, 1730, 1550, 1490, 1440, 1380, 1335, 1235, 1175, 1150, 1120 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ= 11.84 and 11.76 (d, 1H, N-H); 10.60 (s, 1H, N-H); 7.37 (s, 5H arom.); 5.34 and 5.05 (1H, 5-H); 1.81 and 1.68 (3H, CH_3). Anal. Calcd. for $C_{12}H_{11}N_3OS$: C, 58.75; H, 4.52; N, 17.13; S, 13.07. Found: C, 59.09; H, 4.72; N, 17.31, S, 13.36.

Hydrolysis of 4-amino-5-cyano-6-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine (VIII) (Procedure B).- 415 mg (17 mM) of VIII in ethanol (40 ml) were acidified with concentrated hydrochloric

Table 2. IR (KBr, cm^{-1})

	III	VI
a	3250; 3130; 2250; 1715; 1540; 1235.	3370; 3300; 3170; 2180; 1650; 1580; 1475.
b	3125; 2920; 2250; 1700; 1560; 1230.	3380; 3300; 3170; 2180; 1650; 1580; 1475.
c	3100; 2940; 2240; 1700; 1550; 1235.	3300; 3170; 2180; 1650; 1580; 1500; 1470.
d	3300; 3120; 2240; 1700; 1545; 1220.	3290; 3180; 2185; 1650; 1570; 1540; 1480.

Table 3. ^{1}H-NMR (DMSO-d_6, ppm)

	N^3-H	N^1-H	H-C^5 and C^6	Aromatic
IIIa	11.66–11.36 (b.s.)	10.52–10.32 10.06–9.86	5.30–4.73 (m)	7.27 (s)
IIIb	11.60–11.33 (b.s.)	10.23–10.03 9.97–9.77	5.20–4.68 (m)	7.23–6.93 (m)
IIIc	11.68–11.38 (b.s.)	10.32–10.12 10.02–9.82	5.22–4.72 (m)	7.45–6.75 (m)
IIId	11.79–11.46 (b.s.)	10.39–10.16 10.16–9.96	5.56–5.42 (m)	8.60–7.60 (m)

	N^3-H	N^1-H	C^6-H	Amino	Aromatic
VIa	9.68 (s)	9.41+9.36 (d, J=3 Hz)	4.93+4.88 (d, J=3 Hz)	6.00 (s)	7.18 (s)
VIb	9.70 (s)	9.45+9.40 (d, J=3 Hz)	4.87+4.82 (d, J=3 Hz)	5.98 (s)	6.98 (s)
VIc	9.65 (s)	9.38+9.33 (d, J=3 Hz)	4.82+4.77 (d, J=3 Hz)	5.92 (s)	7.03+6.90+ 6.78+6.65 (q)
VId	9.90 (s)	9.65+9.60 (d, J=3 Hz)	5.21+5.16 (d, J=3 Hz)	6.13 (s)	8.20–7.33 (m)

acid (6 ml). The mixture was heated under reflux for 10 hr and afterwards the ethanol was removed up to half volume. Through addition of water a solid precipitated, which was filtered, washed with water and recrystallised from ethanol, giving 417 mg of X. Yield: 98%.

5-Ethoxycarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (XI).- To a solution of sodium (230 mg) in dry isopropanol (35 ml), thiourea (760 mg, 10 mM) and ethyl benzylidenemalonate (2.48 g, 10 mM) were added. The mixture was stirred at room temperature for 24 hr and the solvent was then removed. To the resulting residue ethanol (5 ml) and water, in an amount just to obtain a clear solution, were added. This solution was acidified with 5% acetic acid up to a slightly acidic pH. The white precipitate appeared was kept in freezer for 1 hr. The solid obtained was washed several times with water and recrystallised from ethanol, giving 2.16 g of a white product, whose several recrystallisations fixed its melting point at 170 ºC. Yield: 78%. IR (KBr): ν_{max} = 3180, 2990, 1735, 1715, 1565, 1440, 1350, 1300, 1270, 1210, 1170, 1110, 1025 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 11.15 (b. s., 1H, 3-N); 9.87 (b. s., 1H, 1-N); 7.15 (s, 5H arom.); 5.05-4.73 (m, 1H, C-H); 4.2, 4.06, 3.97, and 3.85 (q, 2H, CH_2); 1.2, 1.08, and 0.98 (t, 3H, CH_3); 1.01 (1H, C-H).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.07; S, 11.52. Found: C, 56.42; H, 5.30; N, 10.03; S, 11.66.

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Note 1. The formation of VId required 72 hr of reaction and the precipitate obtained, according to the general procedure, was purified by column chromatography with silicagel, followed by recrystallisation from ethanol.

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